Critical Care Medicine

Principles of Diagnosis and Management in the Adult

FIFTH EDITION

Joseph E. Parrillo, MD

Justice Marie L. Garibaldi Endowed Chair
Chairman, Heart and Vascular Hospital
Hackensack University Medical Center,
Professor and Chair, Department of Cardiology
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey;
Professor of Medicine
Rutgers New Jersey Medical School
Newark, New Jersey

R. Phillip Dellinger, MD, MSc, MCCM

Professor of Medicine and Distinguished Scholar
Cooper Medical School of Rowan University;
Director Cooper Research Institute,
Senior Critical Care Attending
Cooper University Hospital
Camden, New Jersey

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

CRITICAL CARE MEDICINE: PRINCIPLES OF DIAGNOSIS AND MANAGEMENT IN THE ADULT, FIFTH EDITION

ISBN: 978-0-323-44676-1

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Library of Congress Control Number: 2018958993

Content Strategist: Nancy Duffy
Content Development Specialist: Anne Snyder
Publishing Services Manager: Julie Eddy
Senior Project Manager: Rachel E. McMullen
Design Direction: Patrick Ferguson

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To our families
Gale, Nicholas, Jenny, and Lena
and
Christa, Bart, Michael, Kate, Walker,
Lauren, Reid, and Meg

Preface

Few fields in medicine have grown, evolved, and changed as rapidly as critical care medicine over the past 40 years. From its origins in the postoperative recovery room and the coronary care unit, the modern intensive care unit (ICU) represents the ultimate example of medicine's ability to supply the specialized personnel and technology necessary to sustain and restore seriously ill persons to productive lives. In more recent years critical care has extended beyond the walls of the ICU to the emergency department where partnerships between intensivists and emergency medicine physicians have been forged. Critically ill patients now may be held for significant time periods in the emergency department, the post-operative recovery room or special critical care holding areas while awaiting an ICU bed. While the field continues to evolve rapidly, sufficient principles, knowledge, and experience have accumulated in the past few decades to warrant the production of a textbook dedicated to adult critical care medicine. We chose to limit the subject matter of our book to the critical care of *adult* patients to allow the production of a comprehensive textbook in a single volume.

This book was envisioned to be multidisciplinary and multi-specialty, authored by acknowledged leaders in the field, and aimed primarily at practicing critical care physicians who spend the better part of their time caring for patients in an ICU. Thus the book would be appropriate for critical care internists as well as for surgical or anesthesia critical care specialists. The goal was to produce the acknowledged "best practice" standard in critical care medicine.

The first edition of the textbook was published in 1995, co-edited by Joe Parrillo and Roger Bone. The book sold exceedingly well for a first edition text. After the untimely death of Roger Bone in 1997, Phil Dellinger joined Joe Parrillo as the co-editor for the second, third, fourth, and now this fifth edition. As co-editors, we have labored to produce a highly readable text that can serve equally well for comprehensive review and as a reference source. We felt that it was important for usability and accessibility to keep the book to a single volume. This was a challenge, because critical care knowledge and technology have expanded significantly during the past decade. By placing emphasis on clear, concise writing and keeping the focus on critical care medicine for the adult, this goal was achieved.

Our view of critical care medicine is mirrored in the organization of the textbook. Modern critical care is a multidisciplinary specialty that includes much of the knowledge and technology contained in many disciplines represented by the classic organ-based subspecialties of medicine, as well as the specialties of surgery and anesthesiology. The book begins with a section consisting of chapters on the technology, procedures, and pharmacology that are essential to the practicing critical care physician. This section is followed by sections devoted to the critical care aspects of cardiovascular, pulmonary, infectious, renal, metabolic, neurologic, gastrointestinal, and hematologic-oncologic diseases. Subsequent chapters are devoted to important social, ethical, and other issues such as psychiatric disorders, severity of illness scoring systems, and administrative issues in the ICU. This fifth edition has significant content additions and revisions, including new chapter authors for approximately a third of our chapters. Online videos are also available featuring a variety of content areas, including echocardiograms and bedside ultrasounds from a variety of exam sites. Further, a series of questions and answers with rationale for correct and incorrect answers are provided for each chapter to assist readers in board review and to reinforce the important content of each chapter.

Each chapter is designed to provide a comprehensive review of pertinent clinical, diagnostic, and management issues. This is primarily a clinical text, so the emphasis is on considerations important to the practicing critical care physician; also presented, however, are the scientific (physiologic, biochemical, and molecular biologic) data pertinent to the pathophysiology and management issues. We have aimed for a textbook length that is comprehensive but manageable. Substantial references (most now online) are provided for readers wishing to explore subjects in greater detail. We have identified key points and key references to highlight the most important issues within each chapter. Continued popular features of this fifth edition include a color-enhanced design and clinically useful management algorithms.

We have been fortunate to attract a truly exceptional group of authors to write the chapters for *Critical Care Medicine: Principles of Diagnosis and Management in the Adult.* For each chapter, we have chosen a seasoned clinician-scientist actively involved in critical care who is one of a handful of recognized experts on his or her chapter topic. We have continued the international flavor of our authorship. To provide uniformity in content and style, one or both of us have edited and revised each chapter.

We wish to thank the highly dedicated people who provided us with the assistance needed to complete a venture of this magnitude. Our thanks go to Ellen Lawlor, for her administrative assistance; and to the excellent editorial staff at Elsevier, including Anne Snyder, Nancy Duffy, and Rachel McMullen.

Joseph E. Parrillo, MD
Hackensack, New Jersey
Newark, New Jersey

R. Phillip Dellinger, MD, MSc, MCCM
Camden, New Jersey

Contributors

Wissam Abouzgheib, MD
Section Head, Interventional Pulmonary
Associate Professor of Medicine
Cooper Medical School at Rowan University
Camden, New Jersey

Mohanad Al-Obaidi, MD
Infectious Disease Fellow
University of Texas Health Science Center at Houston
Houston, Texas

Mark B. Anderson, MD
Chief, Division of Cardiac Surgery
Heart and Vascular Hospital
Hackensack University Medical Center
Hackensack, New Jersey

Iram Aqeel, MD
Attending
Hackensack University Medical Center
Hackensack Meridian Health Network
Hackensack, New Jersey

Sean M. Bagshaw, MD, MSc
Associate Professor
Department of Critical Care Medicine
Faculty of Medicine and Dentistry
University of Alberta
Edmonton, Alberta, Canada

Robert A. Balk, MD
Professor of Medicine
Rush Medical College,
Director, Division of Pulmonary, Critical Care, and Sleep Medicine
Rush University Medical Center
Chicago, Illinois

James C. Barrese, MD
Assistant Professor of Neurosurgery
Department of Neurosurgery
Cooper Medical School of Rowan University
Cooper University Hospital
Camden, New Jersey

Richard G. Barton, MD
Professor of Surgery,
Director, Surgical Critical Care Surgery
University of Utah, School of Medicine
Salt Lake City, Utah

Thaddeus Bartter, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Robert Berkowitz, MD, PhD
Director Heart Failure and Pulmonary Hypertension Program
Heart and Vascular Hospital, Hackensack Meridian Health;
Core Associate Professor
Department of Cardiology and Internal Medicine
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey

Thomas P. Bleck, MD, MCCM, FNCS
Professor of Neurology, Neurosurgery, Internal Medicine and Anesthesiology
Rush University Medical Center
Chicago, Illinois

Ziad Boujaoude, MD, FCCP
Associate Professor of Medicine
Cooper Medical School of Rowan University
Division of Pulmonary and Critical Care
Cooper University Hospital
Camden, New Jersey

Frank Bowen, MD
Associate Professor of Surgery
Cooper Medical School of Rowan University
Camden, New Jersey

Samantha K. Brenner, MD, MPH
Cardiothoracic Intensivist
Hackensack University Medical Center
Hackensack, New Jersey

Timothy G. Buchman, MD, PhD
Professor of Surgery, Anesthesiology, and Biomedical Infomatics,
Founding Director, (Emeritus)
Emory Critical Care Center
Emory University School of Medicine
Atlanta, Georgia

Eugene Bunnell, MD
Medical Director of Cardiothoracic Intensive Care Unit,
Vice Chairman of Critical Care Services
Heart and Vascular Hospital
Hackensack University Medical Center
Hackensack, New Jersey

Jeffrey P. Burns, MD, MPH
Chief and Shapiro Chair of Critical Care Medicine
Boston Children's Hospital;
Professor of Anaesthesia (Pediatrics)
Harvard Medical School
Boston, Massachusetts

Pietro Caironi, MD
Anestesia e Rianimazione
Azienda Ospedaliero-Universitaria S. Luigi Gonzaga
Orbassano, Italy;
Dipartimento di Oncologia
Università degli Studi di Torino
Turin, Italy

Eleonora Carlesso, MSc
Dipartimento di Fisiopatologia Mecico-Chirurgica e dei Trapianti
Università degli Studi di Milano
Milan, Italy

Maurizio Cecconi, MD, FRCA, FFICM, MD(Res)
Humanitas Research Hospital and Humanitas University
Milan, Italy

Louis Chaptini, MD
Assistant Clinical Professor
Section of Digestive Diseases
Yale University School of Medicine
New Haven, Connecticut

Cherylee W.J. Chang, MD, FCCM, FACP, FNCS
Medical Director, Neuroscience Institute/Neurocritical Care
The Queen's Medical Center;
Clinical Professor of Medicine and Surgery
John A. Burns School of Medicine
University of Hawaii
Honolulu, Hawaii

Kevin K. Chung, MD
Brooke Army Medical Center
Fort Sam Houston, Texas;
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Ismail Cinel, MD, PhD
Professor
Department of Anesthesiology and Reanimation
Marmara University Faculty of Medicine
Istanbul, Turkey

Damon H. Clark, MD
Assistant Professor of Surgery
Department of Acute Care Surgery
University of Southern California
Los Angeles, California

T.R. Craig, MB, BCh, BaO, FRCP, PhD, DICM (UK)
Consultant
Mater Hospital
Belfast, Northern Ireland, United Kingdom

Quinn A. Czosnowski, PharmD, BCPS
Critical Care Pharmacy Specialist
Indiana University Health Methodist Hospital
Indianapolis, Indiana

Hayan Dayoub, MD
Assistant Professor of Neurosurgery
Cooper Medical School of Rowan University;
Co-Director Interventional Neurosurgery
Cooper University Hospital
Camden, New Jersey

Daniel De Backer, MD, PhD
Professor
Department of Intensive Care
CHIREC Hospitals
Université Libre de Bruxelles
Brussels, Belgium

R. Phillip Dellinger, MD, MSc, MCCM
Professor of Medicine and Distinguished Scholar
Cooper Medical School of Rowan University;
Director Cooper Research Institute,
Senior Critical Care Attending
Cooper University Hospital
Camden, New Jersey

Guillermo Domínguez-Cherit, MD, FCCM
Director
Division of Pulmonary, Anesthesia, and Critical Care
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Mexico City, Distrito Federal, Mexico

David J. Dries, MSE, MD
Chair
Department of Surgery
HealthPartners Medical Group/Regions Hospital
St. Paul, Minnesota;
Professor of Surgery
Department of Surgery
University of Minnesota
Minneapolis, Minnesota

Adam B. Elfant, MD
Associate Professor of Medicine
Cooper Medical School of Rowan University;
Associate Head
Division of Gastroenterology and Liver Diseases
Cooper University Hospital
Camden, New Jersey

E. Wesley Ely, MD
Professor of Medicine and Critical Care,
Associate Director of Aging Research, VA GRECC
Center for Health Services Research
Division of Allergy, Pulmonary and Critical Care Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

Henry S. Fraimow, MD
Associate Professor of Medicine
Division of Infectious Diseases
Cooper Medical School of Rowan University
Camden, New Jersey

Heidi L. Frankel, MD, FACS
Department of Surgery
University of Southern California-LAC
Rancho Palos Verde, California

John F. Fraser, MBChB, PhD, FRCP (Glas), FRCA, FFARCSI, FCICM
Professor of Anaesthesiology and Critical Care
The University of Queensland School of Medicine;
Director, Critical Care Research Group
The Prince Charles Hospital
Brisbane, Queensland, Australia

Bruce C. Friedman, MD
Joseph M. Still Burn Center at Doctor's Hospital
Augusta, Georgia

Luciano Gattinoni, MD, FRCP
Department of Anesthesiology
Emergency and Intensive Care Medicine
University of Göttingen
Göttingen, Germany

Martin Geisen, MD
Institute of Anaesthesiology and Intensive Care Medicine
Triemli Hospital Zurich
Zurich, Switzerland

Fredric Ginsberg, MD
Associate Professor of Medicine
Division of Cardiovascular Disease
Cooper Medical School of Rowan University
Camden, New Jersey

Taya V. Glotzer, MD
Associate Professor of Medicine
Hackensack Meridian Seton Hall School of Medicine
Rutgers New Jersey Medical School;
Director of Cardiac Research
Hackensack University Medical Center
Hackensack, New Jersey

Kevin C. Gordon, MD
Division of Gastroenterology and Liver Disease
Cooper University Hospital
Camden, New Jersey

Sara R. Gregg, MHA
Executive Administrator
Emory Critical Care Center
Emory University School of Medicine
Atlanta, Georgia

David P. Gurka, MD, PhD
Professor of Medicine
Rush Medical College;
Director, Section of Critical Care Medicine
Department of Internal Medicine
Rush University Medical Center
Chicago, Illinois

Carmen M. Hernández-Cárdenas, MD, MSc
Director
Department of Critical Care, Inhalotherapy, and Emergency Medicine
Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas"
Mexico City, Mexico

Steven M. Hollenberg, MD
Professor of Medicine
Cooper Medical School of Rowan University;
Director, Coronary Care Unit
Cooper University Hospital
Camden, New Jersey

Robert C. Hyzy, MD
Professor
Division of Pulmonary and Critical Care Medicine
University of Michigan
Ann Arbor, Michigan

Judith Jacobi, BS, PharmD, BCCCP
Critical Care Pharmacy Specialist
Indiana University Health Methodist Hospital
Indianapolis, Indiana

Vladimir Jelnin, MD
Director, Cardiac Imaging Lab
Hackensack University Medical Center
Hackensack Meridian Health
Hackensack, New Jersey

Amal Jubran, MD
Professor of Medicine
Pulmonary and Critical Care Medicine
Loyola University Medical Center
Maywood, Illinois;
Section Chief
Pulmonary and Critical Care Medicine
Edward Hines Jr. Veterans Affairs Hospital
Hines, Illinois

Navin K. Kapur, MD
Interventional Cardiologist
Division of Cardiology
Tufts Medical Center
Boston, Massachusetts

George H. Karam, MD
Professor of Medicine
Louisiana State University Health Sciences Center
Baton Rouge, Louisiana

Constantine J. Karvellas, MD, SM, FRCPC, FCCM
Associate Professor of Medicine
Division of Gastroenterology (Liver Unit)
Department of Critical Care Medicine;
Adjunct Professor, School of Public Health Sciences
University of Alberta
Edmonton, Alberta, Canada

Steven T. Kaufman, MD
Associate Professor of Medicine
Cooper Medical School of Rowan University;
Medical Director
Urban Health Institute,
Head, Division of Endocrinology
Camden, New Jersey

Tapan Kavi, MD
Assistant Professor of Neurology
Cooper Medical School of Rowan University
Cooper Neurological Institute
Camden, New Jersey

Bernard Kim, MD
Associate Medical Director of Heart Failure and Pulmonary Hypertension Program
Heart and Vascular Hospital, Hackensack Meridian Health;
Core Assistant Professor
Department of Cardiology and Internal Medicine
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey

Jason A. Kline, MD
Assistant Professor of Medicine
Cooper Medical School of Rowan University
Division of Nephrology
Cooper University Health Care
Camden, New Jersey

Zoulficar Kobeissi, MD
Assistant Professor of Clinical Anesthesiology and Critical Care
Anesthesiology and Critical Care
Houston Methodist Hospital
Houston, Texas

James A. Kruse, MD, FCCM
Chief, Critical Care
Bassett Medical Center;
Clinical Professor of Medicine
Columbia University College of Physicians and Surgeons
New York, New York

Anand Kumar, MD
Professor
Section of Critical Care Medicine,
Section of Infectious Diseases
University of Manitoba
Winnipeg, Manitoba, Canada

Neil A. Lachant, MD
Chief, Section of Hematology
MD Anderson Cancer Center at Cooper;
Professor of Medicine
Cooper Medical School of Rowan University
Camden. New Jersey;
Adjunct Professor Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Franco Laghi, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Loyola University of Chicago Stritch School of Medicine
Edward Hines Jr. Veterans Administration Hospital
Hines, Illinois

Stephen E. Lapinsky, MBBCh, MSc, FRCPC
Professor of Medicine
University of Toronto;
Site Director
Intensive Care Unit
Mount Sinai Hospital
Toronto, Ontario, Canada

Jennifer LaRosa, MD, FCCM, FCCP
Newark Beth Israel Medical Center—Robert Wood Johnson Barnabas Health
Newark, New Jersey

G.G. Lavery, MB, BCh, BaO (Hons), MD, FJFICMI, FFARCSI
Consultant
Critical Care
Royal Victoria Hospital
Belfast, Northern Ireland, United Kingdom

Kenneth V. Leeper, Jr., MD[†]
Professor of Medicine
Division of Medicine/Pulmonary and Critical Care
Emory University School of Medicine
Atlanta, Georgia

Hsuan Lu, DO
Department of Neurology
Cedars Sinai Medical Center
Los Angeles, California

Veeranna Maddipati, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Brody School of Medicine
East Carolina University
Greeneville, North Carolina

[†]Deceased.

Dennis G. Maki, MD
Ovid O. Meyer Professor of Medicine
Divisions of Infectious Diseases and Pulmonary/Critical Care Medicine;
Attending Physician, Center for Trauma and Life Support
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

John Marini, MD
Professor of Medicine
Pulmonary and Critical Care Medicine
University of Minnesota
Minneapolis, Minnesota;
Regions Hospital
St. Paul, Minnesota

Annachiara Marra, MD, PhD
Department of Neurosciences
Reproductive and Odontostomatological Sciences
University of Naples, Federico II
Naples, Italy;
Visiting Research Fellow
Center for Health Services Research
Division of Allergy, Pulmonary and Critical Care Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

John C. Marshall, MD, FRCSC
Department of Surgery and the Interdepartmental Division of Critical Care Medicine
University of Toronto
St. Michael's Hospital
Toronto, Ontario, Canada

Henry Masur, MD
Critical Care Medicine Department
Clinical Center
National Institutes of Health
Bethesda, Maryland

Dirk M. Maybauer, MD, PhD
Professor of Anesthesiology
Philipps University
Marburg, Germany

Marc O. Maybauer, MD, PhD
Professor of Anesthesiology
Philipps University
Marburg, Germany;
Honorary Professor
The University of Queensland and the Critical Care Research Group
Prince Charles Hospital
Brisbane, Australia;
Consultant
Lead for Research and Director of ECMO
Cardiothoracic Anaesthesia and Intensive Care
Manchester Royal Infirmary
Manchester University NHS Foundation Trust,
Honorary Senior Lecturer
University of Manchester and Manchester Academic Health Science Centre
Manchester, United Kingdom

Paul Mayo, MD
Professor of Clinical Medicine
Hofstra Northwell School of Medicine,
Division of Pulmonary Medicine, Critical Care, and Sleep Medicine
Northwell LIJ/NSUH Medical Center
Zucker School of Medicine at Hofstra/Northwell
New Hyde Park, New York

Christopher B. McFadden, MD
Associate Professor of Medicine
Cooper Medical School of Rowan University
Camden, New Jersey

Melissa Mercado, MD
Assistant Professor of Neurology and Neurosurgery
Boston University School of Medicine
Boston, Massachusetts

Walter Mickey, DO
Critical Care Fellow
Critical Care Medicine Fellowship
Saint Louis University School of Medicine/Mercy Hospital St. Louis
St. Louis, Missouri

Kristin Miller, MD
Assistant Professor
Division of Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University Health System
Richmond, Virginia

Thomas R. Mirsen, MD
Associate Professor
Neurology
Cooper Medical School of Rowan University
Camden, New Jersey

Farah Morgan, MD
Assistant Professor of Medicine
Division of Endocrinology
Cooper Medical School of Rowan University
Camden, New Jersey

Nicholas Murphy, MBBS, FRCP
Consultant Intensivist
The Liver Unit and Department of Critical Care
Queen Elizabeth Hospital
Birmingham, United Kingdom

Kamyar Nader, MD
Division of Hematology/Oncology
MD Anderson Cancer Center at Cooper
Camden, New Jersey

Hollis R. O'Neal, MD, MSc
Assistant Professor of Clinical Medicine
Louisiana State University Health Sciences Center
Baton Rouge, Louisiana

Luis Ostrosky-Zeichner, MD, FACP, FIDSA
Professor of Medicine and Epidemiology
University of Texas Health Science Center at Houston
Houston, Texas

Joseph E. Parrillo, MD
Justice Marie L. Garibaldi Endowed Chair
Chairman, Heart and Vascular Hospital
Hackensack University Medical Center,
Professor and Chair, Department of Cardiology
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey;
Professor of Medicine
Rutgers New Jersey Medical School
Newark, New Jersey

Tilak K.R. Pasala, MD
Structural and Congenital Heart Disease Fellow
Hackensack University Medical Center
Hackensack Meridian Health
Hackensack, New Jersey

Dave D. Paskar, MD, FRCSC
Division of General Surgery and the Interdepartmental Division of Critical Care Medicine
University of Toronto,
St. Michael's Hospital
Toronto, Ontario, Canada

Stephen M. Pastores, MD
Professor of Medicine and Anesthesiology,
Weill Cornell Medical College and Program Director
Critical Care Medicine
Department of Anesthesiology and Critical Care Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Steven Peikin, MD, FACG, AGAF
Professor of Medicine
Division of Gastroenterology and Liver Diseases
Cooper Medical School of Rowan University and Cooper University Hospital
Camden, New Jersey

Priscilla Peters, BA, RDCS, FASE
Echocardiographic Clinical Specialist
Cooper University Hospital,
Assistant Professor of Medicine
Cooper Medical School of Rowan University
Camden, New Jersey

Melvin R. Pratter, MD
Head, Division of Pulmonary Diseases and Critical Care Medicine
Pulmonary and Critical Care
Cooper University Hospital;
Professor of Medicine
Cooper Medical School of Rowan University
Camden, New Jersey

Nitin Puri, MD
Associate Professor of Medicine
Cooper Medical School of Rowan University
Camden, New Jersey

Annette C. Reboli, MD
Dean,
Professor of Medicine
Division of Infectious Diseases
Cooper Medical School of Rowan University
Camden, New Jersey

John Adam Reich, MD
Assistant Professor
Department of Anesthesiology
Tufts Medical Center
Boston, Massachusetts

Marcos I. Restrepo, MD, PhD
Associate Professor
Department of Medicine
Division of Pulmonary/Critical Care Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Oleksa G. Rewa, MD
Clinical Scholar and Lecturer
Department of Critical Care Medicine
Faculty of Medicine and Dentistry
University of Alberta
Edmonton, Alberta, Canada

Andrew Rhodes, FRCA, FCRP FFICM
Professor
Intensive Care Medicine
St George's University Hospitals NHS Foundation Trust
London, United Kingdom

Fred Rincon, MD
Associate Professor
Neurology and Neurosurgery
Thomas Jefferson University
Philadelphia, Pennsylvania

Brian W. Roberts, MD
Associate Professor of Emergency Medicine
Cooper Medical School of Rowan University
Cooper University Hospital
Camden, New Jersey

Katie M. Rocawich, PharmD, BCPS
Department of Pharmacy
Virginia Commonwealth University Health System
Richmond, Virginia

Axel Rosengart, MD, PhD, MPH
Director
Neuroscience Critical Care
Cedars-Sinai Medical Center
Los Angeles, California

Jennifer Ross, MD, PhD
Department of Anesthesiology
Cedars-Sinai Medical Center
Los Angeles, California

Steven E. Ross, MD, FACS, FCCM
Professor of Surgery
Cooper Medical School at Rowan University
Camden, New Jersey

Aviral Roy, MBBS
Consultant
Department of Critical Care and Internal Medicine
Medica Institute of Critical Care
Medica Superspecialty Hospital
Kolkata, India

Carlos E. Ruiz, MD, PhD, FACC, FESC, MSCAI
Professor of Cardiology in Pediatrics and Medicine
Hackensack Meridian School of Medicine at Seton Hall University;
Director, Structural and Congenital Heart Center
Hackensack University Medical Center
The Joseph M. Sanzari Children's Hospital
Hackensack, New Jersey

Sajjad A. Sabir, MD
Assistant Professor of Medicine
Cooper Medical School of Rowan University,
Director, Cooper Structural Heart Disease Program,
Director, Interventional Echocardiography
Cooper University Hospital
Camden, New Jersey
Chapter 25 Cardiac Tamponade

Farid Sadaka, MD
Adjunct Associate Clinical Professor of Medicine
Saint Louis University School of Medicine,
Associate Program Director
Critical Care Medicine Fellowship
Saint Louis University School of Medicine/Mercy Hospital St. Louis
St. Louis, Missouri

Rommel Sagana, MD
Assistant Professor
Division of Pulmonary and Critical Care Medicine
University of Michigan
Ann Arbor

Thomas L. Salazer, MD
Chief
Nephrology Division
Hackensack University Medical Center
Hackensack Meridian Health Network
Hackensack, New Jersey

Reza Samad, MD
Critical Care Medicine Fellow
Department of Anesthesiology and Critical Care Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

Raul Sanchez, MD
Assistant Professor of Clinical Medicine
Institute for Academic Medicine
Houston Methodist Hospital
Houston, Texas;
Weill Cornell Medical College
New York, New York

Kumar Satya, MD, FRCP
Interventional Cardiology
Heart and Vascular Hospital, Hackensack Meridian Health;
Assistant Professor
Department of Cardiology
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey

Christa Schorr, DNP, MSN, RN
Associate Professor of Medicine
Cooper Medical School of Rowan University;
Clinical Nurse Scientist—Critical Care
Cooper University Hospital
Camden, New Jersey

Curtis N. Sessler, MD, FCCP, FCCM
Orhan Muren Distinguished Professor of Medicine
Division of Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University Health System
Richmond, Virginia

David Shersher, MD
Assistant Professor of Surgery
Cooper Medical School of Rowan University
Division of Thoracic Surgery
Cooper University Hospital
Camden, New Jersey

Eduardo Rivero Sigarroa, MD
Head
Critical Care Unit
Instituto Nacional de Ciencias Médicas y Nutrición Salvado Zubirán
Mexico City, Mexico

Grant R. Simons, MD, FACC, FHRS
Chief, Heart Rhythm Services
Hackensack University Medical Center;
Associate Professor of Cardiology and Medicine
Hackensack Meridian School of Medicine at Seton Hall University
Hackensack, New Jersey

Michael Sterling, MD, FACP, FCCM
Chief, Critical Care Medicine
Emory University Midtown Hospital;
Director, Clinical Operations
Emory Center for Critical Care Medicine;
Medical Director, Surgical ICU
Emory University Hospital Midtown;
Assistant Professor
Emory University School of Medicine
Division of Pulmonary Allergy and Critical Care Medicine
Atlanta, Georgia

Christopher B. Thomas, MD
Assistant Professor of Clinical Medicine
Louisiana State University Health Sciences Center
Baton Rouge, Louisiana

Martin J. Tobin, MD
Professor
Division of Pulmonary and Critical Care Medicine
Edward Hines Jr. Veterans Affairs Hospital and Loyola University of Chicago
Stritch School of Medicine
Hines, Illinois

Sean R. Townsend, MD
Vice President of Quality and Safety
California Pacific Medical Center;
Clinical Associate Professor of Medicine
University of California San Francisco Medical School
San Francisco, California

Victor Tremblay, MD
Critical Care Fellow
Section of Critical Care Medicine
University of Manitoba
Winnipeg, Manitoba, Canada

Richard G. Trohman, MD
Professor of Medicine,
Chief, Clinical Cardiac Electrophysiology
Department of Internal Medicine
Rush University Medical Center
Chicago, Illinois

Steven J. Trottier, MD, FCCM
Adjunct Clinical Professor of Medicine
Department of Critical Care Medicine
Saint Louis University School of Medicine;
Chairman
Adult Clinic Mercy Hospital St. Louis;
Program Director
Critical Care Medicine Fellowship
Saint Louis University School of Medicine/Mercy Hospital St. Louis
St. Louis, Missouri

Robert D. Truog, MD
Senior Associate in Critical Care Medicine
Boston Children's Hospital;
Director, The Center of Bioethics
Frances Glessner Lee Professor of Legal Medicine;
Professor of Anaesthesia (Pediatrics),
Professor of Global Health and Social Medicine
Harvard Medical School
Boston, Massachusetts

Stephen Trzeciak, MD, MPH
Professor of Medicine and Emergency Medicine,
Head of Critical Care Medicine
Cooper Medical School of Rowan University
Cooper University Hospital
Camden, New Jersey

Constantine Tsigrelis, MD
Staff Physician, Infectious Disease
Cleveland Clinic;
Assistant Professor of Medicine
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio

Zoltan G. Turi, MD, MSCAI, FACC
Professor of Cardiology and Medicine
Hackensack Meridian School of Medicine at Seton Hall University;
Co-Director Structural and Congenital Heart Center,
Co-Director Cardiac Catheterization Laboratory
Hackensack University Medical Center
Hackensack, New Jersey

Alan R. Turtz, MD, FACS
Professor and Chair
Department of Neurosurgery
Cooper Medical School of Rowan University;
Chief
Department of Neurosurgery
Cooper University Hospital
Camden, New Jersey

Gloria Vazquez-Grande, MD, MSc
Critical Care Fellow
Section of Critical Care Medicine;
PhD Candidate in Medical Microbiology
University of Manitoba
Winnipeg, Manitoba, Canada

Jean-Louis Vincent, MD, PhD
Professor
Department of Intensive Care
Erasme Hospital
Université Libre de Bruxelles
Brussels, Belgium

Robert A. Weinstein, MD
The C. Anderson Hedberg, MD Professor of Internal Medicine
Rush University Medicine Center;
Chairman Emeritus
Department of Medicine
Cook County Health and Hospitals System
Chicago, Illinois

Lawrence S. Weisberg, MD
Professor of Medicine
Cooper Medical School of Rowan University;
Head, Division of Nephrology
Cooper University Health Care
Camden, New Jersey

Steven Werns, MD
Director, Cardiovascular Disease Fellowship Program
Beaumont Hospital-Dearborn
Dearborn, Michigan

Richard G. Wunderink, MD
Professor of Medicine
Division of Pulmonary and Critical Care
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Faisal Zahiruddin, DO
Houston Methodist Hospital
Houston, Texas

Sergio L. Zanotti-Cavazzoni, MD, FCCM
Director of Critical Care Medicine
Memorial Hermann Memorial City Medical Center;
Chief Medical Officer
Sound Critical Care
Sound Physicians
Houston, Texas

Janice L. Zimmerman, MD
Professor of Clinical Medicine, Institute for Academic Medicine,
Head, Critical Care Division
Houston Methodist Hospital
Houston, Texas;
Professor of Clinical Medicine
Weill Cornell Medicine
New York, New York

John M. Zimmerman, MD
Chief of Electrophysiology
Hackensack University Medical Center
Hackensack, New Jersey

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1

Cardiac Arrest and Cardiopulmonary Resuscitation

BRIAN W. ROBERTS, TAPAN KAVI, AND STEPHEN TRZECIAK

CHAPTER OUTLINE

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- Defibrillation
- Rescue Breathing

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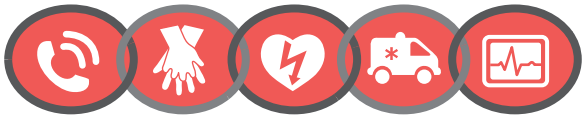
Epidemiology and General Principles

Sudden cardiac arrest is defined as the cessation of effective cardiac mechanical activity as confirmed by the absence of signs of circulation. Sudden cardiac arrest is the most common fatal manifestation of cardiovascular disease and a leading cause of death worldwide. The exact incidence of sudden cardiac arrest is unclear, but in the United States alone, it has been estimated to be as high as 450,000 persons annually.[1] Approximately 21% to 25% of sudden cardiac arrest events are due to pulseless ventricular arrhythmias (i.e., ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]), whereas the rest can be attributed to other cardiac rhythms (i.e., asystole or pulseless electrical activity [PEA]).[2,3] Patients who suffer cardiac arrest due to VF or VT have a much higher chance of surviving the event compared with patients who present with PEA/asystole.[4] The prognosis is better in patients with ventricular arrhythmias because (1) ventricular arrhythmias are potentially treatable with defibrillation (i.e., "shockable" initial rhythm) to restore circulation, whereas the other initial rhythms are not, and (2) ventricular arrhythmias are typically a manifestation of a cardiac etiology of cardiac arrest (e.g., acute myocardial infarction), whereas the other initial rhythms are more likely to be related to a noncardiac etiology and perhaps an underlying condition that is less treatable. Clinical outcomes for cardiac arrest are poor. Approximately 11% of out-of-hospital cardiac arrest (OHCA)[5] and 20% of in-hospital cardiac arrest (IHCA) patients survive to hospital discharge.[6]

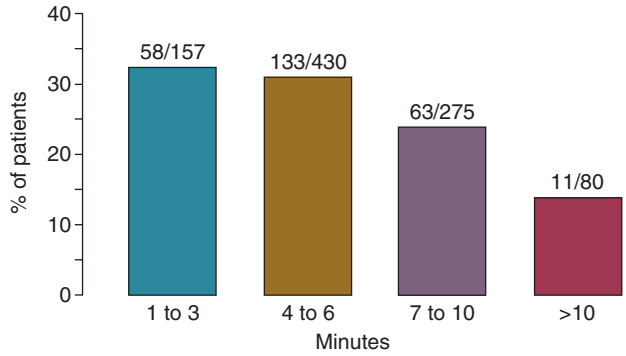
The basic principles of resuscitation are an integral part of training for many health care providers (HCPs). Because timely interventions for cardiac arrest victims have the potential to be truly lifesaving, it is especially important for critical care practitioners to have a sound understanding of the evaluation and management of cardiac arrest. A number of critical actions (*chain of survival*) must occur in response to a cardiac arrest event. The chain of survival paradigm (Fig. 1.1) for the treatment of cardiac arrest remained unchanged in the 2015 American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care from 2010 and is similar to other cardiac arrest guidelines. The chain of survival paradigm consists of five separate and distinct elements: immediate recognition that cardiac arrest has occurred and activation of the emergency response system; application of effective cardiopulmonary resuscitation (CPR); early defibrillation (if applicable); advanced cardiac life support; and initiation of postresuscitation care (e.g., targeted temperature management).[7–9] When the chain of survival is implemented effectively survival for VF, OHCA can exceed 45%.[3]

Cardiopulmonary Resuscitation

For CPR to be effective in restoring spontaneous circulation, it must be applied immediately at the time of cardiac arrest. Therefore immediate recognition that a cardiac arrest has occurred and activation of the emergency response system are essential. Patients become unresponsive at the time of cardiac arrest. Agonal gasps may be observed in the early moments after a cardiac arrest event, although normal breathing ceases. Pulse checks (i.e., palpation of femoral or carotid arteries for detection of a pulse) are often



• **Fig. 1.1** The American Heart Association chain of survival paradigm.[89] This figure represents the critical actions needed to optimize the chances of survival from cardiac arrest. The links (from left to right) include (1) immediate recognition of cardiac arrest and activation of the emergency response system; (2) early and effective cardiopulmonary resuscitation; (3) defibrillation (if applicable); (4) advanced cardiac life support; and (5) post–cardiac arrest care (including target temperature management if appropriate). (From Travers AH, Rea TD, Bobrow BJ, et al. Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S676–S684.)



• **Fig. 1.2** Relationship between the time interval before attempted defibrillation and the proportion of patients discharged from the hospital alive after out-of-hospital cardiac arrest. (Modified from Weaver WD, Cobb LA, Hallstrom AP, et al. Factors influencing survival after out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 1986;7:752–757.)

unreliable, even when performed by experienced HCPs.[10] Because delays in initiating CPR are associated with worse outcome, and prolonged attempts to detect a pulse may result in a delay in initiating CPR, prolonged pulse checks are to be avoided. CPR should be started immediately if the patient is unresponsive and either has agonal gasps or is not breathing.[7]

Chest Compressions

In CPR, chest compressions are used to circulate blood to the heart and brain until a pulse can be restored. High-quality chest compressions are vital for successful resuscitation. The mechanism by which chest compressions generate cardiac output is through an increase in intrathoracic pressure plus direct compression of the heart. As in 2010, the 2015 AHA guidelines recommend HCPs initiate the CPR sequence with chest compressions instead of rescue breaths (i.e., compressions-airway-breathing [C-A-B] vs. airway-breathing-compressions [A-B-C]) to minimize the time to chest compressions.[7] With the patient lying in the supine position, the rescuer applies compressions to the lower half of the patient's sternum. The heel of one hand is placed over the lower half of the sternum and the heel of the other hand on top in an overlapping and parallel fashion. In addition to manual CPR, there has been an increase in the use of mechanical CPR devices. Studies have not demonstrated a difference in patient outcomes between manual and mechanical CPR.[8,11]

The recommended compression depth in adults is at least 2 inches (5 cm) while avoiding chest compression depths greater than 2.4 inches (6 cm).[7–9] The recommended rate of compression per the 2010 AHA guidelines was *at least* 100 compressions per minute.[12] The 2015 AHA guidelines now recommend a rate of 100 to 120 compressions per minute.[7] These new AHA guidelines are in line with the 2010 and 2015 European Resuscitation Council guidelines for resuscitation, as well as the 2015 International Liaison Committee on Resuscitation recommendations.[8,9,13] In addition, incomplete recoil of the chest impairs the cardiac output that is generated. Incomplete recoil occurs when HCPs lean on the chest wall between compressions; thus HCPs should avoid leaning to allow the chest wall to recoil completely between compressions. Owing to rescuer fatigue, the quality of chest compressions predictably decreases as the time providing chest compressions increases, and the persons providing chest compressions (even experienced HCPs) may not perceive fatigue or a decrease in the quality of their compressions.[14] Therefore it is recommended that rescuers performing chest compressions rotate every 2 minutes.[7,9]

The quality of CPR is a critical determinant of surviving a cardiac arrest event.[15] Minimization of interruptions in chest compressions is imperative. Interruptions in chest compressions during CPR have been quite common historically, and the "hands off" time has been shown to comprise a substantial amount of the total resuscitation time.[15] The proportion of time chest compressions are performed during a cardiac arrest has been termed chest compression fraction. A higher chest compression fraction has been associated with increased survival in VF cardiac arrest,[16] and increased return of spontaneous circulation (ROSC) in non-VF cardiac arrest.[17] Guidelines recommend a chest compression fraction as high as possible, with a goal of at least 60%.[7,9] A chest compression fraction of 80% is likely ideal and achievable in many settings.[18] Potential reasons for decreased chest compression fraction include pulse checks, rhythm analysis, switching compressors, procedures (e.g., airway placement), and pauses before defibrillation ("preshock pause"). All of these potential reasons for interruptions should be minimized. Pauses related to rotating compressors, pulse checks, and delivering rescue breaths should take no longer than 10 seconds.[7,9] Eliminating (or minimizing) preshock pauses has been associated with a higher likelihood of ROSC and improved clinical outcome.[19,20]

Defibrillation

The next critically important action in the resuscitation of patients with cardiac arrest caused by pulseless ventricular arrhythmias (i.e., VF or pulseless VT) is rapid defibrillation. Delays in defibrillation are clearly deleterious, with a sharp decrease in survival as the time to defibrillation increases.[21] With the advent of automatic external defibrillators and their dissemination into public places, both elements of effective CPR (effective chest compressions and rapid defibrillation) can be performed by lay rescuers in the field for patients with OHCA. Fig. 1.2 shows the importance of rapid defibrillation, with decreasing success of resuscitation with increasing time to defibrillation. Thus defibrillation should be performed as soon as possible. The amount of energy for defibrillation should be based on the specific manufacturer's guidance. To increase the chest compression fraction, chest compressions should resume immediately after defibrillation for adult cardiac arrest in any setting.[7,9]

Rescue Breathing

Recommendations regarding ventilation during CPR depend on the rescuer (i.e., trained HCPs vs. layperson).[7,9] For trained HCPs, the recommended ventilation strategy is a cycle of 30 chest compressions to 2 breaths until an endotracheal tube is placed, and then continuous chest compressions with 1 breath every 6 seconds after the endotracheal tube is placed. Excessive ventilations can be deleterious from a hemodynamic perspective owing to increased intrathoracic pressure and reduction in the cardiac output generated by CPR and thus should be avoided during resuscitation.[22] Excessive ventilation could also potentially result in alkalemia. For OHCA is it reasonable for emergency medicine service providers to delay positive-pressure ventilation while providing up to 3 cycles of 200 continuous chest compressions with passive oxygenation.[7]

For laypersons who are attempting CPR in the field for a victim of OHCA, rescue breathing is no longer recommended. Rather, the recommended strategy is compression-only (or hands-only) CPR.[7,9] The rationale is that compression-only CPR can increase the number of effective chest compressions that are delivered to the patient (i.e., minimizes interruptions for rescue breaths), and does not require mouth-to-mouth contact. Mouth-to-mouth contact is one of the perceived barriers to CPR in the field. By removing this element, the hope is that an increase in attempts at bystander CPR will result. Hands-only CPR has been found to be noninferior to conventional CPR including rescue breaths for victims of OHCA[23–25]; thus hands-only CPR has become the preferred technique to teach lay rescuers. Fig. 1.3 displays the AHA algorithm for adult basic life support.

Advanced Cardiac Life Support

There are several additional elements of resuscitation that are intended specifically for trained HCPs (e.g., advanced cardiac life support [ACLS]), and specifically this includes pharmacologic therapy. Fig. 1.4 displays the AHA algorithm for ACLS.[26]

It is notable that the impact of recommended ACLS therapies on outcome from cardiac arrest remains a matter of debate. Some studies have shown that ACLS interventions did not improve clinical outcomes when compared to basic life support alone.[27]

Vasopressors

The primary goal of pharmacologic interventions is to assist the achievement and maintenance of spontaneous circulation. The mainstay of pharmacologic interventions is vasopressor drugs. It is reasonable to administer epinephrine (1 mg) by intravenous (IV) or intraosseous (IO) route every 3 to 5 minutes during CPR until ROSC is achieved.[8,26,28] If IV/IO access cannot be established, epinephrine could be administered via an endotracheal tube, but at a higher dose (2–2.5 mg). The optimal timing of epinephrine administration is currently unclear; however, observational studies have demonstrated that early administration of epinephrine is associated with improved outcomes in nonshockable rhythms.[29,30]

Vasopressin as a substitute for epinephrine was removed from the 2015 AHA guidelines. One study found the use of intracardiac arrest vasopressin (20 IU/CPR cycle), epinephrine (1 mg/CPR cycle), and methylprednisolone (40 mg during first CPR cycle) followed by postcardiac arrest hydrocortisone (300 mg daily for 7 days maximum and gradual taper) increased the probability of successful ROSC and discharge with good neurologic outcome[31]; however, the evidence for this practice is not currently strong enough to recommend its routine use.[26]

Antiarrhythmic Drugs

Amiodarone is the preferred antiarrhythmic agent for refractory VF/VT cardiac arrest.[8] Refractory VF/VT refers to VF or pulseless VT that persists or recurs after one or more defibrillation attempts. It is unlikely that antiarrhythmic drug therapy itself will convert refractory VT/VF; rather, the goal of antiarrhythmic drug therapy is to aid in reestablishing and maintaining an organized perfusing rhythm in conjunction with subsequent defibrillation. The recommended dose of amiodarone is 300 mg IV/IO for the first dose, 150 mg IV/IO for the second dose.[26,28] Of note, antiarrhythmic drug therapy has not been demonstrated to improve survival or neurologic outcomes after VF/VT cardiac arrest.

Other Drug Therapies

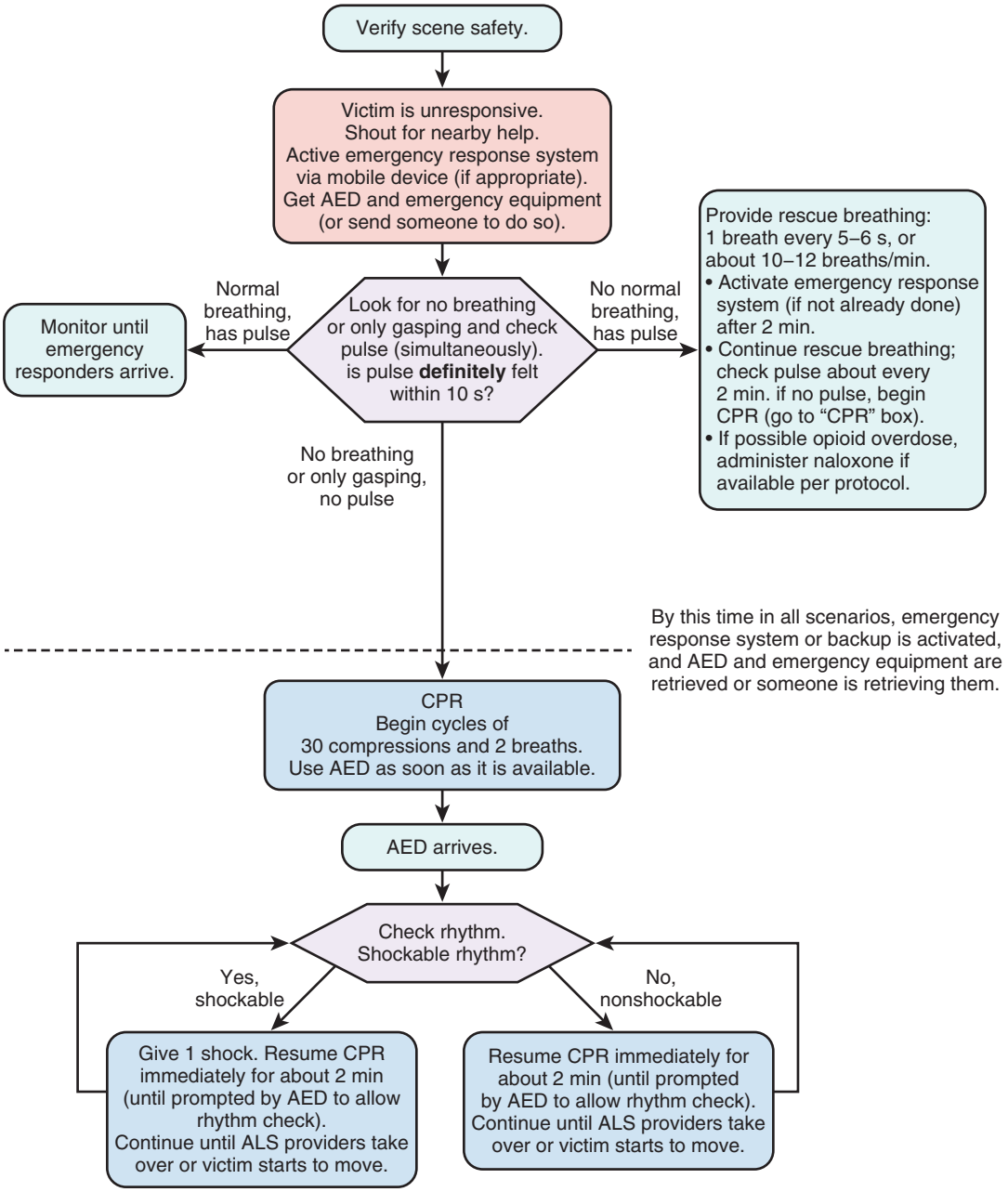
The use of atropine for PEA/asystole was removed from the ACLS guidelines in 2010. Along these lines, there is also insufficient evidence to recommend routine administration of sodium bicarbonate or calcium during CPR.[28,32] In the setting of confirmed or suspected pulmonary embolism, limited evidence suggests that systemic thrombolysis administration during ongoing CPR is associated with ROSC and short-term survival,[33] with earlier administration associated with greater benefit.[34] However, in the setting of presumed cardiac etiology of cardiac arrest there is currently no evidence to support clinical benefit.[35] The decision to administer systemic thrombolytics during cardiac arrest may be considered in cases with a strong suspicion for pulmonary embolism, or cardiac etiology without immediate access to percutaneous coronary intervention.

End-Tidal Carbon Dioxide

End-tidal carbon dioxide ($ETCO_2$) may reflect cardiac output and pulmonary blood flow. $ETCO_2$ can be measured during CPR to monitor the quality of chest compressions in intubated patients. An $ETCO_2$ less than 10 mm Hg after 20 minutes of high-quality CPR has been demonstrated to be predictive of mortality,[36,37] whereas an $ETCO_2$ greater than 20 mm Hg was associated with survival to hospital discharge.[36] Although predictive of outcome, a low $ETCO_2$ should not be used alone to discontinue CPR efforts. It is also important to realize a low $ETCO_2$ could be a result of bronchospasm, plugging or kinking of the endotracheal tube, hyperventilation, or an air leak in the airway.[26] A sudden, sustained increase in $ETCO_2$ (i.e., >40 mm Hg) during chest compressions can be an indication of ROSC.[26,28,38] $ETCO_2$ monitoring in nonintubated patients may not accurately reflect the true $ETCO_2$ level and should not be used as an adjunct prognostication tool.

Extracorporeal CPR

Extracorporeal CPR (ECPR) refers to venoarterial extracorporeal membrane oxygenation and cardiopulmonary bypass during cardiac arrest. In theory ECPR could be used as a bridge to allow physicians time to treat reversible causes of cardiac arrest. To date there has not been a randomized control trial comparing ECPR to conventional CPR for prolonged resuscitations. The limited case reports and observational studies do not provide sufficient evidence to recommend the routine use of ECPR; however, it may be reasonable



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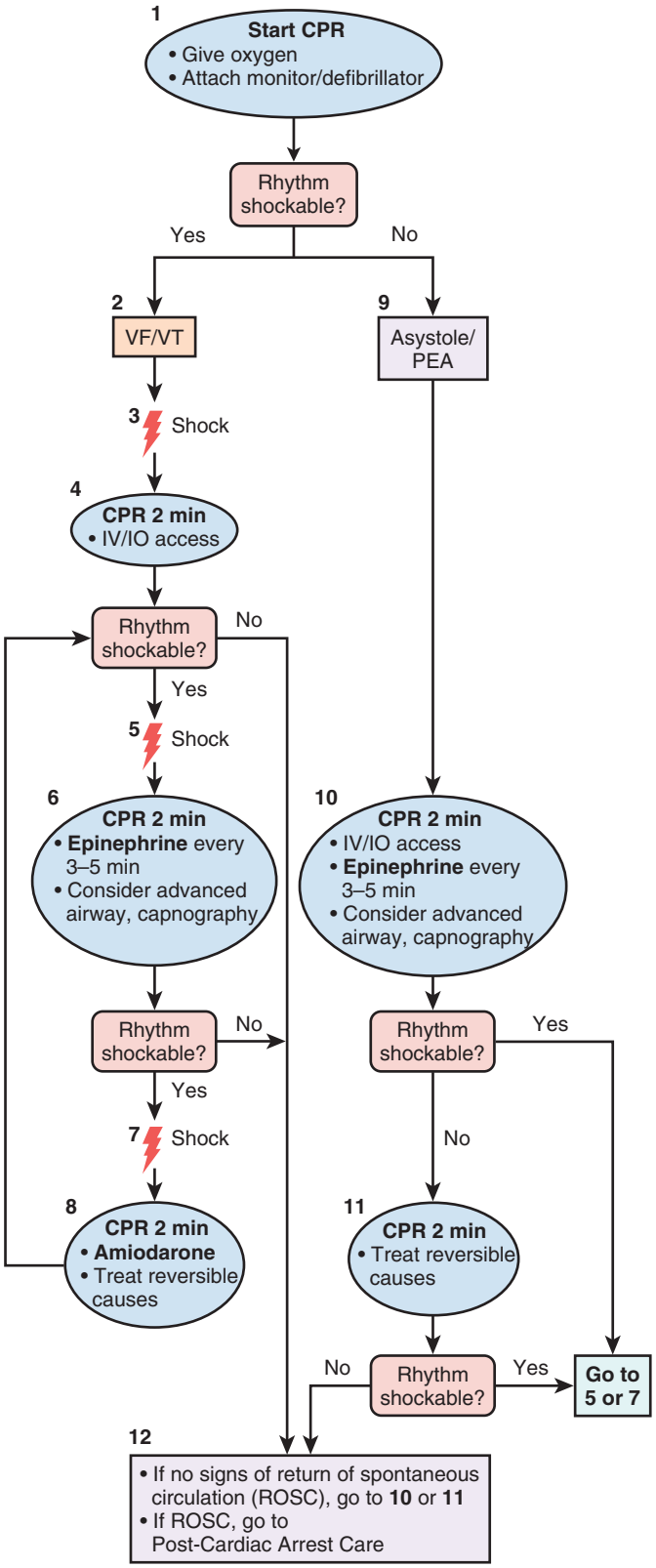
• **Fig. 1.3** American Heart Association adult Basic Life Support *(BLS)* algorithm. *AED,* Automated external defibrillator; *ALS,* advanced life support; *CPR,* cardiopulmonary resuscitation. (From Kleinman ME, Brennan EE, Goldberger ZD, et al. Part 5: adult basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(18 suppl 2):S414–S435.)

to consider ECPR for specific patients with a potentially reversible etiology of cardiac arrest.[26,28]

Reversible Causes

When managing a cardiac arrest it is important to consider the potential etiologies of the arrest. In many situations it is not possible to maintain an organized perfusing rhythm until the underlying cause of the cardiac arrest is reversed. A frequently used pneumonic for common potential reversible causes involves the "Hs and Ts."[28] The "Hs" include hypoxia, hypovolemia (including hemorrhage), hyperkalemia, hypokalemia, hypoglycemia, hydrogen ions (i.e., metabolic acidosis), and hypothermia. The "Ts" include thrombosis (i.e., coronary occlusion and pulmonary embolism), tension pneumothorax, cardiac tamponade, and ingestion of therapeutic or toxic substances. Once the etiology of the cardiac arrest is identified (or strongly presumed), treatment should be aimed at reversing the specific cause.



CPR Quality
- Push hard (2 inches [5 cm]) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 min or sooner if fatigued
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Shock Energy for Defibrillation
- **Biphasic:** Manufacturer recommendation (e.g., initial dose of 120–200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered
- **Monophasic:** 360 J

Drug Therapy
- **Epinephrine IV/IO Dose:** 1 mg every 3–5 min
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus Second dose: 150 mg

Advanced Airway
- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 s (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes
- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

• **Fig. 1.4** American Heart Association Advanced Cardiac Life Support (ACLS) algorithm. *CPR,* Cardiopulmonary resuscitation; *ET,* endotracheal; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; P_{ETCO_2}, partial pressure of end tidal carbon dioxide; *pVT,* pulseless ventricular tachycardia; *ROSC,* return of spontaneous circulation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (From Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(18 suppl 2):S444–S464.)

Postresuscitation Care

Even if ROSC is achieved with CPR and defibrillation, cardiac arrest victims are at extremely high risk of dying in the hospital, and many who survive sustain permanent crippling neurological sequelae. Approximately 50% to 60% of patients successfully resuscitated from OHCA do not survive. After ROSC global ischemia/reperfusion (I/R) injury results in potentially devastating neurologic disability. The primary cause of death among postresuscitation patients is brain injury. However, clinical trials have shown that targeted temperature management (TTM) after ROSC can improve outcomes. These landmark clinical trials have dramatically transformed the classical thinking about anoxic brain injury after cardiac arrest; this condition is, in fact, *treatable*. Early therapeutic interventions such as TTM initiated in the post-ROSC period can improve the trajectory of the long-term disease course. Accordingly, the postresuscitation care is now considered to be a crucial fifth link in the chain of survival paradigm (see Fig. 1.1).[7–9]

General Approach

Post–cardiac arrest syndrome is a heterogeneous disease process with varying precipitating factors and underlying etiologies. As such, post–cardiac arrest management must be tailored on a case-by-case basis for each specific patient. For patients resuscitated from cardiac arrest, admission to a critical care unit with the following capabilities should be considered[39]:

- Critical care support to optimize cardiovascular indices and vital organ perfusion, and prevent repeat cardiac arrest (or provide rapid treatment of rearrest if it occurs)
- Interventional cardiac catheterization for possible percutaneous coronary intervention (PCI) if needed
- TTM for at least 24 hours in attempts to prevent permanent neurologic injury
- Systematic application of an evidence-based approach to neurologic prognostication to refrain from inappropriately early final determinations of poor neurologic prognosis (i.e., to prevent inappropriately early withdrawal of life support before the neurologic outcome can be known with certainty).

Hemodynamic Support

I/R triggers profound systemic inflammation. In clinical studies, ROSC has been associated with sharp increases in circulating cytokines and other markers of the inflammatory response. Accordingly, some investigators have referred to the post–cardiac arrest syndrome as a "sepsis-like" state. The clinical manifestations of the systemic inflammatory response may include marked hemodynamic derangements such as sustained arterial hypotension similar to septic shock. Hemodynamic instability occurs in approximately 50% of patients who survive to intensive care unit admission after ROSC, and thus the need for aggressive hemodynamic support (e.g., continuous infusion of vasoactive agents and perhaps advanced hemodynamic monitoring) should be anticipated.[40]

In addition to a systemic inflammatory response, an equally important contributor to post-ROSC hemodynamic instability is myocardial stunning. Severe, but potentially reversible, global myocardial dysfunction is common after ROSC. The etiology is thought to be I/R injury, but treatment with defibrillation (if applied) could also contribute. Although the myocardial dysfunction occurs in the absence of an acute coronary event, myocardial ischemia may be an ongoing component of myocardial depression if an acute coronary syndrome caused the cardiac arrest. Severe myocardial stunning may last for hours, but it often improves by the 24-hour mark after ROSC. An echocardiogram may be helpful in hemodynamic assessment after ROSC to determine if global myocardial depression is present, as this may affect decisions on vasoactive drug support (e.g., dobutamine) or mechanical augmentation (e.g., intraaortic balloon counterpulsation) until the myocardial function recovers. However, when needed, clinicians should be aware that β-adrenergic agents may increase the likelihood of dysrhythmia.

Observational studies have demonstrated postresuscitation arterial hypotension to be associated with sharply lower survival,[40,41] and a post-ROSC mean arterial blood pressure greater than 70 mm Hg to be associated with improved neurologic outcome at hospital discharge.[42] However, it is currently unclear whether a specific blood pressure target or other hemodynamic goals are beneficial.[43] Expert opinion (and clinical intuition) suggests that hemodynamics and organ perfusion should be optimized, and rapidly reversing and preventing hypotensive after ROSC is recommended.[44,45] Whether or not postresuscitation hypotension has a cause-and-effect relationship with worse neurologic injury or is simply a marker of the severity of the I/R injury that has occurred remains unclear.

Oxygenation and Ventilation

Given the ongoing I/R injury during the early period after ROSC, hypoxia should be avoided in all post–cardiac arrest patients. Exposure to hyperoxia (excessively high partial pressure of arterial oxygen [PaO_2]) has also been associated with poor clinical outcome among adult patients resuscitated from cardiac arrest and admitted to an intensive care unit.[46] These data corroborate the findings of numerous laboratory studies in animal models in which hyperoxia exposure after ROSC worsens brain histopathologic changes and neurologic function.[47–51] A paradox may exist regarding oxygen delivery to the injured brain, where inadequate oxygen delivery can exacerbate cerebral I/R injury, but excessive oxygen delivery can accelerate formation of oxygen free radicals and subsequent reperfusion injury. Although the results of observational studies of hyperoxia are mixed[52,53] and no interventional studies have been performed, expert opinion advocates initially using the highest available oxygen concentration after ROSC to prevent hypoxia, and once the arterial oxygen saturation or PaO_2 can be measured, the fraction of inspired oxygen can be titrated down as much as possible while maintaining an arterial oxygen saturation of at least 94% to limit unnecessary exposure to an excessively high postresuscitation PaO_2.[45,54]

Post-ROSC partial pressure of arterial carbon dioxide ($PaCO_2$) levels have been demonstrated to be associated with clinical outcomes. Specifically, hypocapnia is associated with worse neurologic outcome.[55–57] It is possible that hypocapnia induces cerebral vasoconstriction and decreased cerebral blood flow, resulting in worsening cerebral ischemia. The effects of hypercapnia on clinical outcomes are currently unclear.[58] Current recommendations advocate maintaining normocapnia (i.e., $PaCO_2$ 35–45 mm Hg) after cardiac arrest.[54]

Seizures

Seizures are not uncommon after anoxic brain injury. Routine seizure prophylaxis is not currently recommended in post–cardiac arrest syndrome. However, it is important to be vigilant in clinical assessment for any motor responses that could represent seizure

activity so that it can be treated promptly with anticonvulsant medications. Patients with status epilepticus may not have clinically detectable signs of seizure. Therefore continuous electroencephalography monitoring (if available) can be useful, especially if continuous administration of neuromuscular blocking agents becomes necessary for any reason.[45,54]

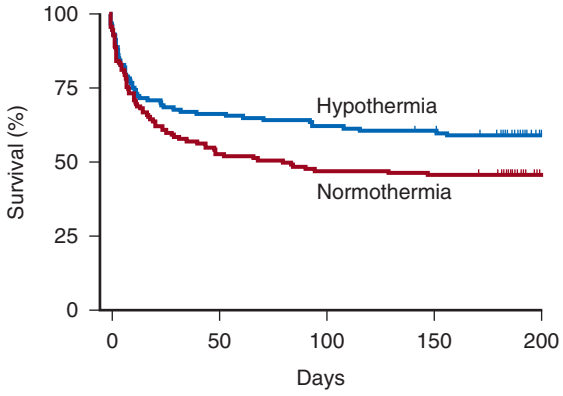
Cardiac Catheterization

Acute coronary syndrome is the most common etiology of sudden cardiac arrest. Clinicians should have a high clinical suspicion of acute myocardial ischemia as the inciting event for the cardiac arrest when no other obvious etiology of cardiac arrest is apparent. Although ST-segment myocardial infarction is an obvious indication for PCI, other subtler electrocardiogram abnormalities may indicate that an acute ischemic event caused the cardiac arrest. In patients with no obvious noncardiac etiology of cardiac arrest, a clinical suspicion of coronary ischemia, and an abnormal electrocardiogram after ROSC, consultation with an interventional cardiologist is encouraged and coronary angiography should be considered.[54] There is insufficient evidence to recommend PCI based on the presenting cardiac arrest rhythm (i.e., VF vs. non-VF). Recent studies and experience indicate that inducing TTM simultaneously with emergent percutaneous coronary intervention is feasible.

Targeted Temperature Management

TTM, previously referred to as therapeutic hypothermia or mild therapeutic hypothermia, is a treatment strategy of rapidly reducing the patient's body temperature after ROSC for the purposes of protection from neurologic injury. The body temperature is typically reduced to 32°C to 36°C for at least 24 hours. After ROSC the severity of the reperfusion injury can be mitigated, despite the fact that the initial ischemic injury has already occurred. Reperfusion injury refers to tissue and organ system injury that occurs when circulation is restored to tissues after a period of ischemia, and is characterized by inflammatory changes and oxidative damage that are in large part a consequence of oxidative stress. Neuronal cell death after I/R injury is not instantaneous, but rather a dynamic process. In animal models of cardiac arrest, brain histopathologic changes may not be found until 24 to 72 hours after cardiac arrest.[59] This indicates that a distinct therapeutic window of opportunity exists. In theory, TTM may protect the brain by attenuating or reversing all of the following pathophysiologic processes: disruption of cerebral energy metabolism, mitochondrial dysfunction, loss of calcium ion homeostasis, cellular excitotoxicity, oxygen free radical generation, and apoptosis.

The two original clinical trials of TTM targeting 32°C to 34°C were published in 2002.[60,61] These trials showed improved outcomes with TTM targeting 32°C to 34°C for comatose survivors of witnessed OHCA with VF as the initial rhythm. The survival data for the largest of these clinical trials (i.e., the Hypothermia After Cardiac Arrest Study Group) appear in Fig. 1.5. For patients with OHCA and a non-VF initial rhythm or IHCA, there are no randomized clinical trials and observational data have conflicting results. In 2013, a randomized control trial of 939 unconscious adults with OHCA of presumed cardiac etiology found no difference between neurologic outcomes and survival at 6 months when temperature was controlled at 36°C versus 33°C (Table 1.1).[62] It is currently unclear if certain subpopulations of post–cardiac arrest patients benefit from lower or higher temperatures.



No. at risk					
Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9

• **Fig. 1.5** Cumulative survival in the normothermia and hypothermia groups from a randomized trial of therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest due to ventricular fibrillation. Censored data are indicated by tick marks. (From Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346(8):549–556.)

The current AHA guidelines for CPR and Emergency Cardiovascular Care recommend at least 24 hours of TTM targeting 32°C to 36°C for comatose survivors of OHCA caused by VF or pulseless VT, as well as non-VF/pulseless VT and IHCA.[54] These recommendations for non-VF/pulseless VT and IHCA are stronger than the 2010 AHA recommendations, the 2015 European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care, and the 2015 International Liaison Committee on Resuscitation recommendations, which state that TTM may be considered for victims of IHCA and other arrest rhythms.[8,45,63]

Appropriate selection of candidates for TTM is clearly important. If a patient does not follow verbal commands after ROSC is achieved, this indicates that the patient is at risk for brain injury and TTM should be strongly considered. If a patient is clearly following commands immediately after ROSC, then significant brain injury is less likely and it is probably reasonable to withhold TTM. There are multiple potential methods for inducing TTM, including specialized external or intravascular cooling devices for TTM, or a combination of conventional cooling methods such as ice packs, cooling blankets, and cold (4°C) intravenous saline infusion. Compared with the use of specialized cooling devices, overshoot (body temperature <31°C) is a not uncommon occurrence with use of ice packs, cooling blankets, and cold saline.[64] Regardless of which method is used, effective achievement of target temperature may be aided by the use of a uniform physician order set for TTM induction.[65] The current recommendation is to maintain TTM for at least 24 hours.[8,45,54] Whether or not a longer duration of therapy could be beneficial is currently unknown.

Shivering with TTM induction is very common and should be anticipated regardless of which target temperature is chosen.[62] Shivering can be detrimental to the patient by making goal temperature more difficult (or impossible) to achieve. Therefore immediate recognition and treatment of shivering is imperative. Adequate sedation and analgesics are an essential component of TTM, especially during the induction phase, and often the administration of additional sedative and/or opioid agents will be

TABLE 1.1 Neurologic Outcome and Mortality at 6 Months With Temperature Control in Comatose Survivors of Cardiac Arrest[a]

Outcome	33°C Group No./total No. (%)	36°C Group No./total No. (%)	Hazard Ratio or Risk Ratio (95% CI)[b]	*P* Value
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes:				
Neurologic function at follow-up[c]				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

[a]The study shows the 6-month outcome and mortality for a randomized trial of temperature control at 33°C vs. 36°C in comatose survivors of out-of-hospital cardiac arrest with presumed cardiac etiology.
[b]The hazard ratio is shown for the primary outcome, and risk ratios are shown for the secondary outcomes.
[c]The neurologic follow-up was specified in the protocol to be performed at 180 days ± 2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Category (CPC) scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.
CI, Confidence interval.
From Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-2206.

sufficient to ameliorate shivering. Magnesium sulfate can also be used to reduce the shivering threshold.[66] If shivering persists despite sedatives or opioid agents and magnesium, neuromuscular blocking agents may be required. If neuromuscular blocking agents are used, they are often necessary only in the induction phase of TTM when the temperature is dropping at a fast rate. Once the target temperature is achieved, patients often stop shivering. It is prudent to try to limit neuromuscular blocking agents to the induction phase of TTM, and they likely can be withheld thereafter. Unnecessarily prolonged neuromuscular blockade should be avoided because prolonged neuromuscular weakness may persist after discontinuation, and this could potentially make the patient's neurologic assessment at a later time point more challenging. When using neuromuscular blocking agents for the induction of TTM, their administration may be titrated to the resolution of shivering rather than complete paralysis, which may result in the administration of a much lower dose of neuromuscular blocker.

A number of potential complications are possible with TTM, including bradycardia, a "cold diuresis" resulting in hypovolemia and electrolyte derangements, hyperglycemia, coagulopathy, and perhaps increased risk of secondary infection. However, these potential complications are often not severe when they do occur, and in terms of risk-benefit determinations, the risk of anoxic brain injury usually greatly outweighs the risks of complications. Specifically, bradycardia is a normal response to hypothermia. It is typically not recommended to treat bradycardia during TTM as long as the blood pressure, lactate, mixed venous saturation, and urine output are sufficient, even with heart rates less than 40 beats/min.[45] In the TTM trial 33°C was associated with a lower heart rate, increased need for vasopressor support, and increased incidence of hypokalemia compared with 36°C.[41,62] There was no difference in the rate of bleeding complications, infection, other cardiac arrhythmias (i.e., atrial fibrillation/flutter, tachycardia, bradycardia requiring pacing, and VT/VF), or other electrolyte derangements (i.e., hypomagnesemia, hypophosphatemia, and hypoglycemia).[62]

Fever is not uncommon in the post–cardiac arrest population because of the intense proinflammatory response to ischemia/reperfusion. The development of hyperthermia after completion of TTM (i.e., rebound hyperthermia) is associated with mortality and poor neurologic outcome.[67] Fever is clearly detrimental in brain-injured patients because it increases the cerebral metabolic rate; it should be treated aggressively after completion of TTM and in patients who do not receive TTM with antipyretic therapies and other techniques (e.g., cooling blankets).

Neurologic Prognostication

Neurologic prognostication after cardiac arrest is challenging, especially with the advent of TTM. Recovery of brain function—and correspondingly the findings on neurologic examination—are delayed with TTM. This delay is likely because of modulation of brain injury and slowed metabolism of sedative medications.[68] Neurologic prognostication immediately (e.g., first 24 hours) after resuscitation from cardiac arrest is especially unreliable. Among patients who are initially comatose after ROSC, 25% to 48% could potentially have a favorable outcome, especially if TTM is used.[62] In general, the recommended approach is to wait a minimum of 72 hours after ROSC before neurologic prognostication.[8,45,54] For neurologic examination findings to be used for neuroprognostication, and specifically for the determination of poor neurologic prognosis, the "false-positive rate" (FPR) (i.e., prognostication of a poor outcome that ultimately proves not to be poor), should approach zero. The reason it is imperative for a neurologic examination finding to show an FPR approaching zero is to prevent premature discontinuation of life support for patients who are potentially salvageable. Neurologic examination findings by themselves may not have an FPR of zero. Hence, a multimodal approach using a combination of clinical examination, neuroimaging, neurophysiologic tests, and biomarkers may be helpful for neurologic prognostication.[69]

Clinical Examination

Motor responses to pain, brainstem reflexes, and myoclonus remain the standard of clinical assessment even after TTM.[69] Bilateral absence of pupillary reflexes at 72 hours after cardiac arrest is

highly predictive of poor neurologic outcome with or without TTM with an FPR of about 0.5%.[70–73] The bilateral absence of corneal reflexes at 72 hours is also predictive of poor neurologic outcome, but with a higher FPR (5%) compared with pupillary reflexes.[70,72] The utility of absent or extensor motor response to pain at 72 hours for the determination of poor prognosis is diminished with TTM.[70,73] Similarly, the use of early post–anoxic myoclonus as a predictor of poor neurologic outcome after TTM is not sufficiently reliable, with recent reports of patients recovering well despite early myoclonus.[74–76] Myoclonus accompanied by malignant electroencephalogram findings is a more reliable predictor of poor neurologic outcome.[77]

Neuroimaging

Loss of gray-white matter differentiation on a computed tomography (CT) scan of the brain has been shown to be a reliable predictor of poor outcome, with an FPR of zero in multiple studies, but the sensitivity of this CT finding remains very low.[78,79] Although it is a higher-resolution study, magnetic resonance imaging has not been shown to be more useful than CT with respect to prognostication. Abnormalities on diffusion and apparent diffusion coefficient sequence of brain magnetic resonance imaging have been evaluated across multiple studies with variable results regarding utility in neuroprognostication.[69] In general, data on the use of neuroimaging for neuroprognostication are few compared with clinical and neurophysiologic testing; thus clinical and neurophysiological testing are considered more reliable.[72]

Neurophysiological Testing

EEG findings such as low voltage or suppressed background, burst suppression pattern, or discontinuous background are suggestive of poor outcome with FPR approaching zero.[80,81] Absence of reactivity on EEG and epileptiform discharges after TTM have been shown to be predictive of a poor outcome with an FPR of 7% and 9%, respectively.[82] Upper extremity somatosensory evoked potential, through stimulation of the median nerve and recording of response at the sensory cortex, is well studied and validated, both with and without TTM. The absence of bilateral cortical responses (N20s) have been shown to be highly predictive of poor outcome (FPR of 0% in multiple studies), but the presence of cortical response does not predict good outcome.[72,83]

Biomarkers

Serum neuron-specific enolase, a marker of neuronal damage, has been the most extensively studied biomarker as a prognostic tool after cardiac arrest. Before the advent of TTM, serum neuron-specific enolase concentration of more than 33 μg/mL was found to be highly predictive of poor outcome (FPR of 0%) when measured between 24 and 72 hours after cardiac arrest.[84] Now in the TTM era, the serum concentration cutoff value seems more difficult to determine because multiple studies have shown high FPR even with higher cutoffs.[70,77,85–87]

New Studies

Long-latency somatosensory evoked potentials, a measurement of cerebral oxygenation and several new blood biomarkers, are among the upcoming promising modalities to improve prognostication after cardiac arrest. At this time, these modalities are considered investigational.

One of the major limitations of all studies regarding neuroprognostication after cardiac arrest is the problem of self-fulfilling prophecy—that is, the presence of the neurologic finding or positive test influences clinician perception of severe anoxic injury and poor prognosis, leading to a withdrawal of care. Hence, instead of using a single modality to determine prognosis, a multimodal approach to neurologic prognosis seems most prudent. Waiting sufficient time (e.g., 72 hours or more in most cases) after cardiac arrest before making a definite prognosis, and paying particular importance to repeated neurologic examination without sedation, are the most important components of this multimodal approach. A multidisciplinary approach involving an intensivist, neurologist, and most importantly the patient's family members is the key to making decisions about goals of care based on neurologic prognosis and the minimally acceptable quality of life for the patient.

Key Points

- The quality of CPR (especially in the quality of and minimization of interruptions in chest compressions) is probably the single most important treatment-related determinant of outcome from cardiac arrest.
- Cellular damage from ischemia/reperfusion injury is a dynamic process, and a therapeutic window exists after resuscitation from cardiac arrest in which the effects can be attenuated.
- TTM is the first proven therapy to improve neurologic outcome after resuscitation from cardiac arrest, indicating that brain injury related to cardiac arrest is in fact a treatable condition.
- Neurologic prognostication can be very challenging in the early period after resuscitation from cardiac arrest, and in most cases attempts at prognostication should be withheld until at least the 72-hour mark from ROSC.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. The recommended chest compression rate during cardiopulmonary resuscitation is (compressions/min):
   a. >100
   b. >120
   c. 100–120
   d. 100–140
   Answer: c. 100–120 compressions/min is the current recommended chest compression rate.[7–9]
2. During cardiopulmonary resuscitation, once a definitive airway is placed (i.e., endotracheal tube) the recommended ventilation strategy is:
   a. 1 breath every 3 seconds
   b. 1 breath every 6 seconds
   c. 2 breaths for every 30 chest compressions
   d. 2 breaths for every 15 chest compressions
   Answer: b. Once a definitive airway is placed the recommended ventilation strategy is 1 breath every 6 seconds.[7–9]
3. The preferred antiarrhythmic agent for refractory ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest is:
   a. Amiodarone
   b. Lidocaine
   c. Procainamide
   d. β-Blocker
   Answer: a. Amiodarone is the current recommended antiarrhythmic agent for refractory ventricular fibrillation/pulseless ventricular tachycardia.[8,26,28]
4. During cardiopulmonary resuscitation, which of the following end-tidal carbon dioxide ($ETCO_2$) levels would be predictive of mortality?
   a. 25 mm Hg immediately after return of spontaneous circulation
   b. 25 mm Hg after 20 minutes of high-quality chest compressions
   c. 9 mm Hg immediately after return of spontaneous circulation
   d. 9 mm Hg after 20 minutes of high-quality chest compressions
   Answer: d. An $ETCO_2$ less than 10 mm Hg following 20 minutes of high-quality chest compressions can be predictive of mortality. However, this criterion should not be used alone to decide to terminate resuscitation efforts.[36,37]
5. After successful resuscitation from cardiac arrest the recommended temperature range and duration for targeted temperature management is:
   a. 32°C–36°C for 12–24 hours
   b. 34°C–36°C for 12–24 hours
   c. 32°C–36°C for at least 24 hours
   d. 34°C–36°C for at least 24 hours
   Answer: c. The recommended temperature range and duration for targeted temperature management is 32°C–36°C for at least 24 hours.[45,54,88]
6. After successful resuscitation from cardiac arrest a definite indication for emergent coronary angiography is:
   a. Electrocardiogram (ECG) consistent with ST-segment elevation myocardial infarction (STEMI)
   b. Ventricular fibrillation/pulseless ventricular tachycardia as the presenting cardiac arrest rhythm
   c. Out-of-hospital cardiac arrest
   d. Pulseless electrical activity as the presenting cardiac arrest rhythm
   Answer: a. Only ECG findings consistent with STEMI are a definite indication for emergent coronary angiography. There is currently insufficient evidence to recommend routine coronary angiography based on initial cardiac arrest rhythm or location of cardiac arrest. For cardiac arrest patients without STEMI the decision to proceed with emergent coronary angiography should be made in conjunction with an interventional cardiologist.[54]
7. The following is true regarding SSEPs when used for neuroprognostication after cardiac arrest:
   a. The absence of bilateral cortical responses (N20s) has not been shown to be predictive of poor outcome, but the presence of cortical response predicts good outcome.
   b. The absence of bilateral cortical responses (N20s) has been shown to be predictive of poor outcome, but the presence of cortical response does not predict good outcome.
   c. The absence of bilateral cortical responses (N20s) has been shown to be predictive of poor outcome, and the presence of cortical response is predictive of good outcome.
   d. Neither the absence nor the presence of bilateral cortical responses (N20s) has been shown to be predictive of outcome
   Answer: b. The absence of bilateral cortical responses (N20s) has been shown to be highly predictive of poor outcome (false-positive rate of 0% in multiple studies), but the presence of cortical response does not predict good outcome.[72,83]

2

Airway Management in the Critically Ill Adult

T.R. CRAIG AND G.G. LAVERY

CHAPTER OUTLINE

Structure and Function of the Normal Airway
- The Nose
- The Oral Cavity and Pharynx
- The Larynx
- The Tracheobronchial Tree
- Overview of Airway Function

Assessing Adequacy of the Airway
- Patency
- Protective Reflexes
- Inspired Oxygen Concentration
- Respiratory Drive

Management of the Airway
- Providing an Adequate Inspired Oxygen Concentration
- Establishing a Patent and Secure Airway
- Providing Ventilatory Support

Physiologic Sequelae and Complications of Tracheal Intubation

The Difficult Airway
- Recognizing the Potentially Difficult Airway
- The Airway Practitioner and the Clinical Setting
- Managing the Difficult Airway

Confirming Tube Position in the Trachea

Surgical Airway
- Cricothyrotomy
- Tracheostomy

Extubation in the Difficult Airway Patient (Decannulation)

Tube Displacement in the Critical Care Unit
- Endotracheal Tube
- Tracheostomy Tube

Human Factors

Common Problems in Airway Management

Appropriate management of the airway is the cornerstone of good resuscitation. It requires judgment (airway assessment), skill (airway maneuvers), and constant reassessment of the patient's condition. Although complex airway procedures have a high profile and are sometimes lifesaving, the timely use of simple airway maneuvers is often very effective and may avoid the need for further intervention.

Structure and Function of the Normal Airway

Knowledge of the structure and function of the airway is required to manage the various conditions that may affect it. The airway begins at the nose and oral cavity and continues as the pharynx and larynx, which lead to the trachea (beginning at the lower edge of the cricoid cartilage) and finally the bronchial tree. The airway provides a pathway between the atmosphere and the lungs for gas/vapor; facilitates filtering, humidification, and heating of ambient air/gas before it reaches the lower airway; prevents nongaseous material from entering the lower airway; and allows phonation by controlling the flow of air through the larynx and oropharynx.[1–6]

The Nose

Key to the respiratory function of the nose are the lateral walls, which on each side lie medial to the orbit, the ethmoid, and maxillary sinuses. Each lateral wall has three horizontal bony projections covered by highly vascular mucosa—the superior, middle, and inferior nasal conchae that greatly increase the surface area. The (nonolfactory) sensory innervation of the nasal mucosa is supplied by two divisions of the trigeminal nerve.

The Oral Cavity and Pharynx

The teeth form the lateral wall of the oral cavity, while the floor is the tongue—a mass of horizontal, vertical, and transverse muscle bundles attached to the mandible and the hyoid bone. The anterior two-thirds of the tongue has sensory innervation from the lingual nerve with taste sensation from the chordae tympani, whereas the posterior one-third has a sensory supply from the glossopharyngeal nerve. All intrinsic and extrinsic muscles of the tongue are supplied by the hypoglossal nerve, except the palatoglossus, which is supplied by the vagus nerve.

The adult pharynx is a midline structure, running anterior to the cervical prevertebral fascia, from the base of the skull to the level of the sixth cervical vertebra (approximately 14 cm), and continuing as the esophagus. It is a muscular tube with three portions: the nasopharynx, oropharynx, and laryngopharynx (or

hypopharynx). It contains three groups of lymphoid tissue: the adenoids, the pharyngeal tonsil (on the posterior wall), and the palatine (lingual) tonsils as well as the inner opening of the eustachian tube on each lateral wall. The vagus nerve supplies all but one of the pharyngeal muscles. Sensory supply is via branches of the glossopharyngeal and vagus nerves. The pharynx is a common pathway for the upper alimentary and respiratory tracts and is concerned with swallowing and phonation.

The Larynx

The larynx sits anteroinferior to the laryngopharynx, anterior to the fourth to the sixth cervical vertebrae, and posterior to the infrahyoid muscles, the deep cervical fascia, and the subcutaneous fat and skin that cover the front of the neck. Laterally lie the lobes of the thyroid gland and carotid sheath. The larynx acts as a sphincter at the upper end of the respiratory tract and is the organ of phonation. The skeleton of the larynx consists of the epiglottis, thyroid, cricoid, and paired arytenoid, cuneiform, and corniculate cartilages, together with the interconnecting ligaments, and has a volume of 4 mL. Two pairs of parallel horizontal folds project into the lumen of the larynx—the false vocal cords (lying superiorly) and the true vocal cords (inferiorly). The opening between the true cords is called the glottis. The larynx communicates above with the laryngopharynx and below with the trachea, which begins at the lower edge of the cricoid ring.

The superior aspect of the epiglottis is innervated by the glossopharyngeal nerve, whereas the inferior surface of the epiglottis and the larynx is innervated by the vagus, via its superior laryngeal nerve (SLN) and recurrent laryngeal nerve (RLN) branches. The external (motor) branch of the SLN supplies the cricothyroid muscle, and the internal branch is the sensory supply to the larynx down to the vocal cords. The RLN supplies all intrinsic laryngeal muscles and is the sensory supply to the larynx below the cords.

In health, the laryngeal abductor muscles contract early in inspiration, separating the vocal cords and facilitating airflow into the tracheobronchial tree. Movements of the thyroid and arytenoid cartilages alter the length and tension of the vocal cords, and sliding and rotational movements of the arytenoid cartilages can alter the shape of the glottic opening between the vocal cords. Fine control of the muscles producing these movements allows vocalization as air passes between the vocal cords in expiration. The sound volume is increased by resonance in the sinuses of the face and skull.

Injury to the SLN causes hoarseness secondary to a loss of tension in the ipsilateral vocal cord. Complete unilateral RLN palsy (loss of function) inactivates both ipsilateral adductor and abductor muscles, but the vocal cord remains adducted (at/near the midline) owing to action of the unopposed SLN-innervated cricothyroid muscle. In bilateral RLN palsy, both cords are in adduction. On inspiration, the adducted vocal cords then act like a Venturi device, generating a negative pressure that pulls the cords even more tightly together, producing inspiratory stridor—the characteristic sign of upper airway obstruction. Sudden complete adduction of the vocal cords caused by muscle spasm (laryngospasm) is a life-threatening form of airway obstruction that may be triggered by mechanical stimulation of the larynx or by cord irritation caused by aspiration of oral secretions, blood, or vomitus.

The Tracheobronchial Tree

The trachea is a midline fibrous tube, 2 cm in diameter, beginning at the level of the sixth cervical vertebra and extending 10 to 14 cm to the level of the fourth thoracic vertebra before dividing into the right and left main bronchi (carina). The tracheal walls include 15 to 20 incomplete cartilaginous rings limited posteriorly by fibroelastic tissue and smooth muscle. The bronchial tree has a similar wall structure to the trachea.

In the neck the trachea lies anterior to the esophagus, with the RLN in the groove between the two. Anteriorly lie the cervical fascia, infrahyoid muscles, isthmus of the thyroid, and the jugular venous arch. Laterally lie the lobes of the thyroid gland and the carotid sheath. In the thorax, the trachea is traversed anteriorly by the brachiocephalic artery and vein (which may be damaged or eroded by the tracheostomy tube). To the left are the common carotid and subclavian arteries and the aortic arch. To the right are the vagus nerve, the azygos vein, and the pleura. The bifurcation of the trachea (carina) lies anterior to the esophagus and behind the pulmonary trunk.

The two main bronchi diverge from the carina, the right main bronchus being shorter, wider, and more vertical and running close to the pulmonary artery and the azygos vein. The left main bronchus passes under the arch of the aorta, anterior to the esophagus, thoracic duct, and descending aorta.[7]

Overview of Airway Function

In the nose, inspired gas is filtered, humidified, and warmed before entering the lungs. Resistance to gas flow through the nose is twice that of the mouth, explaining the need to mouth-breathe during exercise when the required gas flows are high. Warming and humidification continue in the pharynx and tracheobronchial tree. Between the trachea and the alveolar sacs, the airways divide 23 times, thus increasing the cross-sectional area for the gas exchange.

Particles in inspired air with diameters greater than 10 μm are trapped by hairs on the nasal mucosa. Particles less than 2 μm in diameter may reach the alveoli, where they are ingested by macrophages. Particles 2 to 10 μm in diameter fall on the mucus-covered bronchial walls (as airflow slows), initiating reflex bronchoconstriction and coughing. Such particles are moved upward away from the lungs at a rate of 16 mm/min by cilia that beat at a frequency of 1000 to 1500 cycles/min. Ciliated columnar epithelium lines the respiratory tract from the nose to the respiratory bronchioles (except at the vocal cords). Smoking and some inherited disorders (e.g., Kartagener syndrome) cause defective ciliary motility and a failure of this "mucus escalator." This may allow more particles to reach the alveoli, thereby predisposing the patient to chronic pulmonary inflammation.[8]

The larynx prevents food and other foreign bodies from entering the trachea. Reflex closure of the glottic inlet occurs during swallowing and periods of increased intrathoracic (e.g., coughing, sneezing) or intraabdominal (e.g., vomiting, micturition) pressure. In unconscious patients, these reflexes are lost, so glottic closure may not occur, increasing the risk of pulmonary aspiration.

Assessing Adequacy of the Airway

Adequacy of the airway should be considered in four aspects:

- *Patency.* Partial or complete obstruction compromises ventilation of the lungs and likewise gas exchange.
- *Protective reflexes.* These reflexes help maintain patency and prevent aspiration of material into the lower airways.
- *Inspired oxygen concentration.* Gas entering the pulmonary alveoli must have an appropriate oxygen concentration.

- *Respiratory drive.* A patent, secure airway is of little benefit without the movement of gas between the atmosphere and the pulmonary alveoli. This is achieved by the processes of inspiration and expiration.

Patency

Airway obstruction is most frequently due to reduced muscle tone, allowing the tongue to fall backward against the postpharyngeal wall, thereby blocking the airway. Loss of patency by this mechanism typically occurs in an obtunded or anesthetized patient lying supine. Other causes include the presence of blood, mucus, vomitus, or a foreign body in the lumen of the airway or edema, inflammation, swelling, or enlargement of the tissues lining or adjacent to the airway.

Upper airway obstruction has a characteristic presentation in the spontaneously breathing patient: noisy inspiration (stridor), poor expired airflow, intercostal retraction, increased respiratory distress, and paradoxical rocking movements of the thorax and abdomen.[9] These resolve quickly if the obstruction is removed. In total airway obstruction, sounds of breathing are absent entirely, owing to complete lack of airflow through the larynx. Airway obstruction may occur in patients with an endotracheal tube (ET) or tracheostomy tube in situ as the result of mucous plugging or kinking of the tube or the patient's biting down on a tube placed orally. Spontaneously breathing patients with airway obstruction have the symptoms and signs described earlier, whereas patients supported by assisted (positive-pressure) breathing modes exhibit high inflation pressures, decreased tidal and minute volumes, increased end-tidal carbon dioxide ($ETCO_2$) levels, and decreased arterial oxygen saturation.

Protective Reflexes

The upper airway shares a common pathway with the upper gastrointestinal tract. Protective reflexes, which exist to safeguard airway patency and to prevent foreign material from entering the lower respiratory tract, involve the epiglottis, the vocal cords, and the sensory supply to the pharynx and larynx.[10] Patients who can swallow normally have intact airway reflexes, and normal speech makes absence of such reflexes unlikely. Patients with a decreased level of consciousness (LOC) should be assumed to have inadequate protective reflexes.

Inspired Oxygen Concentration

Oxygen demand is elevated by the increased work of breathing associated with respiratory distress[11] and by the increased metabolic demands in critically ill or injured patients. Often, higher inspired oxygen concentrations are required to satisfy tissue oxygen demand and to prevent critical desaturations during maneuvers for managing the airway. A cuffed ET, connected to a supply of oxygen, is a sealed system in which the delivered oxygen concentration also is the inspired concentration. A patient wearing a face mask, however, inspires gas from the mask and surrounding ambient air. Because the patient will generate an initial inspiratory flow in the region of 30 to 60 L/min, and the fresh gas flow to a mask is on the order of 5 to 15 L/min, much of the tidal inspiration will be "ambient air" entrained from around the mask. The entrained air can dilute the concentration of oxygen inspired to less than 50%, even when 100% oxygen is delivered to the mask. This unwelcome reduction in inspired oxygen concentration can be mitigated by (1) using a mask with a reservoir bag, (2) ensuring that the mask is fitted firmly to the patient's face, (3) using a high rate of oxygen flow to the mask (15 L/min), and (4) supplying a higher oxygen concentration if not already using 100%.

Respiratory Drive

A patent, protected airway will not produce adequate oxygenation or excretion of carbon dioxide without adequate respiratory drive. Changing arterial carbon dioxide tension (PCO_2) by changing the hydrogen ion (H^+) concentration in cerebrospinal fluid stimulates the respiratory center, which in turn controls minute volume and therefore arterial PCO_2 (negative feedback). This assumes that increased respiratory drive can produce an increase in minute ventilation (increased respiratory rate or tidal volume, or both), which may not occur if respiratory mechanics are disturbed. Brain injury and drugs such as opioids, sedatives, and alcohol are direct-acting respiratory center depressants.

Ventilation can be assessed qualitatively by looking, listening, and feeling. In a spontaneously breathing patient, listening to (and feeling) air movement while looking at the extent, nature, and frequency of thoracic movement provides an impression of ventilation. These parameters may be misleading, however. Objective assessment of minute ventilation requires PCO_2 measurement in arterial blood or monitoring of $ETCO_2$, which can be used as a real-time measure of the adequacy of minute ventilation. If respiratory drive or minute ventilation is inadequate, positive-pressure respiratory support may be required, and any underlying factors should be addressed if possible (e.g., depressant effect of sedatives or analgesics).

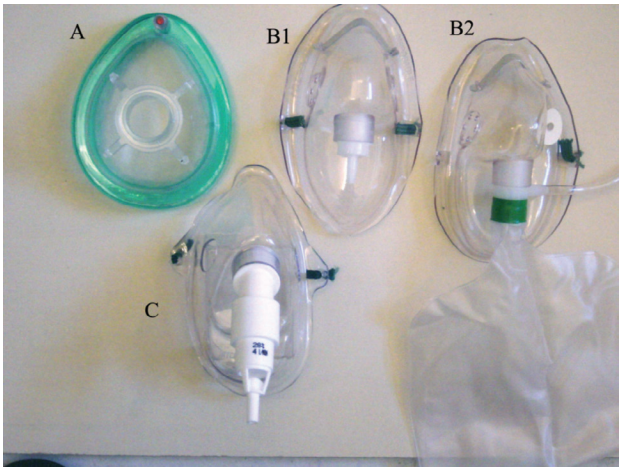
Management of the Airway

The aims of airway management are to provide an adequate inspired oxygen concentration; to establish a patent, secure airway; and to support ventilation if required.

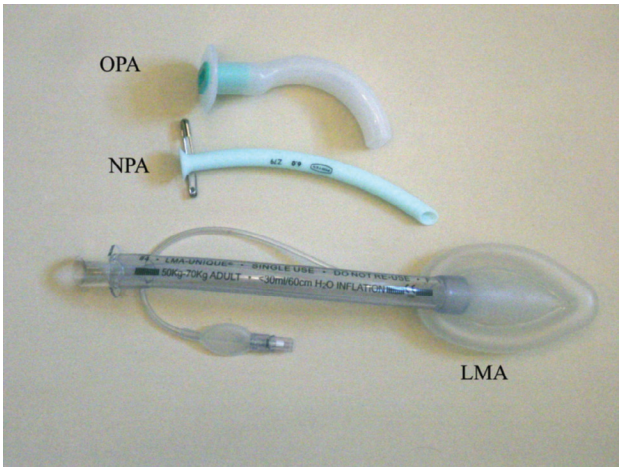
Providing an Adequate Inspired Oxygen Concentration

Although oxygen can be administered via nasal cannula, this method does not ensure delivery of more than 30% to 40% oxygen (at most). Other disadvantages include lack of humidification of gases, patient discomfort with use of flow rates greater than 4 to 6 L/min, and predisposition to nasal mucosal irritation and potential bleeding. Therefore despite being more intrusive for patients, face masks are superior for oxygen administration. The three main types of face masks are shown in Fig. 2.1:

- The anesthesia-type face mask (mask A in Fig. 2.1) is a solid mask (with no vents) with a cushioned collar to provide a good seal. It is suitable for providing very high oxygen concentrations (approaching 100%) because entrainment is minimized and the anesthetic circuit normally includes a reservoir of gas. These masks become unacceptable for many *awake* patients within a few minutes because of the association with heat, moisture, and claustrophobia.
- The simple face mask has vents that allow dissipation of heat or humidity but that also entrain room air. These masks have no seal and are relatively loose-fitting. Such masks may have a reservoir bag (approximately 500 mL) sitting inferior to the mask (B2 in Fig. 2.1) or may not (B1 in Fig. 2.1). Using the latter, it is difficult to reliably deliver an inspired oxygen



• **Fig. 2.1** Face masks: anesthesia mask (A); simple face mask (B1); simple face mask with reservoir bag (B2); Venturi mask (C).



• **Fig. 2.2** Artificial airways: oropharyngeal airway *(OPA)*; nasopharyngeal airway *(NPA)*; laryngeal mask airway *(LMA)*.

concentration in excess of 50% even with tight application and 100% oxygen flow to the mask. Under the same conditions, a simple mask with a reservoir bag can produce an inspired oxygen concentration of about 80%.

- The Venturi mask (C in Fig. 2.1) has vents that entrain a known proportion of ambient air when a set flow of 100% oxygen passes through a Venturi device. Thus the inspired oxygen concentration (usually 24% to 35%) is known.

Establishing a Patent and Secure Airway

Establishing a patent and secure airway can be achieved using simple airway maneuvers, further airway adjuncts, tracheal intubation, or a surgical airway.

Airway Maneuvers

Simple airway maneuvers involve appropriate positioning, opening the airway, and keeping it open using artificial airways if needed.

Positioning for Airway Management

In the absence of any concerns about cervical spine stability (e.g., with trauma, rheumatoid arthritis, or severe osteoporosis), raising the patient's head slightly (5–10 cm) by means of a small pillow under the occiput can help in airway management. This adjustment extends the atlantooccipital joint and moves the oral, pharyngeal, and laryngeal axes into better alignment, providing the best straight line to the glottis ("sniffing" position).

Clearing the Airway

Acute airway obstruction in the obtunded patient is often due to the tongue or extraneous material—liquid (saliva, blood, gastric contents) or solid (teeth, broken dentures, food)—in the pharynx. In the supine position, secretions can be cleared under direct vision using a laryngoscope and a rigid suction catheter.[12] In some cases, a flexible suction catheter, introduced through the nose and nasopharynx, may be the best means of clearing the airway. A finger sweep of the pharynx may be used to detect and remove larger solid material in unconscious patients without an intact gag reflex. During all airway interventions, if cervical spine instability cannot be ruled out, relative movement of the cervical vertebrae must be prevented—most often by manual inline immobilization.[12,13]

Triple Airway Maneuver

The triple airway maneuver often is beneficial in obtunded patients if it is not contraindicated by concerns about cervical spine instability. As indicated by its name, this maneuver has three components: head tilt (neck extension), jaw thrust (pulling the mandible forward), and mouth opening.[14] The operator stands behind and above the patient's head. Then the maneuver is performed as follows:

- Extend the patient's neck with the operator's hands on both sides of the mandible.
- Elevate the mandible with the fingers of both hands, thereby lifting the base of the tongue away from the posterior pharyngeal wall.
- Open the mouth by pressing caudally on the anterior mandible with the thumbs or forefingers.

Artificial Airways

If the triple airway maneuver or any of its elements reduces airway obstruction, the benefit can be maintained for a prolonged period by introducing an artificial airway into the pharynx between the tongue and the posterior pharyngeal wall (Fig. 2.2).

The oropharyngeal airway (OPA) is the most commonly used artificial airway. Simple to insert, it is used temporarily to help facilitate oxygenation or ventilation before tracheal intubation. The OPA should be inserted with the convex side toward the tongue and then rotated through 180 degrees. Care must be taken to avoid pushing the tongue posteriorly, thereby worsening the obstruction. The nasopharyngeal airway has the same indications as for the OPA but significantly more contraindications[15] (Box 2.1). It is better tolerated than the OPA, making it useful in semiconscious patients in whom the gag reflex is partially preserved. These artificial airways should be considered as a temporary adjunct—to be replaced with a more secure airway if the patient's condition fails to improve rapidly to the point at which an artificial airway no longer is needed. Such airways should not be used in association with *prolonged* positive-pressure ventilation.

Advanced Airway Adjuncts

Advanced airway adjuncts fill the gap between simple airway maneuvers and the insertion of a tracheal tube or surgical airway. These devices can be used to facilitate safe reliable airway management and manual ventilation in the prehospital or emergency

• BOX 2.1 Contraindications to Insertion of Oropharyngeal and Nasopharyngeal Airways

Contraindications to Oropharyngeal Airways

Inability to tolerate (gagging, vomiting)
Airway swelling (burns, toxic gases, infection)
Bleeding into the upper airway
Absence of pharyngeal or laryngeal reflexes
Impaired mouth opening (e.g., with trismus or temporomandibular joint dysfunction)

Contraindications to Nasopharyngeal Airways

Narrow nasal airway in young children
Blocked or narrow nasal passages in adults
Airway swelling (burns, toxic gases, infection)
Bleeding into the upper airway
Absence of pharyngeal or laryngeal reflexes
Fractures of the midface or base of skull
Clinical scenarios in which nasal hemorrhage would be disastrous

resuscitation setting, often without expert medical presence. The number of supraglottic airways (SGAs) available has increased dramatically in the past 2 decades. They may be used to maintain airway maintenance during low-risk surgery and have utility in airway management in obese patients, in airway rescue after failed intubation, and during an anticipated difficult airway.[16]

The laryngeal mask airway (LMA) is a small latex mask mounted on a hollow plastic tube.[17,18] The airway is placed "blindly" in the lower pharynx overlying the glottis. The inflatable cuff helps wedge the mask in the hypopharynx, sitting obliquely over the laryngeal inlet. Although the LMA produces a seal that allows ventilation with gentle positive pressure, it does not definitively protect the airway from aspiration. Indications for use of the LMA in critical care are (1) as an alternative to other artificial airways, (2) the difficult airway, particularly the "cannot intubate–cannot ventilate" scenario, and (3) as a conduit for bronchoscopy. It is possible to pass a 6.0-mm ET through a standard LMA into the trachea, but the LMA must be left in situ. The intubating LMA, which was developed specifically to aid intubation with a tracheal tube, has a shorter steel tube with a wider bore, a tighter curve, and a distal silicone laryngeal cuff. A bar present near the laryngeal opening is designed to lift the epiglottis anteriorly. The intubating LMA allows the passage of a specially designed size 8.0 ET.

There is increasing evidence that many of the newer SGAs have better performance characteristics that may improve efficacy compared with the original LMA device. They are often easier to insert, with better oropharyngeal seal pressures, and may reduce the risk of aspiration.[19,20]

Tracheal Intubation

If the foregoing interventions are not effective or are contraindicated, tracheal intubation is required. This modality provides (1) a secure, potentially long-term airway; (2) a safe route to deliver positive-pressure ventilation if required; and (3) significant protection against pulmonary aspiration.

Orotracheal intubation is the most widely used technique for clinicians practiced in direct laryngoscopy (indications and contraindications in Box 2.2). Normally, anesthesia with or without neuromuscular blockade is necessary for this procedure, which is summarized in Box 2.3.

• BOX 2.2 Orotracheal Intubation: Indications and Relative Contraindications

Indications

Long-term correction or prevention of airway obstruction
Securing the airway and protecting against pulmonary aspiration
Facilitating positive-pressure ventilation
Enabling bronchopulmonary toilet
Optimizing access to pharynx, face, or neck at surgery

Contraindications (Relative)

Possibility of cervical spine instability
Impaired mouth opening (e.g., trismus, temporomandibular joint dysfunction)
Potential difficult airway
Need for surgical immobilization of maxilla or mandible (wires, box frame)

• BOX 2.3 Procedure: Orotracheal Intubation

- Position patient and induce anesthesia ± neuromuscular blockade (if needed).
- Perform manual ventilation using triple airway maneuver and oropharyngeal airway.
- Hold laryngoscope handle (left hand) near the junction with blade.
- Insert the blade along the right side of the tongue—moving tongue to the left.
- Advance tip of the blade in the midline between tongue and epiglottis.
- Pull upward and along the line of the handle of the laryngoscope.
- Lift the epiglottis upward and visualize the vocal cords.
- Do *not* use the patient's teeth as a fulcrum when attempting to visualize the glottis.
- Stop advancing tube when cuff is 2 to 3 cm beyond the cords.
- Connect to a bag-valve system and pressurize it by squeezing bag.
- Inflate cuff until audible leak around tube stops.
- Check correct tube position (auscultation) and assess cuff pressure.
- Check end-tidal carbon dioxide trace.

TABLE 2.1 Drugs Used to Facilitate Tracheal Intubation

Drug	Dose (Intravenous)
Induction Agent	
Propofol	1–2.5 mg/kg
Opioids	
Fentanyl	1.0–1.5 μg/kg
Morphine	0.15 mg/kg
Nondepolarizing Agents	
Atracurium	0.4–0.5 mg/kg
Vecuronium	0.1 mg/kg
Rocuronium	0.45–0.6 mg/kg
Depolarizing Agent	
Succinylcholine (suxamethonium)	1.0–1.5 mg/kg

Tracheal intubation requires lack of patient awareness (as in the unconscious state or with general anesthesia) and the abolition of protective laryngeal and pharyngeal reflexes. The drugs commonly used to achieve these states are shown in Table 2.1. Anesthesia is achieved using an intravenous induction agent, although intravenous

sedatives (e.g., midazolam) theoretically may be used. Opioids often are used in conjunction with induction agents because they may reduce the cardiovascular sequelae of laryngoscopy and intubation (tachycardia and hypertension) and may contribute to the patient's unconsciousness.

Abolition of protective laryngeal and pharyngeal reflexes may be achieved by inducing a deep level of unconsciousness using one or more of the aforementioned agents, followed by inhalation of high concentrations of a volatile anesthetic agent (e.g., sevoflurane, isoflurane). This technique sometimes is used in the anticipated difficult airway scenario to obtain conditions suitable for tracheal intubation in a patient who is still breathing spontaneously.

More often, a muscle relaxant is used to abolish the protective reflexes, abduct the vocal cords, and facilitate tracheal intubation. In the elective situation, nondepolarizing neuromuscular blocking agents are used. These drugs have the disadvantage of requiring several minutes to exert their effect, during which the patient must receive ventilation via a mask, thus allowing the possibility of gastric dilation and pulmonary aspiration. In patients at high risk of the latter (e.g., nonfasting patients), a depolarizing muscle relaxant (succinylcholine) can be used because it produces suitable conditions for intubation within 15 to 20 seconds, and mask ventilation is not required. Succinylcholine has several side effects—among them hyperkalemia, muscle pains, and (rarely) malignant hyperpyrexia. Alternatively, the ability to antagonize the effects of rocuronium rapidly with sugammadex may be an advantage. If rapid antagonism of rocuronium with sugammadex is part of the failed intubation plan, then the appropriate dose (16 mg/kg) must be readily available.

Nasotracheal intubation shares the problems and contraindications associated with the NPA. The technique usually is used when there are relative contraindications to the oral route (e.g., anatomic abnormalities, cervical spine instability). Nasotracheal intubation may be achieved under direct vision or (if spontaneously breathing) with the use of a blind technique, either with the patient under general anesthesia or in the awake or lightly sedated patient with appropriate local anesthesia (Box 2.4). If orotracheal or nasotracheal intubation is required but cannot be achieved, then a surgical airway is required (see later text).

With a need for isolation of one lung from another, a double-lumen tube (having one cuffed tracheal lumen and one cuffed bronchial lumen fused longitudinally) can be used.[21] The main indications are (1) to facilitate some pulmonary or thoracic surgical procedures; (2) to isolate a lung containing contaminated fluid (e.g., in lung abscess) or blood, thereby preventing contralateral spread; and (3) to enable differential or independent lung ventilation. Intermitted lung ventilation allows each lung to be treated separately—for example, to deliver positive-pressure ventilation with high positive end-expiratory pressure to one lung while applying low levels to the other. Such a strategy may be advantageous in cases of pulmonary air leak (bronchopleural fistula, bronchial tear, or severe lung trauma) or in severe unilateral lung disease requiring ventilatory support.[21,22]

• BOX 2.4 Procedure: Nasotracheal Intubation (Blind and Under Direct Vision)

Preparation and Assessment of the Patient

1. Use a nasal decongestant such as phenylephrine to reduce bleeding.
2. Provide local anesthesia to the nasal mucosa.
3. Examine each nostril for patency and deformity.
4. Choose the most patent nostril, and use an appropriate-size ET.
5. After induction of anesthesia, position the head and neck as for oral intubation.

Blind Nasotracheal Intubation

- Keep patient breathing spontaneously.
- Insert well-lubricated ET into the nostril (concavity forward, bevel lateral).
- While passing ET along nasal floor, listen for audible breathing through the tube.
- Advance ET, rotating as needed to maintain clear breath sounds.
- ET will pass through cords, and patient may cough.
- Technique takes time, so it is not suitable for a patient experiencing desaturation.
- Do not force passage of ET, because this could cause bleeding.

Nasotracheal Intubation (Direct Vision)

- Patient may be apneic with or without relaxants.
- Gently advance ET through the nose.
- When ET tip is in oropharynx, perform laryngoscopy.
- Visualize ET in pharynx and advance toward glottis.
- Advance ET through cords into trachea, under direct vision if possible.
- Use Magill forceps if required to guide tip while advancing ET.
- Try to avoid damaging cuff if using forceps to help passage through cords.

ET, *Endotracheal tube.*

Providing Ventilatory Support

If a patient has no (or inadequate) spontaneous ventilation, then a means of generating gas flow to the lower respiratory tract must be provided. Negative pressure, mimicking the actions of the respiratory muscles, occasionally is used in some patients who require long-term ventilation. In acute care, however, ventilation is achieved using positive pressure, which requires an unobstructed airway; in the nonintubated patient, this is best achieved by proper positioning, the triple airway maneuver, and use of an OPA or NPA. In a patient without an ET in place, particularly if some degree of airway obstruction exists, positive-pressure ventilation often causes gastric distention and (potentially) regurgitation and pulmonary aspiration.

Bag-Valve-Mask Ventilation

Ventilation with a mask requires an (almost) airtight fit between mask and face. This is best achieved by firmly pressing the mask against the patient's face using the thumb and index finger (C-grip) while pulling the mandible upward toward the mask with the other three fingers. The other hand is used to squeeze the reservoir bag, generating positive pressure. Excessive pressure from the C-grip on the mask may lead to backward movement of the mandible with subsequent airway obstruction, or a tilt of the mask with leakage of gas. If a proper seal is difficult to attain, placing a hand on each side of the mask and mandible is advised, with a second person manually compressing the reservoir bag (four-handed ventilation). Bag-valve-mask systems have a self-reinflating bag, which springs back after compression, thereby drawing gas in through a port with a one-way valve. It is important to have a large reservoir bag with a continuous flow of oxygen attached to this port to achieve a high inspired oxygen concentration.[23,24] Bag-valve-mask ventilation usually is a short-term measure in urgent situations or is used in preparation for tracheal intubation.

Prolonged Ventilation Using a Sealed Tube in the Trachea

Ventilation of the lungs with a bag-valve-mask arrangement is difficult and potentially dangerous if required for more than a few

minutes or if the patient needs to be transported. In these instances, ventilation through a sealed tube in the trachea is indicated. Orotracheal or nasotracheal intubation, surgical cricothyrotomy, and tracheostomy all achieve the same result: a cuffed tube in the trachea, allowing the use of positive-pressure ventilation and protecting the lungs from aspiration.

Apneic Oxygenation

Apneic oxygenation is achieved using a narrow catheter that sits in the trachea and carries a flow of 100% oxygen. The catheter may be passed into the trachea via an ET or under direct vision through the larynx. This apparatus can be set up as a low-flow open system (gas flow rate of 5 to 8 L/min) or as a high-pressure (jet ventilation) system[25] and can be used to maintain oxygenation with a difficult airway either at intubation or at extubation (see later text).

Physiologic Sequelae and Complications of Tracheal Intubation

Laryngoscopy is a noxious stimulus that, in an awake or lightly sedated patient, would provoke coughing, retching, or vomiting and laryngospasm. In clinical practice, however, laryngoscopy and tracheal intubation usually are performed after induction of anesthesia, and in emergency situations, the patient often is hypoxic and hypercarbic, with increased sympathetic nervous system activity. Thus the physiologic effects of laryngoscopy and tracheal intubation tend to be masked.

Laryngoscopy and intubation cause an increase in circulating catecholamines and increased sympathetic nervous system activity, leading to hypertension and tachycardia. This represents an increase in myocardial work and myocardial oxygen demand, which may provoke cardiac dysrhythmias and myocardial hypoxia or ischemia. Laryngoscopy increases cerebral blood flow and intracranial pressure—particularly in patients who are hypoxic or hypercarbic at the time of intubation.[26] This rise in intracranial pressure will be exaggerated if cerebral venous drainage is impeded by violent coughing, bucking, or breath-holding.

Coughing and laryngospasm occur frequently in patients undergoing laryngoscopy and intubation when muscle relaxation and anesthesia are inadequate. Increased bronchial smooth muscle tone, which increases airway resistance, may occur as a reflex response to laryngoscopy or may be due to the physical presence of the ET in the trachea; in its most severe form, termed bronchospasm, this increased tone causes audible wheeze and ventilatory difficulty.

The cross-sectional area of the ET is less than that of the airway and therefore causes increased resistance to gas flow. This difference usually is unimportant with positive-pressure ventilation but causes a significant increase in work of breathing in spontaneously breathing patients. Resistance is directly related to $1/r^4$ (where r is the radius of the ET) and will be minimized by use of a large-bore ET.

Laryngoscopy and intubation may cause bruising, abrasion, laceration, bleeding, or displacement or dislocation of the structures in and near the airway (e.g., lips, teeth or dental prostheses, tongue, epiglottis, vocal cords, laryngeal cartilages). Dislodged structures such as teeth or dentures may be aspirated, blocking the airway more distally. Less common complications include perforation of the airway with the potential for the development of a retropharyngeal abscess or mediastinitis. Over time, erosions resulting from pressure and ischemia may develop on the lips or tongue (or external nares and anterior nose in patients with a nasotracheal tube) and in the larynx or upper trachea. These lesions result in a breach of the mucosa with the potential for secondary infection. In the case of the lips and tongue, such lesions are (temporarily) disfiguring and painful and may inhibit attempts to talk or swallow.

The mucosa of the upper trachea (subglottic area) is subjected to the pressure of the cuff of the ET. This pressure reduces perfusion of the tracheal mucosa and, combined with the mechanical movement of the tube (from patient head movements, nursing procedures, or rhythmic flexion with action of the ventilator), tends to cause mucosal damage and increase the risk of superficial infection. These processes may lead to ulceration of the tracheal mucosa, fibrous scarring, contraction, and ultimately stenosis, which can be a life-limiting or life-threatening problem.

Any tube in the trachea has a significant effect on the mechanisms protecting the airway from aspiration and infection. The mucus escalator may be inhibited by mucosal injury and by the lack of warm humidified airflow over the respiratory epithelium.[27] The disruption of normal swallowing results in the pooling of saliva and other debris in the pharynx and larynx above the upper surface of the tube's inflatable cuff, which may become the source of respiratory infection if the secretions become colonized with microorganisms, or may pass beyond the cuff into the lower airways—that is, pulmonary aspiration (silent or overt).[28,29] The former may occur as a result of (1) colonization of the gastric secretions and the regurgitation of this material up the esophagus to the pharynx or (2) transmission of microorganisms from the health care environment to the pharynx via medical equipment or the hands of hospital staff or visitors (cross-infection).[29–32]

The presence of a tube traversing the larynx and sealing the trachea makes phonation impossible. The implications of this limitation for patients and their families often are ignored. If patients cannot tell caregivers about pain, nausea, or other concerns, they may become frustrated, agitated, or violent. This may result in the excessive use of sedative or psychoactive drugs, which prolong the time ventilation is used and the stay in the intensive care unit (ICU), with the risk of infection increased accordingly.[33] The inability to communicate may therefore be a real threat to patient survival. Potential solutions involve the use of letter and picture boards, "speaking valves" (with tracheostomy), laryngeal microphones, or computer-based communication packages. The involvement and innovations of disciplines such as the speech and language center may be advantageous.

The Difficult Airway

The difficult airway has been defined as "the clinical situation in which a conventionally trained anesthetist experiences difficulty with mask ventilation of the upper airway, tracheal intubation, or both."[34] It has been a commonly documented cause of adverse events, including airway injury, hypoxic brain injury, and death under anesthesia.[35–41] The frequency of difficulty with mask ventilation has been estimated to be between 1.4% and 7.8%,[42–44] whereas tracheal intubation using direct laryngoscopy is difficult in 1.5% to 8.5% and impossible in up to 0.5% of general anesthetics.[40,45] The incidence of failed intubation is approximately 1:2000 in the nonobstetric population and 1:300 in the obstetric population.[46] In the critical care unit, up to 20% of all critical incidents are airway related,[47–49] and such incidents may occur at intubation, at extubation, or during the course of treatment (as with the acutely displaced or obstructed ET or tracheostomy tube).

Recognizing the Potentially Difficult Airway

Many conditions are associated with airway difficulty (Table 2.2), including anatomic abnormalities, which may be associated with an unusual appearance, thereby alerting the examiner. The goal is to identify the potentially difficult airway and develop a plan to secure it. Factors including age older than 55 years, body mass index greater than 26 kg/m^2, presence of a beard, lack of teeth, and a history of snoring have been identified as independent variables predicting difficulty with mask ventilation—in turn associated with difficult tracheal intubation.[43,50]

Mallampati[51] developed a grading system (subsequently modified[46]) that predicted ease of tracheal intubation at direct laryngoscopy. The predictive value of the Mallampati system has been shown to be limited[52,53] because many factors that have no influence on the Mallampati classification—mobility of head and neck, mandibular or maxillary development, dentition, compliance of neck structures, and body shape—can influence laryngeal view.[35,48,54,55] A study of a complex system including some of these factors found the rate of difficult intubation to be 1.5%, but with a false-positive rate of 12%.[56] A risk index based on the Mallampati classification, a history of difficult intubation, and five other variables lacked sufficient sensitivity and specificity.[57] Airway management should be based on the fact that the difficult airway cannot be reliably predicted.[58,59] This is a particularly important consideration in the critical care environment.

TABLE 2.2 Conditions Associated With Difficult Airway

Causative Factors	Associated Conditions/Disorders
Abnormal anatomy/development	Small mouth or large tongue Dental abnormality Prognathia Obesity Advanced pregnancy Acromegaly Syndromic child[a]
Inability to open mouth	Masseter muscle spasm (dental abscess) Temporomandibular joint dysfunction Facial burns Postradiotherapy fibrosis Scleroderma
Cervical immobility/abnormality	Short neck/obesity Poor cervical mobility (e.g., ankylosing spondylitis) Previous cervical spine surgery Presence of cervical collar Postradiotherapy fibrosis
Pharyngeal or laryngeal abnormality	High or anterior larynx Deep vallecula: inability to reach base of epiglottis with blade of scope Anatomic abnormality of epiglottis or hypopharynx (e.g., tumor) Subglottic stenosis
Injury	Traumatic debris Obstructing foreign bodies Basilar skull fracture Bleeding into airway or adjacent swelling/hematoma Fractured maxilla/mandible Cervical spine instability (confirmed or potential) Laryngeal fracture or disruption
Infections	Epiglottitis Abscess Croup, bronchiolitis Laryngeal papillomatosis Tetanus/trismus
Connective tissue/inflammatory disorders	Rheumatoid arthritis: temporomandibular joint or cervical spine involvement, cricoarytenoid arthritis Ankylosing spondylitis Scleroderma Sarcoidosis
Endocrine disorders	Goiter: airway compression or deviation Hypothyroidism, acromegaly: large tongue

[a]For example, Klippel-Feil syndrome (limited neck extension); Beckwith-Weidemann syndrome (restricted TM joint mobility and large tongue); Pierre Robin Syndrome (limited submandibular space)

The Obstructed Airway

Although the most common reason for an obstructed airway in the unintubated patient is posterior displacement of the tongue in association with a depressed LOC, it is the less common causes that provide the greatest challenges. It is important to quickly elucidate the level at which the obstruction occurs and, if possible, the nature of the obstructing lesion: infection or edema (epiglottitis, pharyngeal or tonsillar abscess, mediastinal abscess), neoplasm (primary malignant or benign tumor, metastastic spread, direct extension from nearby structures), thyroid enlargement, vascular lesions, trauma, or foreign body or impacted food.

Airway lesions above the level of the vocal cords are considered to lie in the upper airway and commonly manifest with stridor.[60] If breathing is labored and associated with difficulty breathing at night, rather than just noisy breathing, then the narrowing probably is more than 50%. Patients with these lesions usually fall into one of two groups: (1) those who can be intubated, usually under inhalational induction, with an otorhinolaryngologist or other qualified surgeon/physician immediately available to perform rigid bronchoscopy or tracheostomy if required, or (2) those who require a tracheostomy performed while under local anesthesia. In patients with midtracheal obstruction, computed tomography imaging usually is necessary to discover the exact level and nature of the obstruction and to allow planning of airway management for nonemergency clinical presentations.[60] Tracheostomy often is not beneficial because the tube may not be long enough to bypass the obstruction. In such instances, fiberoptic intubation often may be useful. Lower tracheal obstruction often is due to space-occupying lesions in the mediastinum and necessitates multidisciplinary planning involving otorhinolaryngology, cardiothoracic surgery, anesthesia, and critical care team members.

Trauma and the Airway

Airway management in the trauma victim provides additional challenges because the victim often has other life-threatening conditions and preparation time for management of the difficult airway is limited. Approximately 15% of severely injured patients have maxillofacial involvement, and 5% to 10% of patients with blunt trauma have an associated cervical spine injury (often associated with head injury).[61]

Problems encountered in trauma patients include presence in the airway of debris or foreign bodies (e.g., teeth), vomitus, or regurgitated gastric contents; airway edema; tongue swelling; blood and bleeding; and fractures (maxilla and mandible). Patients must be assumed to have a full stomach (requiring bimanual cricoid pressure and a rapid-sequence induction for intubation), and many will have pulmonary aspiration before the airway is secured. An important consideration in most cases is the need to avoid movement of the cervical spine at laryngoscopy or intubation.[12,13] Direct injury to the larynx is rare but may result in laryngeal disruption, producing progressive hoarseness and subcutaneous emphysema. Tracheal intubation, if attempted, requires great care and skill because it may cause further laryngeal disruption. With Le Fort fractures, airway obstruction or compromised respiration requiring immediate airway control is present in 25% of cases.[62] Postoperative bleeding after operations to the neck (thyroid gland, carotid, larynx) may compress or displace the airway, leading to difficulty in intubation.

The Airway Practitioner and the Clinical Setting

Although airway difficulties often are due to anatomic factors as discussed, it is important to recognize that the inability to perform an airway maneuver also may be due to a practitioner's inexperience or lack of skill.[63–68] Expert opinion and clinical evidence also identify lack of skilled assistance as a factor in airway-related adverse events.[69–72] As might be expected, inexperience and lack of suitable help may contribute to failure in optimizing the conditions for laryngoscopy (Box 2.5). Airway and ventilatory management performed in the prehospital setting or in the hospital but outside an operating room (OR) carries a higher frequency of adverse events and a higher mortality rate compared with those performed using anesthesia in an OR.[73–77] In the critical care unit, all invasive airway maneuvers are potentially difficult.[78] Positioning is more difficult on an ICU bed than on an OR table. The airway structures may be edematous after previous laryngoscopy or presence of an ET. Neck immobility or the need to avoid movement in a potentially unstable cervical spine may be other contributing factors.[79–81] Poor gas exchange in ICU patients reduces the effectiveness of preoxygenation and increases the risk of significant hypoxia before the airway is secured.[82] Cardiovascular instability may produce hypotension or hypoperfusion, or it may lead to misleading oximetry readings (including failure to record any value at all), a further confounding factor for the attending staff.[83,84]

• BOX 2.5 Common Errors Compromising Successful Intubation

Poor patient positioning
Failure to ensure appropriate assistance
Faulty light source in laryngoscope or no alternative scope
Failure to use a longer blade in appropriate patients
Use of inappropriate tracheal tube (size or shape)
Lack of immediate availability of airway adjuncts

Managing the Difficult Airway

Management of the difficult airway can be considered in the framework of three possible clinical scenarios with progressively increasing risks for the patient: (1) the anticipated difficult airway; (2) the unanticipated difficult airway; and (3) the difficult airway resulting in a can't intubate–can't ventilate situation.

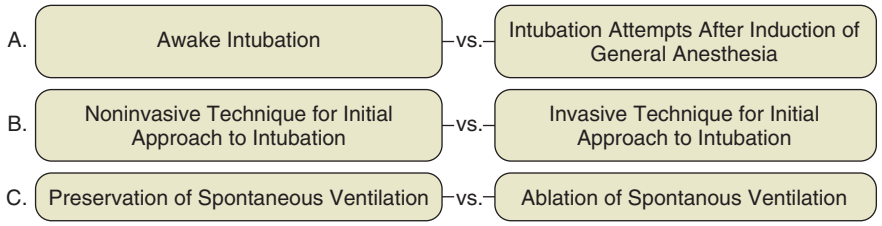
Requirements for clinicians involved in airway management include the following:

- Expertise in recognition and assessment of the potentially difficult airway. This involves the use of the assessment techniques noted previously and a "sixth sense."[58]
- The ability to formulate a plan (with alternatives).[34]
- Familiarity with algorithm(s) that outline a sequence of actions designed to maintain oxygenation, ventilation, and patient safety. The American Society of Anesthesiologists guidelines[34] and the composite plan from the Difficult Airway Society (DAS)[85] are shown in Figs. 2.3 through 2.5. Fig. 2.4 summarizes four airway plans (A–D), available from the DAS website (www.das.uk.com).
- The skills and experience to use a number of airway adjuncts, particularly those relevant to the unanticipated difficult airway.

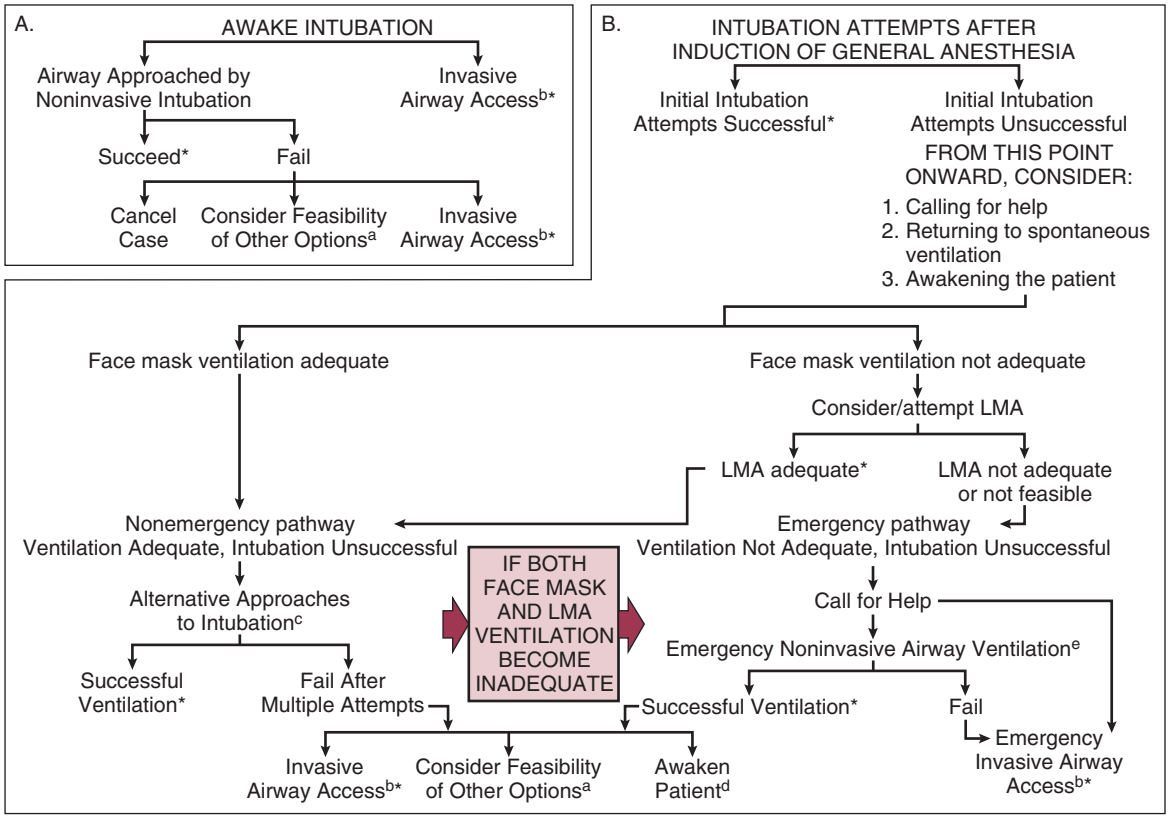
Basic preparation for management of a difficult airway includes (1) the availability of the correct equipment to hand the clinician, (2) informing the patient with a known or suspected difficult airway, (3) assigning an appropriately skilled individual to provide assistance during the procedure, (4) preanesthetic preoxygenation

DIFFICULT AIRWAY ALGORITHM

1. Assess the likehood and clinical impact of basic management problems:
   - Difficult ventilation
   - Difficult intubation
   - Difficulty with patient cooperation or consent
   - Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.
3. Consider the relative merits and feasibility of basic management choices:



4. Develop primary and alternative strategies:



* Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2.

[a] Other options include (but are not limited to) surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration, and regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

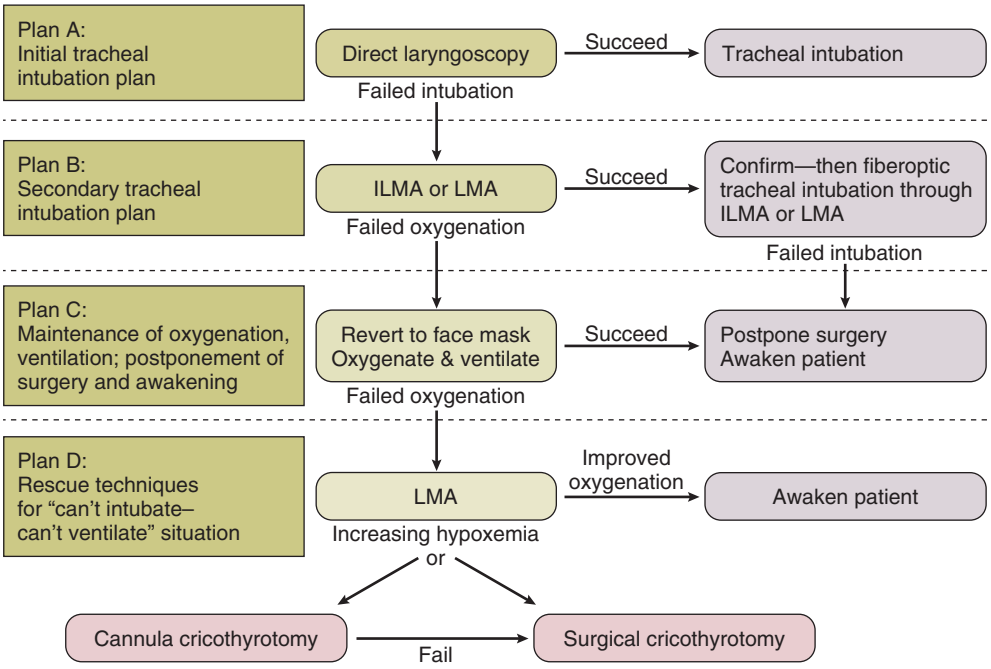
[b] Invasive airway access includes surgical or percutaneous tracheostomy and cricothyrotomy.

[c] Alternative noninvasive approaches to difficult intubation include (but are not limited to) use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.

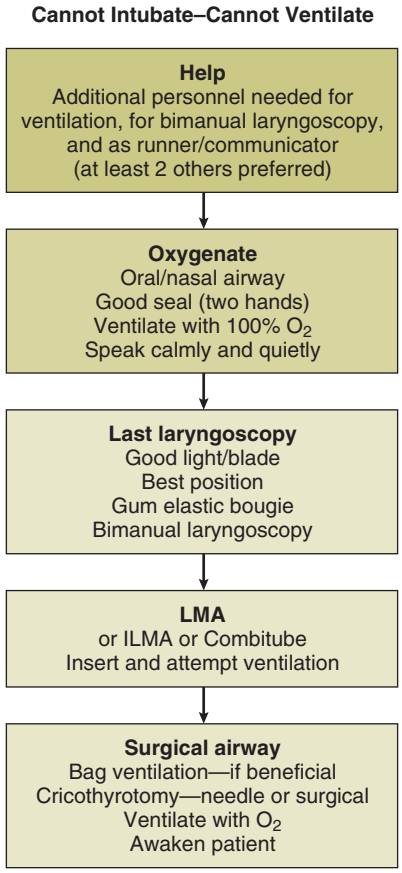
[d] Consider repreparation of the patient for awake intubation or canceling surgery.

[e] Options for emergency noninvasive airway ventilation include (but are not limited to) rigid bronchoscope, esophageal-tracheal Combitube ventilation, and transtracheal jet ventilation.

• **Fig. 2.3** Algorithm for managing the difficult airway. *CO_2,* Carbon dioxide; *LMA,* laryngeal mask airway. (Adapted from Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology.* 2003;98:1269–1277.)



• **Fig. 2.4** A four-component algorithm for managing the difficult airway. *ILMA,* Intubating laryngeal mask airway; *LMA,* laryngeal mask airway. (From Henderson JJ, Popat MT, Latto IP, et al. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. *Anaesthesia.* 2004;59:675–694.)



• **Fig. 2.5** Flow chart for the cannot intubate–cannot ventilate scenario. *ILMA,* Intubating laryngeal mask airway; *LMA,* laryngeal mask airway.

by mask, and (5) administration of supplemental oxygen throughout the process.

The Anticipated Difficult Airway

The anticipated difficult airway is the "least lethal" of the three scenarios—with time to consider strategy, optimize patient status, and obtain appropriate adjuncts and personnel. The key questions are as follows:

1. Should the patient be kept awake or be anesthetized for intubation?
2. Which technique should be used for intubation?

Awake Intubation

Awake intubation is more time-consuming, requires experienced personnel, is less pleasant for the patient (compared with intubation under anesthesia), and may have to be abandoned as a result of the patient's inability or unwillingness to cooperate. Because spontaneous breathing and pharyngeal/laryngeal muscle tone are maintained, however, it is significantly safer. The techniques available are fiberoptic and retrograde intubation. It also may be used in patients judged to be at risk for a difficult airway, whereupon an initial direct laryngoscopic view allows intubation.

Fiberoptic Intubation. Fiberoptic intubation is a technique in which a flexible endoscope with a tracheal tube loaded along its length is passed through the glottis. The tracheal tube is then pushed off the endoscope and into the trachea, and the endoscope is withdrawn. An informed patient, trained assistance, and adequate preparation time make fiberoptic intubation less stressful. The nasotracheal route is used most often and requires the use of nasal vasoconstrictors. Nebulized local anesthetic is delivered to the airway via face mask. Sedation may be given, but ideally the patient should

remain breathing spontaneously and responsive to verbal commands. The procedure often is time-consuming and tends to be used in elective situations[86] (Box 2.6).

Retrograde Intubation. For retrograde intubation,[87] local anesthesia is provided and the cricothyroid membrane is punctured by a needle through which a wire or catheter is passed upward through the vocal cords. The wire is visualized in the pharynx, brought out through the mouth, is used to guide the ET through the vocal cords, and then is withdrawn. This technique also can be used to guide a fiberoptic scope through the vocal cords. Owing to time constraints, it is not suitable for emergency airway access and is contraindicated in the presence of an expanding neck hematoma or coagulopathy.

Intubation Under Anesthesia

It may be decided, despite the safety advantage of awake intubation, to anesthetize the patient before attempted intubation. Preparation of the patient, equipment, and staff is paramount (Box 2.7). Adjuncts such as those described later should be available, either to improve the chances of intubation or to provide a safe alternative airway if intubation cannot be achieved.

Unanticipated Airway Difficulty

The DAS guidelines[85] focus on the unanticipated difficult airway, an unpredictable clinical problem. More focus is placed on the need to be prepared and accountable and to optimize conditions and reduce patient morbidity in this situation. Those involved in the airway management of critically ill individuals must be familiar with alternative airway devices and techniques, including when to perform emergency invasive airway access. The unanticipated difficult airway allows only a short period to solve the problem if significant hypoxemia, hypercarbia, and hemodynamic instability are to be avoided. The patient usually is anesthetized, may be apneic, and may have received muscle relaxants, and previous initial attempt(s) at intubation may have been unsuccessful. If appropriate equipment, assistance, and experience are not immediately at hand, little time is available to obtain them. Nevertheless, it is essential to maintain oxygenation and avoid hypercarbia if possible—commonly by mask ventilation with 100% oxygen. The four-handed technique often is used. Restoration of ventilation is the priority by either an SGA, an invasive intervention, or by wakening the patient if possible. The new DAS guidelines favor the use of second-generation SGAs as they have been designed to provide a better seal and reduce the risk of aspiration.

If the practitioner is inexperienced, if the patient has had no (or a relatively short-acting) muscle relaxant, and if ventilation is not a problem, it may be appropriate to let the patient recover consciousness. An awake intubation can then be planned either after a short period of recovery or on another occasion. With an experienced practitioner, it may be appropriate to continue using techniques to improve the chances of visualizing and intubating the larynx. As discussed next, various adjuncts may be useful in this situation and also in the anticipated difficult airway when it has been decided to intubate with the patient under anesthesia.

The U.K. Royal College of Anaesthetists Fourth National Audit Project (NAP4) provided significant insight into contemporary airway management by identifying several deficiencies that increase the risk of adverse outcomes relating to the airway in critically ill patients.[88] Failure to plan (ahead) appeared to be a common causative factor in a large number of poor airway outcomes. This was sometimes due to (1) poor assessment (no recognition that there was a potential problem needing a plan), (2) failure to plan even when potential problems were recognized, and (3) failure to have alternative plan(s) (in the event that "plan A" was not successful). Many poor outcomes are the result of repeated use of an approach that has already (sometimes repeatedly) failed. NAP4 revealed a number of scenarios or patient-related factors that seemed to predispose to poor airway outcomes. These predictors are summarized in Box 2.8.

• BOX 2.6 Indications for Fiberoptic Intubation

Anticipated difficult intubation
Avoidance of dental damage in high-risk patient
Direct laryngeal trauma
Other need for awake intubation

• BOX 2.7 Checklist for Anticipated Difficult Intubation of Patient Under General Anesthesia

- Prepare and assess the patient.
- Prepare and test the equipment.
- Ensure skilled assistance with knowledge of BURP/bimanual laryngoscopy.
- Have the following available:
  - A range of laryngoscopes including specialized blades and handles
  - Videolaryngoscope
  - A range of tracheal tubes lubricated and cuffs tested for patency (*women:* 7.0–7.5 mm in internal diameter; *men:* 7.5–9.0 mm in internal diameter)
  - Gum-elastic bougie or tracheal tube stylet
  - Supraglottic airways (LMA, ILMA)
  - Flexible fiberoptic intubation equipment
  - Equipment suitable for emergency invasive airway access
  - An exhaled carbon dioxide monitor
- Check battery and bulb function.
- Check functioning of suction devices.
- Use optimal patient position.
- Preoxygenation with 100% oxygen for 3 to 5 minutes if possible

BURP, B*ackward, upward, and rightward pressure.*

Strategies to Improve First-Attempt Success at Intubation in Critical Illness

Airway management in critically ill patients is high risk owing to both anatomic and physiologic characteristics that increase risk of complications, including aspiration, hypoxemia, hemodynamic compromise, hypoxic brain injury, and death.[89,90]

• BOX 2.8 Predictors for Poor Airway Outcomes

Use of a supraglottic airway (only) in patients with a recognized airway difficulty
Cases in which awake fiberoptic intubation was indicated, but not used
Failure to use capnography or failure to interpret capnography trace correctly
Airway maneuvers in obese patients, in the emergency department, or in the intensive care unit
Use of emergency cannula cricothyrotomy (60% failure rate)
Displacement of a tracheostomy tube
Events related to emergence, recovery, and extubation

Preoxygenation

The process of preoxygenation replaces the nitrogen-rich air in the alveoli with oxygen. Optimization of this may be suboptimal in critically ill patients who may have physiologic derangements, including high oxygen requirements, shunt physiology, and lack of cooperation, all of which may increase the possibility of hypoxemia. In addition to oxygen supplementation, 20-degree elevation of the head can improve preoxygenation and increase apnea time.[91] Noninvasive ventilation has also been used to improve preoxygenation before intubation in patients with obesity and shunt physiology.[92] A high-flow nasal cannula can provide humidified high-flow oxygen up to 70 L/min. It is being used increasingly in preoxygenation of patients and also in extubated patients.[93]

Bimanual Laryngoscopy

Application of pressure on the cricoid area or the upper anterior tracheal wall, or both, by the laryngoscopist (a technique sometimes termed bimanual laryngoscopy) may improve laryngeal view.[94,95] When the view is optimized by the laryngoscopist, an assistant maintains the pressure and thus the position of the larynx, freeing the hand of the laryngoscopist to perform the intubation. The use of "blind" cricoid pressure, or BURP (backward, upward, and rightward pressure), by an assistant may impair laryngeal visualization.[94,96,97] The use of cricoid pressure in the difficult intubation scenario has not been extensively studied and opinions remain divided on its effectiveness.

Stylet ("Introducer") and Gum Elastic Bougie

The *stylet* is a smooth, malleable metal or plastic rod that is placed inside an ET to adjust the curvature—typically into a J- or hockey-stick shape to allow the tip of the ET to be directed through a poorly visualized or unseen glottis. The stylet must not project beyond the end of the ET to avoid potential laceration or perforation of the airway.

The *gum elastic bougie* is a blunt-ended, malleable rod that during direct laryngoscopy may be passed through the poorly or nonvisualized larynx by putting a J-shaped bend at the tip and passing it blind in the midline upward beyond the base of the epiglottis. Then, keeping the laryngoscope in the same position in the pharynx, the ET can be "railroaded" over the bougie, which is then withdrawn. For many critical care practitioners, it is the first-choice adjunct in the difficult intubation situation.[95,98]

Different Laryngoscope or Blade

More than 50 types of curved and straight laryngoscope blades are available; the most commonly used is the curved Macintosh blade. Using specific blades in certain circumstances has been both encouraged and discouraged. In patients with a large lower jaw or "deep pharynx," the view at laryngoscopy is often improved significantly by using a size 4 Macintosh blade (rather than the more common adult size 3). This ensures the tip of the blade can reach the base of the vallecula to lift the epiglottis. Other blades, such as the McCoy, may be advantageous in specific situations.

Lighted Stylet

A lighted stylet (light wand) is a malleable fiberoptic light source that can be passed along the lumen of an ET to facilitate blind intubation by transillumination. It allows the tracheal lumen to be distinguished from the (more posterior) esophagus on the basis of the greater intensity of light visible through anterior soft tissues of the neck as the ET passes beyond the vocal cords.[99] In elective anesthesia, the intubation time and failure rate with light wand–assisted intubation were similar to those with direct laryngoscopy,[100] and in a large North American survey, the light wand was the preferred alternative airway device in the difficult intubation scenario.[101] A potential disadvantage is the need for low ambient light, which may not be desirable (or easily achieved) in a critical care setting.

Video Laryngoscopy

Guidelines for unanticipated difficult intubation emphasize the importance of the first attempt at laryngoscopy with the aim of plan A to maximize the likelihood of success at the first attempt or, failing that, to limit the duration and number of attempts at laryngoscopy. The role of video laryngoscopes in difficult intubation has been recognized by the DAS 2015 guidelines[85] and it is recommend that all anesthetists be trained in and have immediate access to them. Videolaryngoscopes provide a better view of the larynx than with a standard Macintosh blade (direct laryngoscopy).[102] The improved laryngeal view is a result of two factors: for videolaryngoscopes with Mactintosh-shaped blades, a camera on the distal end of the blade provides an increased field of view compared with direct laryngoscopy, whereas for videolaryngoscopes with extra curved blades, there is an increased capacity to "see around the corner" and gain a view normally beyond the standard Macintosh blade. They are proposed to have advantages as being less traumatic to the airways and having a higher rate of successful intubation when used as a rescue device if direct laryngoscopy fails.[103] They may be particularly useful in patients with cervical instability, either by providing a better glottic view or by a reduction in upper cervical movement during intubation.[104] However, an improved laryngeal view does not always equate to a successful intubation. Intubation time can also be prolonged with the videolaryngoscope, especially in inexperienced hands.[105]

Videolaryngoscopes may have training advantages—the trainer can observe the screen while the trainee performs a procedure and can help optimize blade position and advise the trainee in real time.

Fiberoptic Intubation

The fiberoptic bronchoscope can be used in the unanticipated difficult airway if it is readily available and the operator is skilled.[40,106,107] With an anesthetized patient, the technique may be more difficult. Loss of muscle tone tends to allow the epiglottis and tongue to fall back against the pharyngeal wall. This can be counteracted by lifting the mandible.

Cannot Intubate–Cannot Ventilate

A cannot intubate–cannot ventilate scenario is an uncommon but life-threatening situation best managed by adherence to an appropriate algorithm.[34,85] Fig. 2.5 presents a flow sheet summarizing the appropriate actions.[108]

All personnel involved will be pressured (and motivated) by the potential for severe injury to the patient. Efficient teamwork is more likely in an environment that is relatively calm. Although it may be difficult, shouting, impatience, anger, and panic should be avoided in such situations, whereas effective communication may be lifesaving (see "Human Factors").

Confirming Tube Position in the Trachea

A critical factor in the difficult airway scenario, potentially leading to death or brain injury, is failure to recognize misplacement of the ET. Attempted intubation of the trachea may result in esophageal

intubation. This alone is not life-threatening unless it goes unrecognized.[78] Thus confirmation of ET placement in the trachea is essential.

Visualizing the ET as it passes between the vocal cords into the trachea is the definitive means of assessing correct tube positioning. This may not always be possible, however, owing to poor visualization. In addition, the laryngoscopist may be reluctant to accept that the ET is not in the trachea. Several clinical observations support the presence of the ET in the trachea.

Chest wall movement with positive-pressure ventilation (manual or mechanical) is usual but may be absent in patients with chronic obstructive pulmonary disease, obesity, or decreased compliance (e.g., in severe bronchospasm). Although condensation of water vapor in the ET suggests that the expired gas is from the lungs, this also may occur with esophageal intubation. The *absence of water vapor* usually is indicative of esophageal intubation. *Auscultation of breath sounds* (in both axillae) supports correct tube positioning but is not absolute confirmation.[109] Apparent inequality of breath sounds heard in the axillae may suggest intubation of a bronchus by an ET that has passed beyond the carina. Of note, after emergency intubation and clinical confirmation of the ET in the trachea, 15% of ETs may still be inappropriately close to the carina.[110]

The use of capnography to detect $ETCO_2$ is the most reliable objective method of confirming tube position.[111] False-positive results may be obtained initially when exhaled gases enter the esophagus during mask ventilation[112] or (rarely) when the patient is generating carbon dioxide in the gastrointestinal tract (as with recent ingestion of carbonated beverages or bicarbonate-based antacids).[113] A false-negative result (ET in trachea but no carbon dioxide gas detected) may be obtained when pulmonary blood flow is minimal, as in cardiac arrest.[114] Visualizing the trachea or carina through a *fiberoptic bronchoscope,* which may be readily available in critical care, also will confirm correct placement of the ET.

Surgical Airway

The indication for a surgical airway is inability to intubate the trachea in a patient who requires it, and the techniques available are cricothyrotomy and tracheostomy.

Cricothyrotomy

Cricothryotomy may be performed as a percutaneous (needle) or open surgical procedure (Box 2.9). The indication for both these techniques is the cannot intubate–cannot ventilate situation. Although needle cricothyrotomy is an emergency airway procedure, the technique is similar to that for "mini-tracheostomy," which is performed electively. Unlike the other surgical airway techniques, a needle cricothyrotomy does *not* create a definitive airway. It will not allow excretion of carbon dioxide but will produce satisfactory oxygenation for 30 to 40 minutes. It can be viewed as a form of apneic ventilation (see later discussion). There are several methods of connecting the intravenous cannula to a gas delivery circuit with the facility to ventilate, using equipment and connections readily available in the hospital. The appropriate method thus should be thought out in advance with equipment available on the difficult airway trolley or bag. New commercial kits that come preassembled also are available.

A surgical cricothyrotomy allows a cuffed tube to be inserted through the cricothyroid membrane into the lower larynx or upper trachea. This allows positive-pressure ventilation for considerable periods and also protects against pulmonary aspiration.

• BOX 2.9 Procedure: Needle and Surgical Cricothyrotomy

The cricothyroid membrane is diamond-shaped and lies between the thyroid and the cricoid cartilages. Inject subdermal lidocaine and epinephrine (adrenaline) for local anesthesia.

Needle Cricothyrotomy

- Identify the cricothyroid membrane and the midline.
- Insert a 14-gauge intravenous cannula and syringe through the skin and membrane.
- Continuously apply negative pressure until air enters the syringe.
- Stop at this point and push the cannula off the needle into the trachea.
- The insertion of the cannula into the trachea allows apneic (low-pressure) ventilation or jet (high-pressure) ventilation.

Surgical Cricothyrotomy

- Make a 1.5-cm skin incision over the cricothyroid membrane.
- Incise the superficial fascia and subcutaneous fat.
- Divide the cricothyroid membrane (short blade, blunt forceps, or the handle of a scalpel often is used).
- Insert (size 6.0) cuffed tracheostomy tube through membrane between the thyroid and cricoid cartilages.

• BOX 2.10 Tracheostomy: Indications and Contraindications

Indications for Tracheostomy

Inability to maintain a patent airway
Suspected cervical spine instability (percutaneous technique only)
Prevention of damage to vocal cords and (possibly) subglottic stenosis
Abnormal anatomy (percutaneous only)
Upper airway obstruction
Requirement for tracheobronchial toilet with suctioning
Part of larger surgical procedure (e.g., laryngectomy)

Contraindications to Tracheostomy

Local inflammation
Bleeding disorder (relative)
Arterial bleeding in neck/upper thorax

Tracheostomy

A tracheostomy is an opening in the trachea—usually between the second and third tracheal rings or one space higher—that may be created surgically or made percutaneously.[115,116] The indications for and contraindications to tracheostomy are summarized in Box 2.10. Compared with long-term orotracheal or nasotracheal intubation, tracheostomy often contributes to a patient who is less agitated, requires less sedation, and who may be weaned from ventilation more easily.[33,117] This increased ability to wean is sometimes attributed to reduced anatomic dead space. The potential reduction in sedation after tracheostomy, however, is a much greater advantage to weaning than the small reduction in dead space. The benefits and complications of tracheostomy are listed in Box 2.11. Percutaneous tracheostomy is normally carried out by medical staff in the ICU (Box 2.12).

• BOX 2.11 Tracheostomy: Benefits and Complications

Benefits

Comfort
Reduced need for sedation
Improved weaning from ventilation
Improved ability to suction trachea
Prevention of ulceration of lips and tongue or healing of such ulcers
Reduced upper airway injury
Potential for speech and oral nutrition

Complications

Misplacement of tube
Primary hemorrhage
Pneumothorax or tension pneumothorax; hemothorax
Surgical emphysema
Infection
Late hemorrhage—erosion of innominate (or other) vessels
Tracheoesophageal fistula

• BOX 2.12 Procedure: Bronchoscopy-Assisted Percutaneous Tracheostomy

- Withdraw endotracheal tube until the cuff lies at or just below the cords.
- Pass a flexible bronchoscope down endotracheal tube to distal end.
- Make a 1.5- to 2-cm transverse incision at midpoint between cricoid cartilage and suprasternal notch.
- Strip away tissue down to pretracheal fascia using blunt dissection (forceps).
- Under direct vision, use a 14-gauge cannula to puncture anterior tracheal wall (in midline).
- Advance cannula into trachea, aspirate air, and insert Seldinger guidewire.
- Dilate around guidewire using dilator(s) or special forceps.
- Pass tracheostomy tube over guidewire into trachea.
- Pass bronchoscope through tracheostomy to check position.

Although no consensus exists on the definition of prolonged tracheal intubation, or when tracheostomy should be performed,[118] most ICUs convert the intubated airway to a tracheostomy after 1 to 3 weeks, with earlier tracheostomy increasingly favored in some patient subgroups.[119]

Conventional wisdom states that the procedure for tracheostomy is more complex and time-consuming than a surgical cricothyrotomy and should be performed only by a surgeon. Studies in the elective ICU situation suggest that cricothyrotomy is simpler and (at worst) has a similar complication rate.[120,121] Although needle cricothyrotomy has long been advocated as a lifesaving emergency intervention,[122] work suggests that surgical cricothyrotomy is the more advantageous procedure.[123] In patients with unfavorable anatomy, surgical cricothyrotomy is a viable alternative to elective tracheostomy.[120] Surgical cricothyrotomy has been viewed as a temporary airway that should be converted to tracheostomy within a few days, but it may be used successfully as a definitive (medium-term) airway,[124,125] thereby avoiding conversion from cricothyrotomy to tracheostomy, which can cause significant morbidity.[126,127]

Extubation in the Difficult Airway Patient (Decannulation)

The patient with a difficult airway still poses a problem at extubation, because reintubation (if required) may be even more difficult than the original procedure. Between 4% and 12% of surgical ICU patients require reintubation[128] and may be hypoxic, distressed, and uncooperative at the time of reintubation. The presence of multiple risk factors for difficult intubation,[81] as well as acute factors such as airway edema and pharyngeal blood and secretions, makes reestablishing the airway in such patients challenging. Before extubation of any critical care patient, the critical care team should have formulated a strategy that includes a credible plan for reintubation.

Tube Displacement in the Critical Care Unit

Endotracheal Tube

ET displacement in the ICU is a life-threatening emergency that may result in significant morbidity.[129] Although tube dislodgment sometimes is viewed as unavoidable, often preventable factors are involved.[130–132] Changes in patient posture or head position cause significant movement of the tube within the trachea.[133] The frequency of tube displacement can be reduced by good medical and nursing practice,[134] attention to the arrangements and ergonomics around the bed, achieving appropriate sedation levels, and ensuring adequate ICU nurse staffing.[135,136] Experience and the ability to anticipate possible glitches constitute an important part of prevention. The management of ET displacement starts with an assessment of whether the patient can manage without the ET.[132] If replacement is required, preparations for a potentially difficult reintubation are indicated.

Tracheostomy Tube

Adverse events with tracheostomy tubes are quite common.[132,137] Displacement may be a life-threatening event,[138] especially if the tube has been in place less than 5 to 7 days (before a well-defined tract between skin and trachea is formed) or if the procedure has been performed percutaneously (so that the external opening of the tract may not easily admit a new tube of the same size). The option to leave the patient without a tube should be considered, and if this option is pursued, the tracheostomy opening should be dressed to make it (to some degree) "airtight"—thus facilitating effective coughing. If the patient needs a tube but replacing the tracheostomy is not possible, then oral reintubation should be performed, after which the tracheostomy should be dressed. With a more mature tracheostomy (>7 days old), it usually is possible to insert a new tube through the mature tract between skin and trachea.

Tracheostomy tubes may be displaced from the lumen of the trachea but appear to be normal when viewed externally. Difficulty with breathing, ventilation, or tracheal suctioning or the presence of a pneumothorax, pneumomediastinum, or surgical emphysema may be due to tracheostomy tube displacement. Fiberoptic assessment of the tube position and patency may be very useful. Assessing tracheostomy tube position on the chest x-ray film is of no value.

Human Factors

Many challenging airway scenarios are predictable and are successfully managed using a plan drawn up by the clinician(s) involved.

Sometimes, however, the problem is unrecognized until the situation is potentially life-threatening, or the airway management plan does not deliver the expected outcome/solution. In such crises, a successful outcome depends not only on the knowledge and skill of the clinicians but also on the human factors influencing the entire clinical team.

Human factors (sometimes termed *ergonomics*) is the scientific discipline concerned with understanding the interactions of humans, environment, and other elements of a system. We can enhance clinical performance through an understanding of the effects of teamwork, tasks, equipment, workspace, culture, and organization on human behavior and abilities and applying that knowledge in clinical settings.[139] The outcome of all emergency situations may be influenced significantly by the behaviors of the entire team with success depending on factors such as situational awareness, authority gradient, and (avoiding) cognitive overload. The well-documented case of Elaine Bromiley[140,141] shows how unfavorable human factors can lead to a bad outcome despite the presence of well-trained, highly motivated, and caring professionals. Successful management of all challenging clinical problems, including the difficult airway, starts by building a team culture of openness, mutual respect, and collective leadership. Although this takes time, failure to do so will result in a team that is unlikely to perform at its best under pressure.

Common Problems in Airway Management

• PROBLEM 2.1 Ineffective (Spontaneous) Breathing Despite Artificial Airway

Underlying Causes

1. Obstructed airway
2. Depressed respiratory drive (influence of drugs)
3. Inefficient respiratory effort (e.g., from fractured ribs or diaphragmatic injury)
4. Pulmonary pathologic process (pneumonitis, contusion, collapse, consolidation)

Action

Attempt to deliver 100% oxygen. Check airway. When airway obstruction has been corrected or ruled out, the patient's respiratory status should improve unless another underlying pathologic process is present. If no improvement is obtained, manually ventilate the patient. If the respiratory status still fails to improve, proceed to tracheal intubation with manual or mechanical ventilation. Investigate and treat any underlying condition.

• PROBLEM 2.2 Ineffective Manual Ventilation Despite Artificial Airway

Potential Causes

1. Obstructed airway
2. Poor seal or poor technique with mask or manual ventilation
3. Pulmonary pathologic process (pneumonitis, contusion, collapse, consolidation)

Action

Attempt to deliver 100% oxygen at 15–20 L/min. Check and readjust airway and patient head position. When airway obstruction has been corrected or ruled out, use a two-handed approach for mask and airway with an assistant squeezing the bag. If no improvement is obtained, check for availability of someone with more airway experience. If no such person is available, proceed to tracheal intubation with manual or mechanical ventilation. Investigate and treat any underlying condition.

• PROBLEM 2.3 Unilateral Chest Movements in the Intubated Ventilated Patient

Potential Causes

1. Bronchial intubation
2. Bronchial obstruction
3. Lung collapse, pneumothorax
4. Hemothorax, pleural effusion
5. Consolidation, absent lung (pneumonectomy)

Action

If bronchial intubation is suspected, deflate the tracheal tube cuff and slowly withdraw the tube 1–2 cm. Reinflate the cuff, and manually ventilate the patient while auscultating both sides of the chest. Is air entry present and equal on both sides? Be suspicious if the tube has to be withdrawn more than 3–4 cm or if the tube length at the teeth is much less than the expected correct length; another underlying cause may be involved. In an adult, the average distance from the vocal cords to the carina is 12 cm. The tip of a size 8.0 (adult) tracheal tube typically is 6.5 cm below the upper surface of the balloon, which must sit below the vocal cords. Therefore if the upper surface of a cuff is only 3 cm below the vocal cords, the tip will be within 2–3 cm of the carina. It is easy to inadvertently intubate a bronchus or leave the tip of the tube close enough to enter the bronchus with head movement or when moving the patient. In adults with normal bronchial anatomy, the tube tip usually will pass into the right main bronchus.

• PROBLEM 2.4 Sudden Airway or Ventilatory Compromise in Ventilated Patient With Orotracheal Tube

A ventilated patient with an orotracheal tube in place may suddenly develop dyspnea, hypoxemia, hypercarbia, and a seesaw respiratory pattern. The mechanical ventilator alarm will sound.

Potential Causes

1. Failure of oxygen or air supply to the ventilator
2. Ventilator disconnection or obstruction in ventilator circuit
3. Obstructed tracheal tube
   - Plugged by mucus or clot
   - Kink in tracheal tube
   - Biting on tube (previous biting may have narrowed the tube)
   - Obstruction of tube tip by side wall of lower airways or carina
4. Patient's fighting against ventilator
5. Respiratory fatigue (e.g., with weaning from mechanical support or new infection)
6. Pneumothorax or tension pneumothorax
7. Rapid development of large hemothorax or pleural effusion

Action

Disconnect the patient from the ventilator and ventilate through the tracheal tube manually. Have the ventilator and circuit checked by another appropriate staff member. High resistance or inability to inflate the lungs suggests tube obstruction or an intrathoracic problem. The (recent) inability to pass a suction catheter down the lumen is suggestive of tube obstruction. If the patient's condition is stable or improving, a small fiberoptic bronchoscope or laryngoscope (if readily available) may be passed down the tube. An obstruction may be removed by suction catheter, or removal of the tube and use of mask ventilation (to reverse hypoxemia and hypercarbia) followed by reintubation, may be required. If no answer to the problem is found, consider whether the patient's condition could be due to a tension pneumothorax. If appropriate, use needle decompression. Otherwise, order an emergency chest film and continue either manual or mechanical ventilation as appropriate.

• PROBLEM 2.5 Sudden Airway or Ventilatory Compromise in Ventilated Patient With Tracheostomy

A ventilated patient with a tracheostomy may suddenly develop dyspnea, hypoxemia, hypercarbia, and a seesaw respiratory pattern. The mechanical ventilator alarm will sound.

Potential Causes

Causes may include all those listed for Problem 2.4.

Action

Appropriate interventions are the same as for Problem 2.4, with an appreciation of the fact that tracheostomy tubes are shorter, more curved, and more rigid than tracheal tubes. They rarely kink but may become blocked with secretions or blood.[31,178] Suctioning the tube may resolve this. Double-skinned tracheostomy tubes may be unblocked by removing the inner tube (containing the obstruction) for washing, leaving the outer tube in place to maintain a clear airway. Such double-skinned tubes are safer for patients discharged to general wards. Tracheostomy tubes also may become obstructed when the distal opening is blocked by a mucosal flap, the side wall of the trachea, or (rarely) the carina.

Key Points

- The difficult airway may be unanticipated despite expert preassessment. All critical care physicians should be familiar with unanticipated difficult intubation guidelines.
- Use of the appropriate size and type of laryngoscope blade in conjunction with other adjuncts and techniques is an important element of successful tracheal intubation—particularly with the unanticipated difficult airway.
- Airway difficulty in critical care is common and may be precipitated long after intubation by acute events such as tube dislodgment or obstruction.
- Tube dislodgment in critical care is potentially avoidable and may be influenced by staffing levels, sedation policy, and other bedside factors.
- Surgical cricothyrotomy is a relatively simple procedure and may be used to establish a medium-term airway, avoiding the need for tracheostomy.
- In critical care, removal of a tracheal tube may precipitate an acute difficult airway scenario. A protocol for handling a difficult reintubation should always be in place.
- Knowledge and application of human factors are an important element of managing the difficult airway.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. A 36-year-old female is admitted via the emergency department with a severe headache and altered level of consciousness. On your arrival, she vomits, becomes obtunded, and is unable to protect her airway. Which one of the following statements is most correct?

a. Removal of vomit can only be performed using a flexible suction catheter via the nose and nasopharynx.
b. The triple airway maneuver is the most appropriate airway intervention if there are concerns regarding the stability of the cervical spine.
c. A finger sweep of the pharynx can be useful in clearing the airway in a patient with an intact gag.
d. The triple airway maneuver consists of head tilt/neck extension, jaw thrust/pulling mandible forward and opening the mouth

Answer: d. Vomitus can be removed using a rigid suction catheter and a laryngoscope if required. The triple airway maneuver should *not* be used if there are concerns regarding cervical instability, and an approach that maintains in-line immobilization approach should be used. A finger sweep is recommended only in patients with an impaired gag reflex. The triple airway maneuver can be beneficial in the early management of the airway in an obtunded patient.

2. Which one of the following is *not* a contraindication to an oropharyngeal airway?

a. Airway swelling
b. Vomiting
c. Fracture of the base of skull
d. Inhalation injury

Answer: c. Contraindication to an oropharyngeal airway includes inability to tolerate, which includes vomiting and any cause of airway swelling. Fracture of the base of skull is a contraindication to a *naso*pharyngeal airway (see Box 2.1).

3. It is decided that tracheal intubation is required as the patient's condition continues to deteriorate. Initial laryngoscopy views are suboptimal. Which of the following statements is most correct?

a. Neuromuscular blockade may be detrimental.
b. Appropriate oxygenation and anesthesia must be maintained.
c. Four attempts at direct laryngoscopy should be attempted.
d. A bougie is contraindicated in the difficult airway.

Answer: b. Appropriate oxygenation and anesthesia are vital in the management of an unanticipated difficult tracheal intubation. Lack of full neuromuscular blockade may be a cause of suboptimal view at laryngoscopy. Three attempts at direct laryngoscopy are recommended according to the Difficult Airway Society guidelines. A bougie can be a helpful tool in these circumstances (see Fig. 2.5).

4. An endotracheal tube is inserted. What method is best routinely to ascertain that the tube is in the correct position?

a. Chest wall movement with positive-pressure ventilation
b. End-tidal carbon dioxide ($ETCO_2$) monitoring
c. Visible condensation in the endotracheal tube
d. Auscultation of breath sounds bilaterally

Answer: b. $ETCO_2$ monitoring is the most objective reliable way of confirming tube positon. Bronchoscopy via the tracheal tube can be used but is not always available and may be time-consuming. Chest wall movement with positive-pressure ventilation is not reliable in certain lung conditions, including pneumothorax. There may be no condensation in the endotracheal tube even if appropriately placed. Breath sounds may be diminished with a pleural effusion, collapse, or pneumothorax.

3

Assessment of Cardiac Filling and Blood Flow

MARTIN GEISEN, MAURIZIO CECCONI, AND ANDREW RHODES

CHAPTER OUTLINE

Cardiac Filling
- Preload
- Contractility
- Afterload
- Clinical Limitations of Systemic Vascular Resistance and Pulmonary Vascular Resistance
- Clinical Interpretation of Indicators of Preload

Hemodynamic Status and Blood Flow
- Measurement of Cardiac Output
- Assessment of Adequacy of the Circulation

Conclusions

The accurate assessment and manipulation of the circulation are important parts of the management of critically ill patients. The principal objective of cardiorespiratory manipulation is to ensure optimal oxygen delivery. Adequate cellular respiration, adequate delivery of substrates and pharmaceuticals, and improved organ function is possible only when this has been achieved. This chapter deals with the physiologic principles governing the cardiovascular system and discusses interpretation of hemodynamic data in a clinical context. With the increasing number of medical devices available to monitor the circulation, this chapter also outlines the principles underlying the design and function of these devices, as well as their uses and limitations (Tables 3.1–3.4).

Cardiac Filling

One of the fundamental concepts in optimizing the circulation of a critically ill patient is the manipulation of cardiac output as a major determinant of blood flow and oxygen delivery. Cardiac output is defined as the product of stroke volume (SV) and heart rate (HR). Although options to control HR are limited, clinical studies have largely focused on interventions to increase SV. The SV of the heart is determined by the complex interaction of three components: preload, contractility, and afterload. A thorough understanding of the physiology and pathophysiologic principles that define these components is essential for the clinician to successfully control and improve cardiovascular dynamics.

Our current understanding of the relationship between preload and contractility and their effect on SV is based on the experiments of Dario Maestrini, Otto Frank, and Ernest Starling, culminating in Starling's "law of the heart," which states that the force of myocardial contraction is directly proportional to the end-diastolic myocardial fiber length (or "preload"), as determined by the ventricular end-diastolic volume (EDV).[1,2] It is this relationship, commonly known as the Frank-Starling mechanism, that matches venous return to cardiac output (Fig. 3.1).

The most common intervention used by clinicians to improve SV—the administration of fluids—is aimed at increasing venous return as a main determinant of EDV. In this regard, two factors are important to consider: the position of an individual heart on the Frank-Starling curve and the expected response to fluid administration, as well as giving the right amount of fluid in an appropriate time frame to achieve a hemodynamic response. The dynamics of venous return have been extensively described by Arthur Guyton, whose theories contribute to our current understanding of the circulation and may help to optimize venous return.[3,4]

Preload

Based on Ernest Starling's observations, preload is defined as the tension developed by the stretch of the myocardial fibers. An increase in venous return leads to an increase in EDV, which in turn increases myocardial sarcomere length, resulting in an increase of contractility and a rise in SV and cardiac output. Conversely, a decrease in venous return will reduce EDV, resulting in a decreased SV and cardiac output. This mechanism matches the mechanical activity of both ventricles under changing physiologic conditions and functions independent of nervous supply to the flow of blood back to the heart from the venous system (venous return).

Preload is determined by the following factors:

- Circulating blood volume
- Venous capacitance (i.e., sympathetic stimulation resulting in venoconstriction, mechanical compression)
- Posture: The Trendelenburg position (supine, head down) increases venous return. Clinically, a passive leg-raising test may be performed to assess volume responsiveness by autotransfusion of approximately 300 mL of blood from the splanchnic and lower limb compartments to the central circulation, increasing preload.
- Intracavitary pressures: Abdominal hypertension and increased intrathoracic pressures (i.e., during positive-pressure ventilation

TABLE 3.1 Primary Measured Hemodynamic Data

Parameter/Formula	Normal Range
Arterial blood pressure (BP)	
Systolic (SBP)	90–140 mm Hg
Diastolic (DBP)	60–90 mm Hg
Mean arterial pressure (MAP): [SBP + (2 × DBP)]/3	70–105 mm Hg
Right atrial pressure (RAP)	2–6 mm Hg
Right ventricular pressure (RVP)	
Systolic (RVSP)	15–25 mm Hg
Diastolic (RVDP)	0–8 mm Hg
Pulmonary artery pressure (PAP)	
Systolic (PASP)	15–25 mm Hg
Diastolic (PADP)	8–15 mm Hg
Mean pulmonary artery pressure (MPAP): [PASP + (2 × PADP)]/3	10–20 mm Hg
Pulmonary artery occlusion pressure (PAOP)	6–12 mm Hg
Left atrial pressure (LAP)	6–12 mm Hg
Cardiac output (CO): HR × SV/1000	4.0–8.0 L/min

HR, Heart rate; *SV,* stroke volume.

TABLE 3.2 Derived Hemodynamic Data

Derived Parameter/Formula	Normal Range
Cardiac index (CI): CO/BSA	2.5–4.0 L/min per m^2
Stroke volume (SV): CO/HR × 1000	60–100 mL/beat
Stroke volume index (SVI): CI/HR × 1000	33–47 mL/m^2 per beat
Systemic vascular resistance (SVR): 80 × (MAP – RAP)/CO	1000–1500 dyne • s/cm^5
Systemic vascular resistance index (SVRI): 80 × (MAP – RAP)/CI	1970–2390 dyne • s/cm^5 per m^2
Pulmonary vascular resistance (PVR): 80 × (MPAP – PAOP)/CO	<250 dyne • s/cm^5
Pulmonary vascular resistance index (PVRI): 80 × (MPAP – PAOP)/CI	255–85 dyne • s/cm^5 per m^2

BSA, Body surface area; *CO,* cardiac output; *HR,* heart rate; *MAP,* mean arterial pressure; *MPAP,* mean pulmonary artery pressure; *RAP,* right atrial pressure; *PAOP,* pulmonary artery occlusion pressure.

TABLE 3.3 Hemodynamic Parameters: Adults

Parameter/Formula	Normal Range
Left ventricular stroke work (LVSW): SV × (MAP – PAOP) × 0.0136	58–104 g-m/beat
Left ventricular stroke work index (LVSWI): SVI × (AP – PAOP) × 0.0136	50–62 g-m/m^2 per beat
Right ventricular stroke work (RVSW): SV × (MPAP – RAP) × 0.0136	8–16 g-m/beat
Right ventricular stroke work index (RVSWI): SVI × (MPAP – RAP) × 0.0136	5–10 g-m/m^2 per beat
Coronary artery perfusion pressure (CPP): Diastolic BP – PAOP	60–80 mm Hg
Right ventricular end-diastolic volume (RVEDV): SV/EF	100-160 mL
Right ventricular end-systolic volume (RVESV): EDV – SV	50–100 mL
Right ventricular ejection-fraction (RVEF): SV/EDV	40%–60%

BP, Blood pressure; *EDV,* end-diastolic volume; *EF,* ejection fraction; *MAP,* mean arterial pressure; *MPAP,* mean pulmonary artery pressure; *PAOP,* pulmonary artery occlusion pressure; *RAP,* right atrial pressure; *SV,* stroke volume; *SVI,* stroke volume index.

and application of positive end-expiratory pressure [PEEP]) can oppose venous return.
- Ventricular compliance: Ventricular compliance determines the relationship between EDV and end-diastolic pressure (i.e., diastolic dysfunction or impaired relaxation as in ventricular hypertrophy).
- HR: The filling time influences EDV.
- Atrial contraction: Atrial contraction contributes to EDV and may be impaired (i.e., in atrial fibrillation).

Indicators of Preload

In vivo measurement of sarcomere length is not possible. To assess this variable in the clinical setting, ventricular end-diastolic pressures have been traditionally used as surrogate parameters to estimate EDV. Although EDV can be assessed by echocardiography, continuous monitoring of this parameter is usually not possible. Static indices of preload include traditional parameters assessing filling pressures or volumes as well as parameters derived from techniques based on thermodilution (see later text), which have been classified as volumetric indices of preload. In addition, parameters based on the cyclic changes in intrathoracic pressure during mechanical ventilation have been described as estimates of preload responsiveness under certain circumstances, although they do not measure preload per se. These dynamic indices of preload can play a role in predicting an increase of SV after an increase of preload, or in other words, the "fluid responsiveness" of the ventricle.

Static Indicators of Preload

These parameters give an estimate of preload, but their ability to predict a response to fluid administration is limited. Static preload indices have been defined for both sides of the heart:

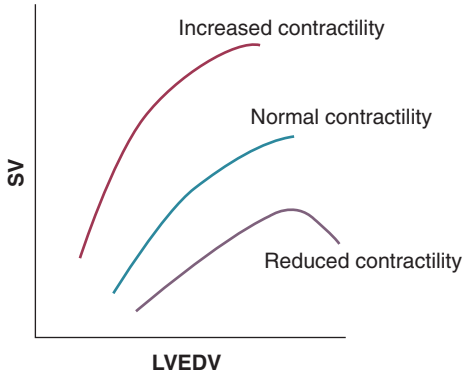
Static indices of the left side of the heart:
- Left ventricular end-diastolic volume (LVEDV)
- Left ventricular end-diastolic pressure (LVEDP)
- Left atrial pressure (LAP)
- Pulmonary artery occlusion or "wedge" pressure (PAOP or PAWP)

Static indices of the right side of the heart:
- Right ventricular end-diastolic volume (RVEDV)
- Right ventricular end-diastolic pressure (RVEDP)
- Right atrial pressure (RAP)
- Central venous pressure

TABLE 3.4 Oxygenation Parameters: Adults

Parameter/Formula	Normal Range
Partial pressure of arterial oxygen (Pao_2)	80–100 mm Hg
Partial pressure of arterial carbon dioxide ($Paco_2$)	35–45 mm Hg
Bicarbonate (HCO_3^-)	22–28 mEq/L
pH	7.38–7.42
Arterial oxygen saturation (Sao_2)	95%–100%
Mixed venous oxygen saturation (Svo_2)	60%–80%
Arterial oxygen content (Cao_2): (0.0138 × Hb × Sao_2) + (0.0031 × Pao_2)	17–20 mL/dL
Venous oxygen content (Cvo_2): (0.0138 × Hb × Svo_2) + (0.0031 × Pvo_2)	12–15 mL/dL
Arteriovenous oxygen content difference [$C(a-v)o_2$]: $Cao_2 - Cvo_2$	4–6 mL/dL
Oxygen delivery (Do_2): $Cao_2 \times CO \times 10$	950–1150 mL/min
Oxygen delivery index (Do_2I): $Cao_2 \times CI \times 10$	500–600 mL/min per m^2
Oxygen consumption (Vo_2): $C(a-v)o_2 \times CO \times 10$	200–250 mL/min per m^2
Oxygen consumption index (Vo_2I): $C(a-v)o_2 \times CI \times 10$	120–160 mL/min per m^2
Oxygen extraction ratio (O_2ER): [($Cao_2 - Cvo_2$)/Cao_2] × 100	22%–30%
Oxygen extraction index (O_2EI): [($Sao_2 - Svo_2$)/Sao_2] × 100	20%–25%

CI, Cardiac index; *CO,* cardiac output; *Cvo_2,* mixed venous oxygen content; output; *Hb,* hemoglobin.



• **Fig. 3.1** Graph demonstrating the Frank-Starling principle: the effect of preload on stroke volume in three different myocardial contractility states. *LVEDV,* Left ventricular end-diastolic volume; *SV,* stroke volume.

It is generally postulated that EDVs correspond to myocardial sarcomere length just before ventricular contraction and that end-diastolic pressures correspond with EDVs.

For the left side of the heart these relationships are as follows:

$$PAOP = LAP = LVEDP \approx LVEDV$$

For the right side of the heart these relationships are as follows:

$$CVP = RAP = RVEDP \approx RVEDV$$

It is important to note that these assumptions do not hold true in most clinical conditions and all parameters are influenced by physiologic and technologic factors. Ventricular pressures and volumes are both influenced by ventricular compliance, so there is only a poor relationship between the two, and the traditional assumption that CVP, RAP, PAOP, and LAP estimate LVEDP as an indicator of LVEDV is usually not valid. PAOP reflects left ventricular function only if the vascular system between the catheter tip and the left ventricle is free from any pathologic condition that could influence the pressures detected by the catheter.

PAOP *overestimates* LVEDP in the following conditions:

- Chronic mitral stenosis
- PEEP
- Left atrial myxoma
- Pulmonary hypertension

PAOP *underestimates* LVEDP in the following conditions:

- Poorly compliant left ventricle
- LVEDP greater than 25 mm Hg

PAOP readings are accurate only if the tip of the pulmonary artery catheter (PAC) is appropriately wedged in West lung zone 3, corresponding to the lower third of the lung where continuous blood flow can be assumed.

The PAOP does not predict preload and bears little or no relationship to the subsequent response to a volume challenge. It is important to realize, however, that pressure is one of the driving forces responsible for edema formation in the lungs. In this regard, the PAOP may function as more of a safety limit rather than as a guide to therapy.[5]

The CVP reflects RAP and has been traditionally used as a marker of right ventricular preload and, assuming a relationship among CVP, RVEDP, and RVEDV, of left ventricular preload. However, CVP does not accurately reflect left ventricular preload and has been shown to correlate poorly with blood volume. The main clinical value of measuring CVP is to provide information about the right side of the heart, as in cases of right ventricular failure or in assessing the right ventricular response to pulmonary hypertension. A low CVP in the setting of clinical signs of tissue hypoperfusion may be predictive of a benefit from fluid administration, and a rapid significant rise of CVP during a fluid challenge may indicate that the heart is not fluid responsive.[6]

Volumetric Indicators of Preload

Based on cardiac output measurements using thermodilution and incorporating indicator passage times, volumetric preload parameters have been introduced as an alternative to conventional "static" parameters and have become available with thermodilution-based monitoring techniques marketed by a number of companies. The continuous end-diastolic volume index is a surrogate of RVEDV. Global end-diastolic volume index, intrathoracic blood volume index, and extravascular lung water index are parameters provided by devices that require transpulmonary thermodilution for the measurement of cardiac output based on pulse pressure analysis. The global end-diastolic volume index represents the total intracardiac volume, and the volume of the descending aorta has been shown to be a better indicator of preload than CVP.[7]

Dynamic Indicators of Preload (or Preload Responsiveness)

Based on the study of heart-lung interactions a number of so-called dynamic preload indicators have been described. Although these

parameters are not measures of preload per se, they play an important role in the prediction of the hemodynamic response (i.e., by an increased cardiac output) to an increase in preload (preload or "volume" responsiveness). Generally, these parameters are based on the observation that transient changes in preload occur during mechanical ventilation.[8,9]

Stroke Volume Variation

During mechanical ventilation each positive-pressure breath induces a decrease in venous return. In conditions of decreased volume status, when the right ventricle is responsive to an increase in preload, a reduction in right ventricular outflow will occur and result in a decrease of left ventricular preload after the number of cardiac cycles it takes to pump blood through the lung (pulmonary transit time). If the left ventricle is preload responsive as well, a transient decrease in SV will occur. This cyclic variation in SV (stroke volume variation, SVV) can indicate volume responsiveness if it reaches a certain degree and may describe the response to a volume challenge in relation to changes in cardiac output.

Pulse Pressure Variation

Similar to SVV, a marked respiratory variation of the arterial pulse pressure (pulse pressure variation, PPV) has been found to accurately predict volume responsiveness.

SVV, PPV, and systolic pressure variation (SPV) can be automatically calculated by an array of cardiac output monitors.

Plethysmographic Variability Index

The pulse oximeter plethysmographic waveform has been shown to display respiratory variations during mechanical ventilation, which can be predictive of volume responsiveness. Calculation of the plethysmographic variability index (PVI) is performed by measuring changes of the perfusion index (PI = pulsatile infrared signal/nonpulsatile infrared signal × 100) over at least one respiratory cycle.[9]

Indices Derived by Echocardiography

Finally, respiratory variations of the inferior vena cava diameter as measured by transthoracic echocardiography or the superior vena cava (SVC) diameter as measured by transesophageal echocardiography (TEE) have been shown to accurately predict volume responsiveness.

It is important to note that these variables are reliable only during controlled mechanical ventilation. Other conditions in which the use of these parameters cannot be advised are as follows:

- Cardiac arrhythmias
- Application of low tidal volumes (i.e., <8 mL/kg)
- Open chest conditions
- Right ventricular failure

Contractility

Ventricular contractility, or inotropy, describes the strength of ventricular contraction. It is defined as the tension developed by myocardial fibers at a given preload and afterload and the velocity of the shortening of the myocardial sarcomeres. It represents the intrinsic ability of the myocardium to generate a force independent of filamental stretch or ventricular loading conditions. Contractility is influenced by the following factors:

Factors that *increase* myocardial contractility:

- Circulating catecholamines
- Drugs (inotropes, digoxin, calcium solutions)
- Metabolic state (i.e., hyperthermia)
- Sympathetic nervous system activity
- Increased HR

The following factors *reduce* myocardial contractility:

- Hypoxia or hypercapnia
- Metabolic state (acidosis, hypothermia, hyperkalemia, hypocalcemia)
- Drugs (e.g., β-adrenergic receptor antagonists, digoxin)
- Acute and chronic cardiomyopathies
- Parasympathetic nervous system activation

Contractility is difficult to assess in the clinical setting. The temporal rate of change of ventricular pressure (dP/dt) and its maximum value (peak dP/dt) can be derived invasively (i.e., in the cardiac catheterization laboratory) or estimated less invasively with varying accuracy by echocardiography and some cardiac output monitoring devices. This parameter has been shown to be related to ventricular function in clinical studies. Echocardiography provides additional functional assessment of ventricular wall motion and blood velocity kinetics. Parameters such as the fractional area change and ejection fraction (EF) are not accurate measures of contractility but are related to the contractile state of the myocardium and can be used to guide therapy.[10]

Afterload

The afterload of the heart may be considered as the ventricular wall tension required to eject the SV during systole. According to the law of Laplace, afterload relates to the stress within the wall of the ventricle developing during systolic ejection:

$$T = (P \times r)/2,$$

where T is tension, P is intraventricular pressure, and r is the intraventricular radius. In this equation, afterload is mainly dependent on wall thickness and ventricular radius. At a given pressure, an increase in ventricular radius (i.e., dilatation of the ventricle) will increase afterload. An increase in wall thickness (i.e., ventricular hypertrophy) will reduce afterload.

Afterload for the left ventricle is increased by the following factors:

- Anatomic obstruction (e.g., aortic valve stenosis, subvalvular obstruction)
- Raised systemic vascular resistance (SVR)
- Decreased elasticity of the aorta and great vessels
- Increased ventricular volume

Afterload for the right ventricle is increased by the following factors:

- Anatomic obstruction (e.g., pulmonary valve stenosis)
- Raised pulmonary vascular resistance (PVR) (e.g., pulmonary hypertension, pulmonary embolism, hypoxia, and hypercarbia)
- Increased ventricular volume

The *Anrep effect* describes an intrinsic regulatory mechanism of the heart in response to an acute increase in afterload, which results in an initial reduction in SV followed by an increase in EDV, which restores the SV toward near-normal values.

Indicators of Afterload

SVR and PVR are the most commonly used indicators of afterload in the clinical setting for the left and right ventricle, respectively. Vascular resistance can be described as the mechanical property of the vascular system opposing flow of blood into a vascular bed. There are two main components of vascular resistance:

- *Flow component*—frictional opposition to blood flow through the vessels, with blood viscosity being the major determinant. Vascular resistance increases with an increase in viscosity.
- *Frequency-dependent or "reactive" component*—related to the compliance of the vessel walls and the inertia of the ejected blood. A low vascular compliance increases vascular resistance.

SVR and PVR cannot be measured directly and thus are calculated from Ohm's law:

$$V = I \times R,$$

where V is voltage, I is current, and R is resistance. Applied to cardiovascular physiology this principle looks as follows:

$$\Delta P = CO \times R,$$

in which ΔP is the pressure gradient, CO (cardiac output) is "flow," and R is the resistance.

SVR is calculated as follows:

$$SVR\left(\text{dyne} \bullet \frac{s}{cm^5}\right) = 80 \times \frac{MAP - RAP}{CO},$$

where MAP is mean arterial pressure (mm Hg), RAP is right atrial pressure (mm Hg), and CO is cardiac output. To convert from mm Hg to dyne × s/cm^5 the multiplication by 80 is necessary. Normal values for SVR range from 800 to 1200 dyne × s/cm^5. If standardized to body surface area, SVR is quoted as SVRI (SVR index) with normal values for SVRI ranging from 1900 to 2400 dyne × s/cm^5 per m^2.

The following factors affect SVR:

- *Vessel diameter:* According to the law of Hagen-Poiseuille resistance is inversely related to the fourth power of the radius. This means that a decrease in vessel diameter during vasoconstriction will result in a significant increase in SVR. Vasodilation decreases SVR.
- *Compliance* of the systemic circulation
- *Blood viscosity and hematocrit*

In the same way as SVR, PVR may be calculated using the pressure differential across the pulmonary vasculature, between the mean pulmonary artery pressure (MPAP) and PAOP:

$$PVR\left(\text{dyne} \times \frac{s}{cm^5}\right) = 80 \times \frac{MPAP - PAOP}{CO}$$

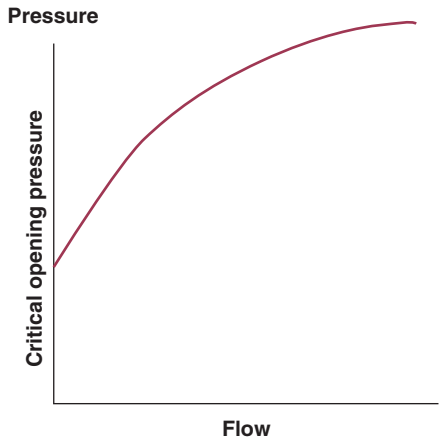
Values for PVR are normally below 250 dyne × s/cm^5. Again, PVR is often quoted as the PVR index (PVRI) with a normal range between 255 and 285 dyne × s/cm^5 per m^2.

The following factors affect PVR:

- *Vessel diameter:* Pulmonary vasoconstriction increases PVR (i.e., during hypoxia), and vasodilation reduces PVR.
- *Positive-pressure ventilation* increases PVR.
- *Established pulmonary hypertension* increases PVR.
- *Compliance* of the pulmonary circulation affects PVR.
- *Blood viscosity and hematocrit* affect PVR.

Clinical Limitations of Systemic Vascular Resistance and Pulmonary Vascular Resistance

Although the concept of vascular resistance permits an intuitive understanding of the circulation, a number of limitations make it unreasonable to use SVR and PVR to guide therapy. First, because SVR and PVR are derived variables, errors inherent in the measurement of their components (i.e., filling pressures) are multiplied, making the derived number less accurate. Further, these calculations assume a linear relation between pressure and flow, which does not exist in vivo (Fig. 3.2). It is therefore wise to use these parameters with caution and consider their limitations in clinical practice.



• **Fig. 3.2** Relationship among pressure, flow, and resistance. The critical opening pressure reflects the pressure in the vasculature at zero flow. The important point to recognize is that this is not at the origin of the graph. This means that even when the flow is zero, a baseline pressure exists. Estimating systemic vascular resistance by calculating the gradient of pressure and flow for any given point will therefore be inaccurate, because the "line" is actually nonlinear and does not go through the zero origin.

Clinical Interpretation of Indicators of Preload

It has already been stressed that accurate assessment of the preload status of the heart is important as it allows for the application of interventions that may improve cardiovascular dynamics. However, without knowing whether the heart will respond to an increase of a certain status of volume or preload, this information is of limited value. This concept—the individual response of cardiac output to a volume challenge—has become known as *volume responsiveness.*[8] Intravascular volume expansion is often the initial intervention in patients with circulatory failure. However, only approximately 50% of patients given a fluid challenge will respond by increasing cardiac output. The ability to distinguish fluid-responsive patients from nonresponders is important to avoid inappropriate and potentially harmful fluid challenges in situations in which other interventions (i.e., inotropes or vasopressors) should be preferentially used. Consequences of inappropriate fluid therapy include pulmonary edema, deterioration in gas exchange, and cardiac failure.

There are currently a number of parameters available with different monitoring modalities that can be used as estimates of preload and may predict volume responsiveness under defined conditions.

Static Indicators of Preload

Conventional static markers of cardiac preload, such as CVP and PAOP, are poor predictors of fluid responsiveness. CVP and PAOP reflect intracavitary pressures that frequently show poor correlation with transmural pressures, which are actually related to EDV through chamber compliance. Therefore EDV is overestimated (i.e., under the application of PEEP) or underestimated (i.e., in concentric left ventricular hypertrophy) in many clinical situations.

Furthermore, static parameters do not determine the position of the heart on the "individual" Frank-Starling curve as contractile function is not taken into the account. A patient may not respond to a fluid challenge because of ventricular dysfunction or poor ventricular compliance (see Fig. 3.1). It is important to realize, however, that pressure is one of the driving forces responsible for edema formation in the lungs. Thus, although the PAOP is considered to have limited utility for predicting and guiding fluid challenges, it does have a role in determining how much volume should be administered to patients and may be regarded as more of a safety limit, rather than as a guide to therapy.[6]

Volumetric Indicators of Preload

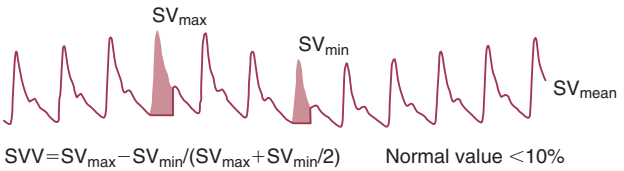
The continuous EDV, global EDV, and intrathoracic blood volume are computed by some monitoring systems. Although continuous and global EDVs seem to be better indicators of preload than static parameters, they are still poor predictors of a response to a fluid challenge in most situations. Extravascular lung water has been shown to help in the identification of noncardiogenic pulmonary edema and has the potential to increase the safety of fluid therapy in patients with structural lung disease or acute lung injury and acute respiratory distress syndrome.[11]

Dynamic Indicators of Preload

A number of dynamic parameters have been described that allow the clinician at the bedside to predict with some accuracy which patients will or will not respond to a fluid challenge. These parameters include the SVV, PPV, SPV, and the PVI and changes of vena cava diameters as derived by echocardiography. Generally, an SPV, PPV, SVV, or PVI variation greater than approximately 10% suggests that the patient will be volume responsive (Fig. 3.3). As stressed earlier in this chapter, these parameters require controlled mechanical ventilation and a tidal volume of at least 8 mL/kg of body weight to be maintained to remain reliable. Further, the presence of arrhythmias and severe tricuspid regurgitation precludes the safe use of these variables.[8]

The Passive Leg-Raising Test

Patients who are critically ill seldom fulfill criteria to allow for dynamic preload indices to be accurate predictors of volume responsiveness. The passive leg-raising test has been suggested to overcome these limitations. When traditionally performed by lifting the legs up at a 45-degree angle in a supine position, approximately 150 mL of blood can be recruited to increase venous return to predict a response of cardiac output to a noninvasive, endogenous fluid challenge. However, by starting the passive leg raising from a 45-degree semirecumbent position, a substantial increase of mobilized venous blood can be achieved by adding venous blood from the splanchnic compartment to that from the lower extremities, increasing the sensitivity of the maneuver for the prediction of fluid responsiveness. It is important to note that when performing the passive leg-raising test, the monitoring modality used must be able to track changes in cardiac output within a time frame of approximately 60 to 90 seconds.[8]



• **Fig. 3.3** Stroke volume variation *(SVV).* The arterial pressure trace can be used to generate stroke volume *(SV)* on a beat-to-beat basis. The variation in SV (SVV) with mechanical ventilation is a useful marker for identifying patients who are likely to respond to an increase in intravascular volume. This tracing demonstrates the fluctuations in SV in a patient with an increased SVV. *min,* Minimum; *max,* maximum.

The Diagnostic Fluid Challenge

In the care of critically ill patients situations do exist in which the preceding parameters are not reliable and a passive leg-raising test may be contraindicated owing to technical constraints or based on the patient's underlying illness, such as in brain injury with elevated intracranial pressure. In this scenario, the clinician may rely on the administration of fluids as a diagnostic intervention to indicate a potential benefit from further fluid therapy by assessing the response of various hemodynamic parameters, with SV being the parameter most widely used in studies investigating fluid responsiveness, with an increase of 10% to 20% indicating a positive response. Although the optimal volume to function as a fluid challenge has yet to be determined, it can be recommended in this situation to use the CVP as an indicator of a sufficient challenge of the right ventricle to ensure that an adequate preload has been achieved.[12]

It is important to recognize, however, that identification of a patient who is fluid responsive is not the same as saying that the patient should be given fluid without an appreciation of the clinical context. Most healthy patients will be volume responsive; however, few will benefit from volume challenges. In critically ill patients, other clinical factors need to be taken into account. Does the patient actually need a higher cardiac output? Or is cardiac output adequate, so that further increase may actually cause harm?

Hemodynamic Status and Blood Flow

Cardiac output (or blood flow) is an important variable to be considered in a critically ill patient. Although arterial pressure has been used as the target for therapy, this focus is perhaps related more to convenience in measurement than to a sound physiologic rationale. When patients become critically ill, it is extremely difficult to predict cardiac output from routine clinical assessment, so sensible and logical use of vasoactive therapy requires monitoring of both pressure and flow. Arterial blood pressure often is mistakenly used as a surrogate marker for blood flow; however, no direct relationship between pressure and flow exists. Moreover, clinical estimation of cardiac output can be difficult and inaccurate, although clinical assessment must not be ignored. Often these signs constitute the only tool that a clinician may have to estimate a patient's hemodynamic status before admission to a critical care unit. At this stage the response of clinical assessment to simple therapeutic maneuvers can give important information. If, however, the patient does not respond in a suitable fashion, monitoring of these variables becomes necessary to direct therapy.

Cardiac output is the volume of blood ejected by the left ventricle per minute. It is the product of HR and SV. It should be borne in mind that excessive HRs will reduce diastolic ventricular filling time, with a negative impact on SV. Heart rhythm also is essential in determining cardiac output, and in general any rhythm other than sinus rhythm will result in a reduction in SV. For example, the loss of atrial contribution to diastolic ventricular filling in atrial fibrillation results in a subsequent reduction in SV and hence cardiac output.

Cardiac output should not be considered in isolation from other relevant variables. The concept of oxygen delivery describes the relationship between cardiac output and arterial oxygen content:

$$\text{Oxygen delivery} = \text{Arterial } O_2 \text{ content} \times \text{Cardiac output}$$

Measurement of Cardiac Output

The ideal method of measuring cardiac output would be noninvasive, accurate, continuous, safe, easy to use, and operator independent; would provide rapid data acquisition; and would be cost-effective. None of the cardiac output monitoring devices currently available possesses all of these properties. Conventional thermodilution remains the clinical gold standard for accuracy in cardiac output measurement; however, newer, less (almost non) invasive monitoring methods that provide continuous cardiac output data are establishing a role in patients' hemodynamic management.[9,13]

The Fick Principle

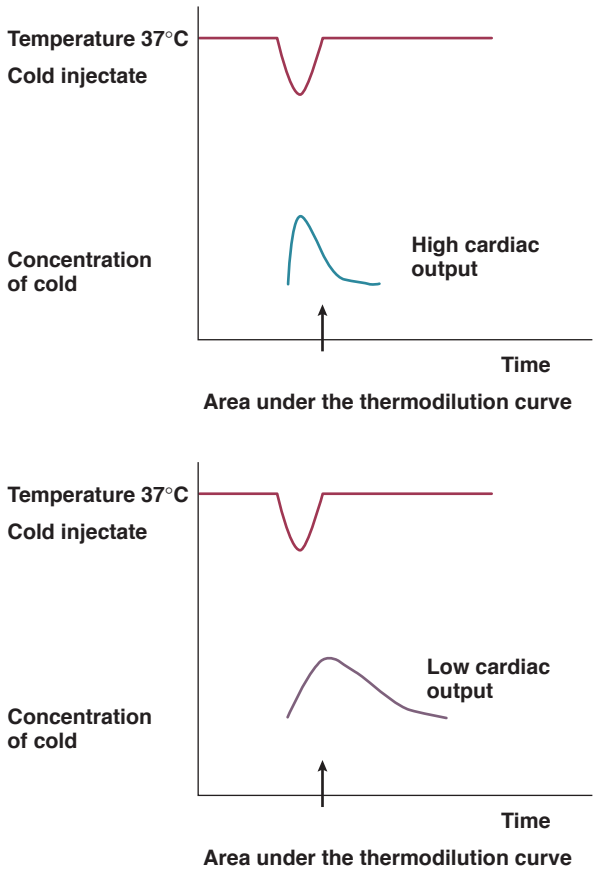
Fick described the following relationship in the nineteenth century: $Q = M/(A - V)$. That is, the uptake or release of a substance (M) by an organ is the product of the blood flow (Q) through that organ and the arteriovenous concentration difference (A − V) of the substance in question.

Applying the Fick principle to cardiac output measurement of the pulmonary blood flow over 1 minute may be achieved by measuring the arteriovenous oxygen content difference across the lungs and the rate of oxygen uptake. Oxygen uptake may be determined using spirometry by measuring the expired gas volume over a known time and calculating the difference in oxygen concentration between the expired gas and that of inspired gas. Accurate collection of the gas is difficult, unless the patient has an endotracheal tube, because of the leaks that occur around a face mask or mouthpiece. Analysis of the gas is straightforward if the inspired gas is air, but if it is oxygen-enriched air, two possible problems need to considered. (1) The addition of oxygen may fluctuate, producing an error owing to the nonconstancy of the inspired oxygen concentration. (2) Measurement of small changes in oxygen concentration at the top end of the scale is difficult. Blood oxygen content is measured via blood gas analysis. In the absence of intrapulmonary or intracardiac shunts, the pulmonary blood flow is equal to the systemic blood flow and thus cardiac output.

The technique just described based on the Fick principle may thus be used as an accurate and reliable static measure of cardiac output, but it remains a time-consuming and largely laboratory-based tool. Several variants of the basic method have been devised, but usually their accuracy is less reliable.

Thermodilution

Thermodilution from the PAC has traditionally been considered as the gold standard of cardiac output measurement for accuracy and acceptability in the clinical setting. Newer methods are routinely validated against the PAC thermodilution technique. A bolus of 5 to 10 mL of cold 0.9% sodium chloride or 5% dextrose is injected through the proximal port of a PAC into the right atrium. Temperature changes are measured by a distal thermistor in the pulmonary artery. A plot of temperature change against time gives a thermodilution curve from which cardiac output can be calculated from the Stewart-Hamilton equation (Fig. 3.4). Application of this equation assumes three major conditions: complete mixing of blood and indicator, no loss of indicator between place of injection and place of detection, and constant blood flow. For accurate results with this technique, it is important to ensure adherence to these conditions.



• **Fig. 3.4** Thermodilution curves show a plot of temperature change versus time after a bolus of cold injectate. Cardiac output is inversely proportional to the area under the thermodilution curve. With a large cardiac output, the bolus is pumped rapidly past the thermistor, so the area is small.

The degree of change in the temperature is inversely proportional to the cardiac output.

- Increased blood flow (and cardiac output) = minimal temperature change
- Decreased blood flow (and cardiac output) = pronounced temperature change

Modern PACs are able to provide a continuous reading of cardiac output. They contain an electrical heating coil that sits in the right atrium, which heats up the blood in a semirandom binary fashion. The pulsed heating bursts can be detected by the thermistor in the pulmonary artery, which after autocorrelation with the inputting signal can provide continuous cardiac output. It has to be noted, however, that this technique has a latency of 7 to 10 minutes.

Dye/Indicator Dilution

A number of techniques are available to measure cardiac output with the use of either a dye (indocyanine green) or an indicator (lithium). The concept is exactly the same as that for thermodilution: injection of a substance into the right side of the heart and detection of the same substance distally, either in the pulmonary artery or in the aorta. A curve is generated, which is replotted semilogarithmically to correct for recirculation of the dye. Cardiac output is

calculated from the injected dose, the area under the curve, and the duration of effect (short duration indicates high cardiac output) from the Stewart-Hamilton equation:

$$\dot{Q} = \frac{V(T_B - T_I)K_1K_2}{T_B(t)dt},$$

where $\dot{Q}$ is cardiac output, V is volume of injectate, T_B is blood temperature, T_I is injectate temperature, K_1K_2 are computer constants, and $T_B(t)dt$ is the change in blood temperature over time.

Arterial Pulse Pressure Analysis

Arterial pulse pressure analysis is a technique of measuring and monitoring SV on a beat-to-beat basis from the arterial pulse pressure waveform. This technique has several advantages over technologies such as the PAC, including its less invasive nature, as arterial access is available in most patients. Changes in both SV and cardiac output are then shown on an almost continuous basis. A fair number of less invasive cardiac output monitoring devices based on pulse pressure analysis are now commercially available and have resulted in a decreased use of the pulmonary catheter in most institutions.

The fluctuations of blood pressure around its mean value occur as a specific volume of blood—the SV—is forced into the aorta by each cardiac contraction. The magnitude of this pressure change, the pulse pressure, is a function of the magnitude of the SV. On a beat-to-beat basis, the only factor that determines changes in pulse pressure is change in SV, owing to the relatively slow nature of reactive vascular changes. To translate the pressure waveform into an accurate SV, however, an estimate of the arterial compliance and resistance must be made. The greater the compliance, the less will be the vascular resistance to the pulsatile increase in the arterial pressure, and the less will be the pressure required to distend the vessel to accommodate a given SV.

The need to incorporate arterial compliance and resistance into the measurement system has hindered this technology for many years. The origins of the pulse contour method for estimation of beat-to-beat SV are based on the Windkessel model described by Otto Frank in 1899. Only recently have methods been described that can compensate or correct for these compliance or resistance changes to provide an accurate determination of SV. Different technologies address this by different methods. Both lithium dilution and thermodilution techniques have been validated to calibrate pulse pressure tracking systems. Other devices are being marketed with the ability to self-calibrate after identifying vascular compliance and resistance directly from the pressure waveform.

Transesophageal Doppler

The esophageal Doppler cardiac output monitor, described in the early 1970s, provides a safe and minimally invasive means of continuously monitoring the circulation.[14,15] Compared with suprasternal probes, esophageal probes have the advantage of less positional variety owing to the smooth muscle tone of the esophagus and less signal interference from bone, soft tissue, and lung owing to the close proximity of the aorta to the esophagus. The esophageal Doppler monitor measures blood flow velocity in the descending thoracic aorta using a flexible ultrasound probe. When these data are combined with the aortic cross-sectional area, other hemodynamic variables including SV and cardiac output can be calculated, providing minimally invasive, continuous cardiac output assessment. Abrupt changes in cardiac output are much better followed with Doppler systems than with the PAC-based continuous cardiac output systems.

Despite several potential sources of error, good correlation has been observed between measures of cardiac output made simultaneously with the esophageal Doppler monitor and with conventional thermodilution. Esophageal Doppler ultrasonography has been used for intravascular volume optimization both in the perioperative period and in the critical care setting. One of the main advantages of the technique is the capability of rapid data acquisition after esophageal probe insertion.

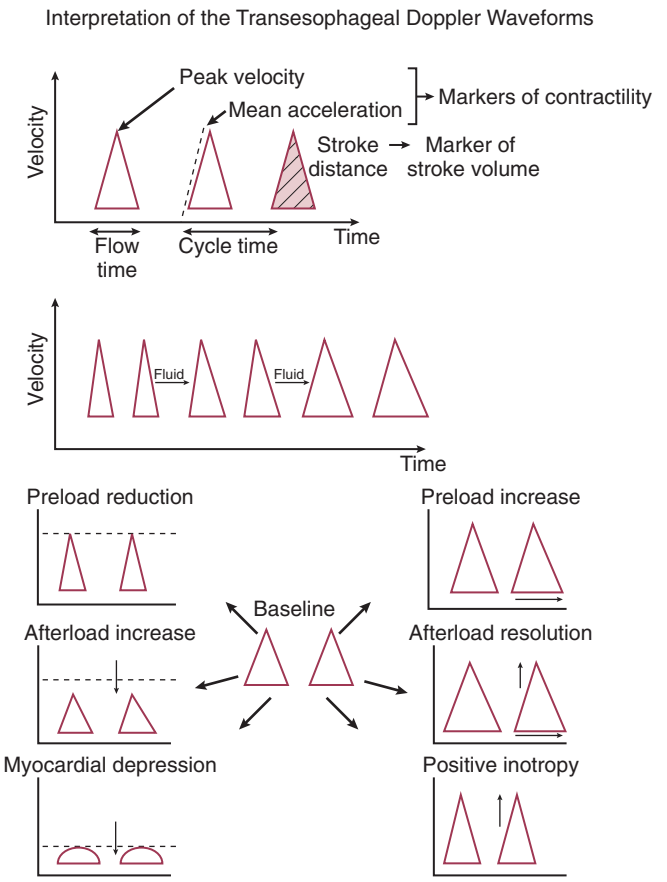
Identification of the descending aortic waveform is essential for the correct use of the esophageal Doppler cardiac output monitor. Waveforms from other structures, such as the pulmonary artery, azygos vein, or celiac axis, may be encountered, leading to misinterpretation. After the characteristic descending aortic waveform is acquired, the signal is optimized before data acquisition by movement of the probe a centimeter up or down until the waveform indicates the best possible velocity and color intensities, followed by rotation of the probe to optimize the signal further if possible. The "peak velocity" display is used as a reference to the highest identified wave.

Esophageal Doppler waveform analysis has been increasingly evaluated as a method for determining optimal cardiac preload. The key preload parameter of interest is the flow time (FT)—the time required from the start of the waveform upstroke to return to baseline. FT represents the duration of left ventricular systole and makes up one-third of the cardiac cycle (cycle time). Because the FT is HR dependent, it typically is corrected (FTc) to a rate of 60 beats/min to compensate for the change in duration of systole. The FTc reflects the afterload status of the circulation. Decreased levels commonly are seen in hypovolemic patients, but caution in interpretation is advised because this pattern also can be seen with profound vasoconstriction. A more sensible use of this device is in following the effects of a fluid challenge. Because SV can be determined on a beat-to-beat basis, it is easy to see the effects on the circulation of a small fluid bolus. Diagrammatic representations of characteristic Doppler waveform patterns are shown in Fig. 3.5.

Echocardiography

Transthoracic echocardiography and TEE both are evolving tools in the critical care setting, and particularly TEE has become a standard of care for intraoperative monitoring in patients undergoing cardiac valvular replacement or repair.[6] TEE has been used for a number of years for acute hemodynamic monitoring and diagnostic purposes in the cardiothoracic critical care setting, and its use in the general critical care setting is now becoming commonplace.

Echocardiography provides a dynamic assessment of cardiac function, allowing visualization of cardiac chamber dimensions, functional assessments such as estimation of ventricular ejection fractions, detection of regional and global wall motion abnormalities, detection of valvular abnormalities, and exclusion of pericardial effusion. It also can be used to derive cardiac output from measurement of blood flow velocity by recording the Doppler shift of ultrasound signals reflected from the red blood cells. The time-velocity integral, which is the integral of instantaneous blood flow velocities during one cardiac cycle, is obtained for the blood flow in the left ventricular outflow tract (other sites can be used). This is multiplied by the cross-sectional area and the HR to give cardiac output. The results for cardiac output measured by this device in skilled hands are comparable to those obtained with use of the PAC.



• **Fig. 3.5** Diagrammatic representation of characteristic Doppler waveform patterns. The characteristic flow "triangles" generated in an esophageal Doppler study can be used to monitor cardiac output and stroke volume. The width of the base of the triangle (flow time) when corrected for heart rate provides an estimate of afterload. This diagram demonstrates the changes seen after a volume challenge in a variety of clinical conditions.

The main disadvantages of the method are that a skilled operator is needed, the probe is large and therefore heavy sedation or anesthesia is needed, the equipment is very expensive, and an expert user is needed to adjust the probe to provide continuous cardiac output readings. Nonetheless, echocardiography has an important and established clinical role. The modality is covered in detail in Chapter 8.

Assessment of Adequacy of the Circulation

Resuscitation of critically ill patients is a complex process. The rationale for most resuscitation maneuvers is that the delivery of oxygen to the tissues is inadequate, resulting in tissue hypoxia. Resuscitation is therefore aimed at increasing the oxygen delivery to a level at which enough oxygen is brought to the tissues to ensure efficient metabolism, so that normal cellular processes can occur. Part of this process entails measuring cardiac output and then increasing this variable to an "adequate" level. Unfortunately, this strategy is complicated as a result of the fact that all patients' cardiac output requirements differ—no "normal" level of flow can be specified for any patient in any given situation. To assess adequacy of perfusion, therefore, a number of surrogate markers need to be assessed that provide an estimate of the underlying metabolic status. The cardiac output then needs to be assessed in combination with these surrogate markers of metabolism to ensure that resuscitation is improving the clinical situation.

Clinical Assessment

The first step in the hemodynamic assessment must be a thorough clinical assessment. Pulse rate and quality, respiratory rate, skin temperature, capillary refill time, core-peripheral temperature gradient, level of consciousness, and urine output are strongly related to cardiovascular dynamics, and a change in these clinical parameters may indicate deterioration as well as a positive response to a hemodynamic intervention. Skin mottling, pallor, and diaphoresis are alarming signs that require immediate and appropriate intervention. Several studies have shown a strong relationship between clinical and microcirculatory parameters and underline their importance in hemodynamic assessment.[16,17]

Mixed Venous Oxygenation

Venous oxygen saturation (SvO_2) is the oxygen saturation of mixed venous blood in the pulmonary artery. It reflects the overall venous saturation after the blood has been fully mixed in the right side of the heart. SvO_2 is related to the balance between oxygen delivery (DO_2I) and the ability to extract oxygen, or the oxygen extraction ratio (O_2ER). Under normal circumstances, oxygen consumption is independent of supply until oxygen delivery falls below the anaerobic threshold. The normal O_2ER is approximately 25%, giving an SvO_2 of 75%. In the face of a reduction in oxygen delivery, the tissues maintain oxygen consumption by increasing oxygen extraction, so SvO_2 decreases. However, SvO_2 does not necessarily vary with cardiac output. Not all patients can increase their O_2ER if DO_2I falls. Clinically, the response of SvO_2 to an increase in cardiac output or oxygen delivery can aid hemodynamic manipulation. SvO_2 can be measured by sampling blood from the distal lumen of a PAC and then measuring oxyhemoglobin saturation by means of co-oximetry, or by using an oximetric PAC that is able to continuously display SvO_2. A flow diagram of a published protocol using PAC-derived parameters is shown in Fig. 3.6.

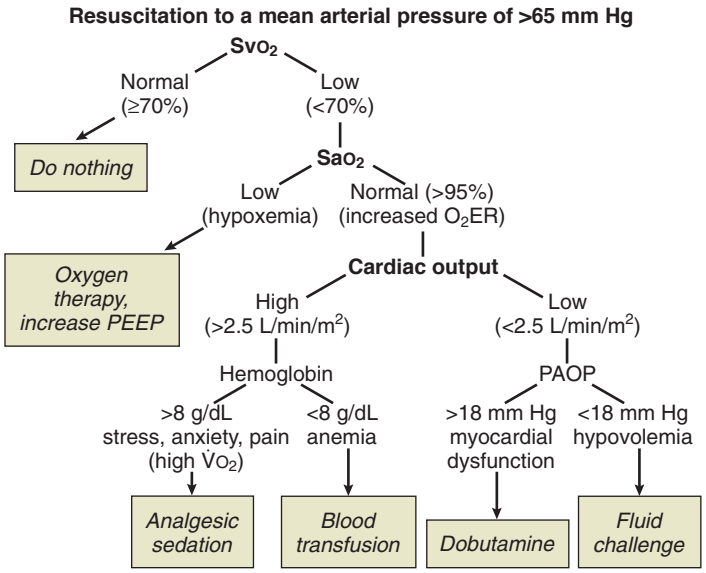
It has been suggested that SvO_2 should be monitored and the key variables manipulated to keep it within the normal range (65%–75%). In practice, this means ensuring that the hemoglobin concentration and arterial oxygen saturation are normal and then either increasing cardiac output or decreasing oxygen utilization (such as by sedation or cooling). Thus SvO_2 monitoring provides a means of assessing the adequacy of cardiac output for a given patient. This strategy has been used with success in patients who have undergone cardiac surgery and has been suggested for use in critically ill patients.[5]

Central Venous Oxygen Saturation

In patients without PACs in place, central venous oxygen saturation ($ScvO_2$) may be measured by sampling from the distal lumen of a central venous line in the SVC. This variable bears some relationship to the mixed SvO_2, although because the venous blood is not totally mixed in the SVC, the relationship should be considered as representing a guide rather than reflecting reality. In practice, the $ScvO_2$ should be used as a screening tool rather than as an accurate marker of adequacy. If the level is very low, then the inference can be made that the circulation is inadequate; however, near-normal levels do not preclude underlying problems.

Blood Lactate

Blood lactate levels represent the balance between lactate production and lactate metabolism. The liver is responsible for the major part



• **Fig. 3.6** Flow chart for the Pinsky-Vincent protocol. A diagnostic and treatment algorithm for the use of pulmonary artery catheter–derived variables. *O_2ER,* Oxygen extraction ratio; *PAOP,* pulmonary artery occlusion pressure; *PEEP,* positive end-expiratory pressure; *Sa_{O_2},* arterial oxygen saturation; *$\dot{V}_{O_2}$,* oxygen consumption. (Adapted from Pinsky MR, Vincent JL. Let us use the PAC correctly and only when we need it. *Crit Care Med.* 2005;33:1119–1122.)

of lactate metabolism. Inadequate oxygen delivery and tissue hypoxia, irrespective of the underlying cause, results in increased lactate generation. In critically ill patients, high blood lactate levels develop from a combination of inadequate oxygen delivery secondary to poor perfusion (in terms of both perfusion pressure and flow), impaired cellular oxygen utilization from mitochondrial damage, and reduced hepatic clearance of lactate. A resolving lactic acidosis along with clinical signs of improved perfusion is an important indicator of improving perfusion after resuscitation. Lactate levels and lactate clearance have been shown to predict mortality risk and morbidity, and studies investigating protocols aimed at decreasing lactate levels have shown the potential role of lactate as a treatment goal.[18]

Venous-to-Arterial Carbon Dioxide Difference (P_{CO_2} Gap)

Oxygen-derived parameters, namely S_{VO_2} and S_{cVO_2}, may falsely indicate adequate tissue perfusion in the presence of anaerobic metabolism owing to microcirculatory compromise. In this situation, a decrease in oxygen consumption ($\dot{V}_{O_2}$) may occur, either because of impaired oxygen delivery or reduced oxygen demand, resulting in normal levels of S_{VO_2} or S_{cVO_2}. In hypoxic conditions as the result of an impaired tissue perfusion, a rise in the partial pressure of carbon dioxide (P_{CO_2}) is usually seen, widening the gap between arterial and venous P_{CO_2}. Recent clinical studies have suggested that the venous-to-arterial CO_2 difference using a central venous and an arterial blood sample ($P(cv-a)CO_2$ or P_{CO_2} gap) may be used as a complementary tool to unmask inadequate tissue perfusion in patients who are apparently resuscitated to target goals—namely, an S_{cVO_2} of 70%. Further prospective clinical studies will show if this parameter has the potential to function as a treatment goal in the resuscitation of critically ill patients with hemodynamic compromise.[19]

Monitoring the Microcirculation

The goal of interventions that manipulate the macro-hemodynamics of a patient should be improving the microcirculation and tissue perfusion. Microcirculatory parameters have been shown to be associated with patients' outcomes in both medical and surgical patients.[20,21] Until recently, monitoring the microcirculation required complex and long offline analysis of images acquired at the bedside. The inability to use these techniques as real-time monitoring tools and the lack of evidence from trials using microcirculation targets as goals in clinical practice have prevented the mainstream use of these devices at the bedside. Recently, however, new devices with faster (almost real-time) software analysis have become available.[22] Validation and outcome studies in this new field are largely awaited.

Conclusions

Resuscitation of critically ill patients is a complex process. Several simple steps need to be taken to ensure delivery of an appropriate level of resuscitation. First, the patient should attain an optimal level of preload. This is best achieved by identifying the group of patients who are likely to benefit from volume loading and then providing this intervention, while at the same time not giving excess intravascular volume to patients who are unlikely to benefit from it. If it is impossible to predict which patients will benefit, then the fluid should be given under tightly controlled circumstances in the form of a fluid challenge with close monitoring of the circulation. After appropriate volume resuscitation, the circulation of some patients will still be inadequate for their metabolic demands. These patients may then benefit from either a reduction in oxygen requirements or an increase in oxygen delivery. This approach necessitates the monitoring of the circulation and the metabolic status.

Key Points

- Isolated measurements of either right atrial pressure or pulmonary artery pressure are not good markers for identifying patients who will respond to a fluid challenge.
- Dynamic measurements of pulse or stroke volume variation can predict volume responsiveness with a high degree of sensitivity and specificity.
- No "normal" cardiac output can be specified for any patient, so cardiac output must be compared with other markers of metabolic status.
- Cardiac output can be measured by a number of techniques. Less important than how it is measured is how this knowledge is applied.

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Review Questions

1. Which of the following variables is best placed to predict the response to an increase in intravenous volume with regard to an improvement in cardiac output?
a. Central venous pressure
b. Pulmonary artery occlusion pressure
c. Pulse pressure variation
d. Heart rate
e. Urine output
Answer: c. Static measures of the circulation are very poor predictors of volume responsiveness. Functional parameters, such as the pulse pressure response to mechanical ventilation, when used appropriately are good predictors of the response to fluid.

2. Which of the following variables is *not* directly related to oxygen delivery?
a. Hemoglobin concentration
b. Mean arterial pressure
c. Cardiac output
d. Heart rate
e. Arterial oxygen saturation
Answer b. Oxygen delivery is the product of article oxygen capacity and cardiac output. Mean arterial pressure is not directly related to oxygen delivery.

3. Which of the following variables cannot be used to identify an adequate response to resuscitation of the cardiovascular system?
a. Cardiac output
b. Mixed venous oxygen saturation
c. Central venous oxygen saturation
d. Venous-to-arterial carbon dioxide (CO_2) difference (Pco_2 gap)
e. Arterial lactate concentration
Answer: a. There is no normal value of cardiac output for a patient and thus other markers need to be used to assess adequacy of resuscitation.

4

Arterial, Central Venous, and Pulmonary Artery Catheters

JEAN-LOUIS VINCENT

CHAPTER OUTLINE

Arterial Catheters
- What Do They Offer?
- Access
- Complications

Central Venous Catheters
- What Do They Offer?
- Access
- Complications

Pulmonary Artery Catheters
- What Do They Offer?
- Complications
- Technical Limitations
- Applications: Diagnosis Versus Monitoring
- Assessing Effects of Interventions
- Clinical Indications for Pulmonary Artery Catheter Insertion
- Pulmonary Artery Occlusion Pressure and Partial Occlusion
- Does the Use of a Pulmonary Artery Catheter Improve Outcome?

Arterial Catheters

What Do They Offer?

The placement of an arterial catheter permits (1) reliable and continuous monitoring of arterial pressure and (2) repeated blood sampling. Analysis of the arterial pulse pressure curve may also have other applications, including assessment of fluid responsiveness and estimation of cardiac output. The appearance of arterial pressure waves varies according to the site at which the artery is sampled. As the arterial pressure wave is conducted away from the heart, three effects are observed: the wave appears narrower, the dicrotic notch becomes smaller, and the perceived systolic and pulse pressures rise and the perceived diastolic pressure falls.

Arterial Pressure Measurement

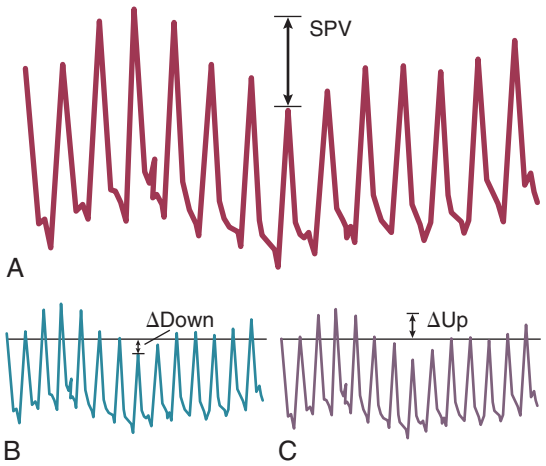
The optimal range of arterial pressure depends on individual patient characteristics, on underlying diseases, and also on treatment. Hence, it is impossible to give an optimal range of arterial pressure that is applicable in all patients. When arterial pressure needs to be evaluated accurately, oscillometric measurements become unreliable,[1] and insertion of an arterial catheter is indicated.

Four potential indications for insertion of an arterial catheter for measurement of arterial pressure are recognized:

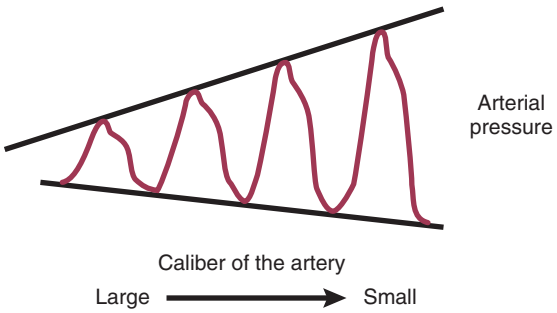
1. *Hypotensive states associated with (a risk of) altered tissue perfusion.* Hypotension that is resistant to fluid administration requires the administration of vasopressor agents, and invasive measurement of arterial pressure is then necessary to titrate this form of therapy. Norepinephrine is the vasopressor agent most commonly used in this setting. A mean arterial pressure (MAP) of 65 to 70 mm Hg is usually targeted, but this level must be adapted to the individual patient and the clinical scenario[2,3]; in particular, elderly patients with atherosclerotic disease may require higher levels than younger individuals with normal arteries.
2. *Intravenous vasodilator therapy.* Vasodilating therapy (e.g., nitrates and hydralazine) is a mainstay in the management of heart failure because it can increase cardiac output. Close monitoring of arterial pressure is essential to avoid excessive hypotension.
3. *Severely hypertensive states.* Extreme hypertension may result in organ impairment, especially of the brain and the heart. Calcium entry blockers or sodium nitroprusside usually are used to lower arterial pressure, and careful, accurate monitoring is essential to titrate the antihypertensive therapy.
4. *Induction of hypertension.* Hypertension is sometimes induced in patients with neurologic diseases. Severe cerebral edema with intracranial hypertension, in particular, requires vasopressor support to maintain cerebral perfusion pressure (the gradient between the MAP and the intracranial pressure); likewise, hypertension may be used to treat or prevent the development of vasospasm secondary to subarachnoid hemorrhage. Norepinephrine is usually used for this purpose.

Fluid Responsiveness

Variations in arterial pressure during positive-pressure ventilation have been used as a measure of fluid responsiveness. The transient increases in intrathoracic pressure influence venous return in patients who are likely to respond to fluid administration. This fluctuation



• **Fig. 4.1** The systolic pressure variation *(SPV)* is the difference between the maximum and the minimum systolic blood pressures during one ventilatory cycle (A). The SPV is the sum of the ΔDown (B) and the ΔUp (C). (From Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology.* 1987;67:498.)



• **Fig. 4.2** Schematic representation of an arterial pressure tracing showing that the pulse pressure increases as arterial size decreases.

in ventricular filling translates into fluctuations in arterial pressure a few beats later. Accordingly, the greater the degree of systolic arterial pressure, or pulse pressure, variation during the respiratory cycle, the greater the increase in cardiac output in response to fluid administration (Fig. 4.1). However, this observation is valid primarily in patients without spontaneous respiratory movements and without significant arrhythmias, and only when a sufficient tidal volume is applied.[4]

Cardiac Output Assessment

The pulse contour analysis also can serve to estimate cardiac output less invasively than with the pulmonary artery catheter (PAC). Because the only determinants of arterial pressure are the stroke volume and the resistance and compliance factors of the blood and arteries, analysis of the pulse contour trace can help to monitor cardiac output over time. This can be done with regular calibrations whenever changes in vascular tone or blood volume occur, or even in the absence of calibration. These measurements are still approximations, so further technological developments can be expected to improve accuracy.

Blood Sampling

The presence of an arterial catheter can greatly facilitate blood sampling, especially in terms of enabling easy access to the circulation for regular monitoring of blood gases, such as may be required in severe respiratory failure or with acute metabolic alterations. Sensors can measure blood gases continuously, but widespread use of such sensors is limited by their cost.

Access

The radial artery is usually used for placement of arterial catheters. The femoral artery can be easily cannulated and gives a better signal, but the presence of a femoral catheter interferes more with patient mobility and warrants concern about infection.[5] Use of other sites, such as the brachial or the axillary artery or even the dorsalis pedis artery, can be considered. An important point to remember is that the pulse pressure increases from the core to the periphery. In other words, the systolic pressure is overestimated in smaller arteries (Fig. 4.2). Hence, it may be better to rely more on mean values than on systolic or diastolic pressures.

Complications

The most feared complication with use of arterial catheters is ischemia. With any suspicion of ischemia, the catheter must be removed immediately. The Allen test, used to determine occlusive arterial lesions distal to the wrist, is unreliable and is no longer widely used. The accidental disconnection of arterial lines can be associated with severe hemorrhage and even exsanguination. Infectious complications are rare.

Central Venous Catheters

What Do They Offer?

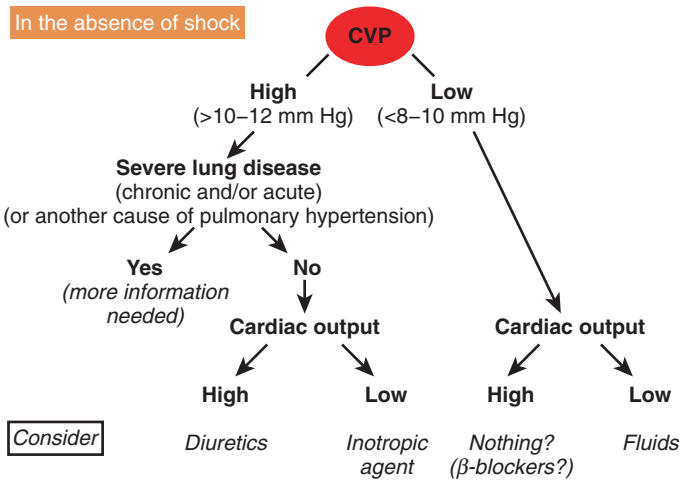
The central venous catheter can facilitate fluid administration. It also allows measurement of the central venous pressure (CVP) and enables access to central venous blood for sampling.

Trace Analysis

Analysis of the CVP waveform can provide some interesting information. In particular, a large y descent indicates a restrictive cardiac state, but not all restrictive patterns are associated with this finding.

Fluid Administration

The large-bore central venous catheter allows fluids to be administered fast and reliably in the presence of acute hemorrhage. Placement of a central catheter is therefore essential in patients with hemorrhage caused by polytrauma or with other forms of acute bleeding. It also allows irritant or hypertonic fluids to be administered, such as parenteral solutions, potassium-enriched solutions, and some therapeutic agents. Central venous lines also can be convenient in patients who need prolonged intravenous therapy when peripheral venous access becomes problematic.



• **Fig. 4.3** Interpretation of central venous pressure *(CVP)* must be made in conjunction with a measure of cardiac output.

Measurement of Central Venous Pressure

CVP is identical to right atrial pressure (RAP) (in the absence of vena cava obstruction) and to right ventricular (RV) end-diastolic pressure (in the absence of tricuspid regurgitation). It is thus equivalent to the right-sided filling pressure. CVP is determined by the interaction of cardiac function and venous return, which is itself determined by the blood volume and the compliance characteristics of the venous system. Hence, an elevated CVP can reflect an increase in blood volume as well as an impairment in cardiac function. The cardiac output must therefore be taken into consideration when interpreting a CVP value (Fig. 4.3). Because the CVP evaluates the right-sided filling pressures, CVP can be increased in the presence of pulmonary hypertension, even if left ventricular (LV) function is normal. The normal value in healthy persons is very low, not exceeding 5 mm Hg in the patient breathing spontaneously. Thus the CVP value may not be much lower than normal in the presence of hypovolemia. In general, a CVP below 10 mm Hg can be considered as indicative that the patient is more likely to respond to fluid resuscitation, but exceptions to this rule exist. A high CVP suggests a certain blood volume but does not guarantee sufficient LV filling.

Clinically, CVP can be assessed by evaluation of the degree of jugular distention or liver enlargement. An isolated CVP measurement is not very useful and is not a good indicator of a positive response to fluids; an increase in CVP without a concurrent increase in cardiac output is not only useless but also harmful, because it will lead to increased edema formation. Hence, changes in CVP during rapid fluid administration are important components of the fluid challenge.[6,7]

Access to Blood in the Superior Vena Cava

Measuring the central venous oxygen saturation ($ScvO_2$) is a surrogate for measurement of the true mixed venous oxygen saturation (SvO_2). Although absolute values of $ScvO_2$ are not identical to single SvO_2 values, trends in $ScvO_2$ over time may follow the same pattern as trends in SvO_2, making $ScvO_2$ a useful measure in patients who do not require a PAC.[8] $ScvO_2$ can be obtained either intermittently (by withdrawal of blood samples) or continuously (with the use of a catheter equipped with fiberoptic fibers). The so-called early goal-directed therapy in septic shock was initially proposed by Rivers et al.[9] and consisted of targeting an $ScvO_2$ of at least 70% in all patients with septic shock. This strategy did not result in improved outcomes in three large randomized controlled trials,[10–12] which included patients who were already resuscitated and already had normal $ScvO_2$ values. Nevertheless, monitoring $ScvO_2$ can still be useful in complex cases.[13]

Access

The central venous catheter generally is introduced via the internal jugular vein or the subclavian vein, although the risk of pneumothorax may be somewhat higher with this latter route.[14] Peripherally inserted central catheters (PICCs) can also be placed via the cephalic vein, basilic vein, or brachial vein. Introduction of a femoral catheter through the abdominal inferior vena cava to the right atrium can also yield reliable CVP measurements. The use of femoral catheters, however, is associated with a greater risk of infections and thrombophlebitis[14] and does not provide a true CVP (as the tip of the catheter is not located in the thorax).

Complications

Complications of central venous catheterization are related primarily to puncture of the central vein; hemothorax can be life-threatening, especially in the presence of severe respiratory failure. In the presence of unilateral pathology, the catheter must be introduced on the affected side. Arterial puncture resulting in a local hematoma is not uncommon, but hematoma formation usually is without major consequences. Bedside ultrasonography can help guide the introduction of the catheter into the vein. Excessive advancement of a long catheter in a small patient can result in arrhythmias; such arrhythmias have been described with advancement of the catheter tip into the right ventricle, but this problem can be identified by the presence of an RV trace on the monitor display.

Catheter-related infections constitute the major long-term complication. Adherence to basic hygiene guidelines can decrease the incidence of catheter-related sepsis. Triple-lumen catheters may be associated with a higher incidence of catheter-related infection,[15] primarily as a result of increased catheter manipulation. The use of antimicrobial-coated catheters may decrease the risk of infections,[16] but fears remain about the risks of development of resistant organisms.[17] Routine replacement of catheters after 3 to 7 days is not recommended.[18,19]

Pulmonary Artery Catheters

What Do They Offer?

PACs allow collection of data on right atrial, pulmonary artery, and pulmonary artery occlusive pressures (Fig. 4.4); flow (cardiac output); and oxygenation (SvO_2).

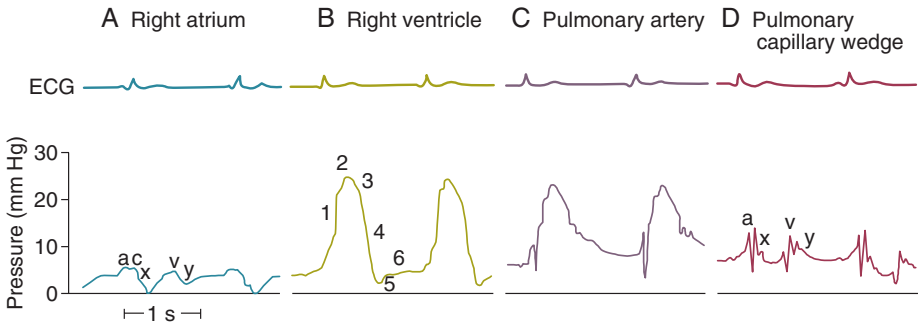
Pressures

Right Atrial Pressure

As indicated earlier, the RAP is identical to the CVP in the vast majority of cases.

Pulmonary Artery Occlusion Pressure

When the balloon on the catheter is inflated, it causes an obstruction (becomes wedged) in a small branch of the pulmonary artery, interrupting the flow of blood locally (but blood flow continues normally in the rest of the pulmonary circulation), so that (assuming the absence of an abnormal obstacle) a continuous column of



• **Fig. 4.4** Pressure waveforms. A, The normal right atrial (RA) tracing. The a wave is the RA pressure rise resulting from atrial contraction and follows the P wave of the electrocardiogram *(ECG)*. On simultaneous ECG and RA tracings it usually occurs at the beginning of the QRS complex. The c wave, caused by closure of the tricuspid valve, follows the a wave and is coincident with the beginning of ventricular systole. Atrial relaxation (x descent) is followed by a passive rise in RA pressure resulting from atrial filling during ventricular systole and occurs during the T wave of the simultaneously recorded ECG. The y descent reflects the opening of the tricuspid valve and passive atrial emptying. B, The normal right ventricular (RV) tracing. The sharp rise in RV pressure *(1)* is due to isometric contraction and is followed by a rapid pressure decrease *(2)* as blood is ejected through the pulmonary valve. This rapid ejection is followed by a phase of more reduced pressure decrease, which is often reflected in a small step in the downslope of the RV pressure waveform *(3)*. The subsequent sharp decline in RV pressure *(4)* occurs as a result of isometric relaxation and is noted once the RV pressure falls below the pulmonary artery (PA) pressure (with consequent closure of the pulmonary valve). As RV pressure falls below RA pressure, the tricuspid valve opens, and passive refilling *(5)* of the right ventricle occurs, followed by atrial contraction, causing a biphasic wave of ventricular filling to appear on the RV tracing *(6)*. C, The normal pulmonary arterial waveform. A pulmonary artery systolic elevation is caused by ejection of blood from the right ventricle, followed by a decline in pressure as RV pressure falls. As RV pressure falls below pulmonary artery pressure, the pulmonary valve closes, which causes a momentary rise in the declining pulmonary artery pressure. This is the dicrotic notch characteristic of the pulmonary arterial (and also the systemic arterial) waveform. The pulmonary artery systolic wave usually occurs in synchrony with the T wave of the ECG. Pulmonary artery diastolic pressure (PADP) does not fall below RA pressure and therefore is higher than right ventricular end-diastolic pressure; it is an approximation to left ventricular end-diastolic pressure (LVEDP). D, The normal pulmonary artery occlusion pressure (PAOP) waveform. The waveform of the pulmonary capillary wedge pressure (PCWP) is subject to the same mechanical variables as the RA waveform, but because of the damping that occurs through the pulmonary circulation, the waves and descents often are less distinct. Similarly, the mechanical events are recorded later in the cardiac cycle, as seen on the ECG. Thus the a wave is not seen until after the QRS complex, and the v wave occurs after the T wave of the ECG. The PCWP is a closer approximation to LVEDP than is PADP. (From Grossman W: Cardiac catheterization. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 3rd ed. Philadelphia: WB Saunders; 1992.)

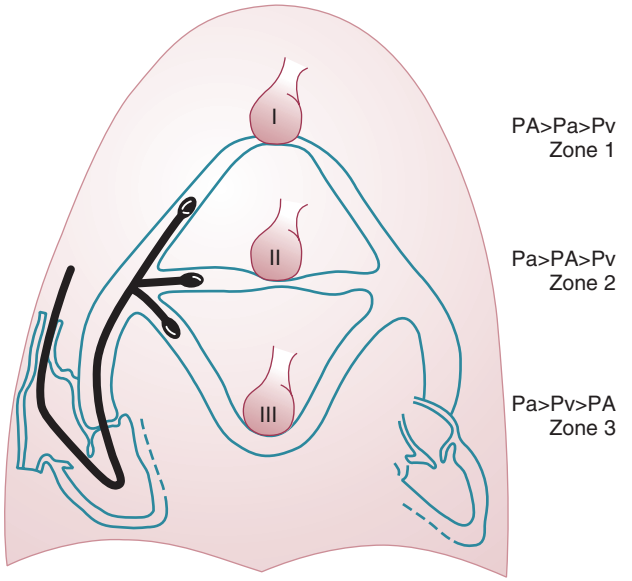
blood is present between the tip of the PAC and the left atrium. This pulmonary artery occlusion pressure (PAOP), or pulmonary artery wedge pressure, generally reflects the left atrial pressure well. Nevertheless, a number of steps must be taken to ensure the adequacy of the measurement.

A first question is whether the PAOP reflects the pressure in the pulmonary veins and not the alveolar pressure. The tip of the catheter should be in a West zone III position, where a continuous column of blood exists between the catheter tip and the left atrium (Fig. 4.5). These considerations are less important with fluid optimization and with today's lower positive end-expiratory pressures (PEEPs).

To exclude a possible influence of airway pressure on PAOP readings, the changes in PAOP can simply be compared with the changes in pulmonary artery pressure (PAP) during the respiratory cycle. If PAOP reflects the pressure within the pulmonary veins, these changes should be identical, because the pulmonary artery and vein should be subjected to identical changes in intrathoracic pressures. If, on the other hand, the catheter tip is not in a West zone III, the changes in PAOP will be more significant than the changes in PAP. In these latter conditions, either fluid administration or some reduction in the PEEP level may abolish the differences.

The next question is whether the measured pressure is truly a transmural pressure—that is, the pressure difference between the vascular structures and the environmental structures. In other words, will changes in surrounding intrathoracic pressures influence the pressures measured? In the case of intrathoracic pressures, the changes in pleural pressure are particularly relevant. Hence, all measurements should be performed at end-expiration, when the pleural pressure is closest to zero. A marked fall in intrapleural pressure, as with a Mueller maneuver (forced inspiration against resistance), may dramatically increase the transmural pressures. A more common problem in the intensive care unit (ICU) is the increase in pleural pressure owing to positive-pressure ventilation, sometimes with high PEEP levels.

One method of combating this problem could be to subtract the esophageal pressure from the measured PAOP, but this approach has a number of technological limitations. Simple disconnection of the respirator to measure PAOP after obtaining an equilibration state is not recommended, because the measured PAOP will not represent the real value when PEEP is applied. A better method consists of measuring the lowest (nadir) PAOP, within seconds after a very transient disconnection from the ventilator, to identify the true transmural pressure before a new equilibrium is reached.[20]



• **Fig. 4.5** The position of the pulmonary artery catheter tip in relation to the zones of the theoretical lung model described by West. For pulmonary artery occlusion pressure (PAOP) to be a valid estimate of "left heart" filling pressure, a continuous column of blood must exist between the catheter tip and the left atrium. In zones I and II, pulmonary vasculature is either totally or partially compressed by the intraalveolar pressure, and measurements of PAOP will be misleading. *PA,* Alveolar pressure; *Pa,* pulmonary artery pressure; *Pv,* pulmonary venous pressure. (From Marini JJ: *Respiratory Medicine and Intensive Care for the House Officer.* Baltimore: Williams & Wilkins; 1991.)

Such a maneuver suppresses the high intrathoracic pressure and eliminates the influence of the extramural pressure, but the values obtained may not be valid in the presence of intrinsic PEEP. Other methods have been suggested, some relatively sophisticated[21] and others more simple, involving subtraction of approximately one-third of the PEEP level from the measured PAOP, for example. The question is whether this is really so important because absolute PAOP values are not very helpful.

In respiratory failure, PAOP does not represent true capillary pressure, which may be somewhat higher. The true capillary pressure may be estimated from the measurement of the intersection point of the rapid and slow pressure decay curves recorded after a rapid interruption of the blood flow; such measurements of capillary pressure are possible from the pressure trace. This pressure is well correlated with extravascular lung water in animal experiments. The need to know these values is questionable, however, because the primary goal remains to keep these hydrostatic pressures as low as possible while maintaining adequate cardiac output.

PAOP may not adequately reflect LV end-diastolic pressure. It may be lower in patients with aortic regurgitation or higher in the presence of significant tachycardia or mitral valve disease. LV end-diastolic pressure may not even accurately predict LV end-diastolic volume. This was already demonstrated many years ago with radionuclide techniques.[22] Preload is more directly defined as the end-diastolic volume. A stiff, noncompliant ventricle can result in a relatively high end-diastolic pressure for a given end-diastolic volume. An evaluation of end-diastolic volumes can be obtained less invasively with echocardiographic techniques. Likewise, the use of transthoracic thermodilution techniques allows the estimation of intrathoracic blood volume and global end-diastolic volumes. However, these assessments of end-diastolic volumes do not provide additional information about the likelihood of fluid responsiveness.

In sum, then, a given level of cardiac filling pressures does not provide much information about fluid responsiveness, but monitoring can be very helpful to guide a fluid challenge.[6] During fluid administration, the goal is to obtain a significant increase in cardiac output (by the Frank-Starling mechanism), with the least increment in cardiac filling pressures, to minimize the risk of edema formation. The goal is not to keep the cardiac filling pressures within predefined arbitrary limits; rather, PAOP is a direct determinant of edema formation in the lungs. The key principle is to keep the PAOP as low as possible, provided that all of the other organs are happy.

Pulmonary Artery Pressures

Normally the pulmonary vasculature is a low-resistance circuit, so that the diastolic PAP should be equal to or only slightly higher than the PAOP. An increased pressure gradient between the diastolic PAP and the PAOP indicates active primary pulmonary hypertension related to pulmonary vascular changes (hypoxia) or diseases (primary pulmonary artery hypertension). Pulmonary hypertension may result in RV dilation with septal shifts that may compromise LV function.

Cardiac Output

The reference method for measurement of cardiac output is use of the Fick equation; however, this equation is difficult to apply in practice. The indicator dilution technique has been used instead. Indocyanine green clearance has been used for many years, but this method is time-consuming and quite difficult to perform. The thermodilution technique developed by Ganz is a convenient technique that today allows the almost continuous measurement of cardiac output. The presence of tricuspid insufficiency is the major limitation to this technique. Other techniques, including transpulmonary and lithium dilution techniques, have been developed but are somewhat less precise.

The thermodilution technique estimates cardiac output over several cardiac cycles, whereas other techniques, including those based on pulse contour analysis, may assess beat-to-beat variations. These techniques may be useful for estimating the influence of changes in intrathoracic pressures on the stroke volume variation, an estimate of fluid responsiveness.

Right Ventricular Volumes

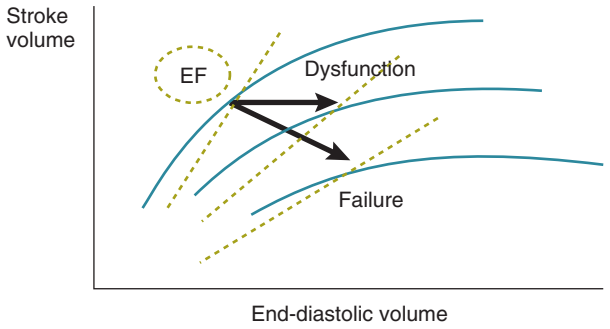
The use of a modified PAC equipped with a fast-response thermistor also allows evaluation of the right ventricular ejection fraction (RVEF) (Fig. 4.6). With knowledge of the stroke volume, it becomes easy to calculate the end-systolic and end-diastolic volumes. This measurement can be particularly useful in the presence of RV failure, but this also is a situation in which the measurement is least reliable: tricuspid regurgitation secondary to pulmonary hypertension.

Mixed Venous Oxygen Saturation

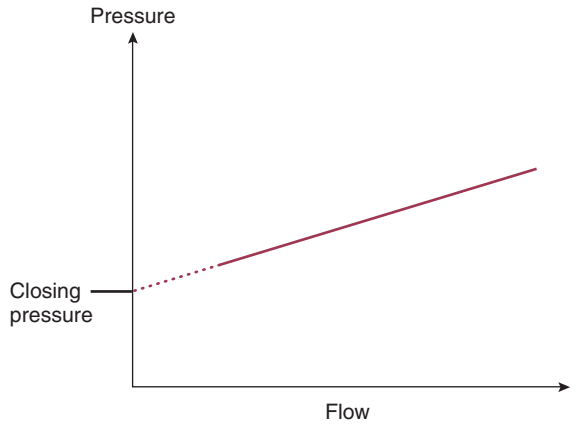
$S\bar{v}O_2$ represents the balance between oxygen consumption and oxygen supply. According to the Fick equation:

$$\dot{V}O_2 = \text{Cardiac output} \times (CaO_2 - C\bar{v}O_2)$$

where $\dot{V}O_2$ is oxygen uptake and CaO_2 and $C\bar{v}O_2$ are the arterial and mixed venous oxygen content, respectively. If the dissolved



• **Fig. 4.6** Ventricular function curve depicting the difference between ventricular dysfunction (decrease in the ventricular ejection fraction *[EF]* but preservation of stroke volume) and ventricular failure (defined as the inability of the heart to pump enough flow). The EF, the ratio between stroke volume and end-diastolic volume, is represented by the *dashed lines*; it is decreased in all cases.



• **Fig. 4.7** Relationship between pressure and blood flow, illustrating the limitations in the calculation of the vascular resistance. Note that the line defining that relationship does not go through the origin, because the pressure is not zero in the absence of blood flow.

oxygen in the blood is neglected for the purposes of calculation, then:

$$VO_2 = \text{Cardiac output} \times Hb\,(SaO_2 - SvO_2) \times C$$

and

$$SvO_2 = SaO_2 - (VO_2/\text{Cardiac output} \times Hb \times C),$$

where Hb is hemoglobin and C represents the oxygen-carrying capacity of saturated hemoglobin.

Accordingly, a decrease in SvO_2 can reflect either a decrease in SaO_2 (hypoxemia), anemia, or a relative inadequacy of cardiac output in relation to the oxygen demand of the tissues.

SvO_2 can be measured continuously using catheters equipped with fiberoptic fibers, and measurements are helpful to guide therapy. $ScvO_2$ has been proposed as a surrogate for SvO_2, but the relationship between $ScvO_2$ and SvO_2 is rather vague. Indeed, the $ScvO_2$ is lower than the SvO_2 in healthy conditions (as a result of the low O_2 extraction by the kidneys) but is higher than the SvO_2 in critically ill patients (because of relative increase in O_2 extraction in the kidneys and in the gut).[23] Moreover, O_2 extraction is high in the coronary circulation, and this is missed in the measurement of $ScvO_2$.

Derived Variables

Hemodynamic assessment can include a number of derived variables, including resistance, ventricular stroke work, oxygen transport, oxygen consumption, and venous admixture, as described next.

Resistance

In steady-flow conditions, Ohm's law indicates that resistance is the ratio between the pressure drop and the flow in the system. In the pulmonary circulation, the inflow pressure would be the mean PAP and the outflow pressure would be PAOP; for the systemic circulation, these would be the MAP and the CVP, respectively. In either case, flow would be cardiac output. This approach is limited, however, by the fact that the extrapolated intercept of the PAP–cardiac output relationship represents the average closing pressure of the small pulmonary arterioles, and the slope represents the upstream arterial resistance. Accordingly, the increased PAP in pulmonary hypertension can be explained by both an increase in pulmonary vascular closing pressure and an increase in vascular tone, and pulmonary vascular resistance is not a good reflection of vasomotor tone in the pulmonary vasculature. Pulmonary hemodynamics are therefore best assessed by altering blood flow to better evaluate this relationship (Fig. 4.7).

Calculation of systemic vascular resistance (SVR) is not very helpful either. It is better to base clinical decisions on primary variables. Simply stated, a relatively high cardiac output in relation to arterial pressure reflects a low SVR state, whereas a relatively low cardiac output reflects a high SVR state.

Ventricular Stroke Work

The work developed by the ventricles is determined by the ventricular work as derived from the product of flow and the pressure generated. The relationship between stroke work (SW) and the respective filling pressure represents a better assessment of contractility than does the stroke volume. LV stroke work index (LVSWI) can be calculated using the equation:

$$LVSWI = SVI\,(MAP - PAOP) \times 0.0136,$$

where SVI represents the stroke volume index.

Oxygen-Derived Variables

Oxygen delivery (DO_2) can be assessed as the product of cardiac output and the arterial oxygen content, according to the equation:

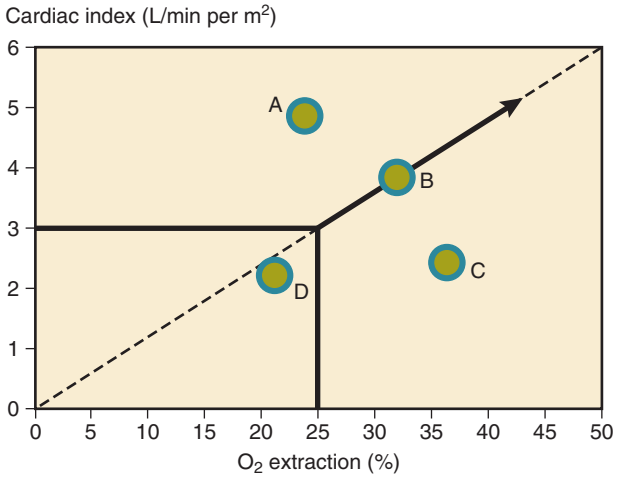
$$DO_2 = \text{Cardiac output} \times CaO_2$$
$$= \text{Cardiac output} \times ([Hb] \times SaO_2 \times 1.39) + 0.0031 \times PaO_2$$

Calculations of this variable benefit from combining measurements of cardiac output, hemoglobin, and SaO_2 but have the limitation that the corresponding oxygen demand is unknown. Some studies have suggested that maintaining supranormal DO_2 in the perioperative period in high-risk patients[24] or early after trauma may result in better outcomes.

Oxygen consumption also can be calculated from the product of cardiac output and the arteriovenous oxygen difference, according to the formula:

$$VO_2 = \text{Cardiac output} \times (CaO_2 - CvO_2),$$

where CvO_2 is calculated in the same way as for CaO_2, using the SvO_2 instead of the SaO_2.



• **Fig. 4.8** Diagram illustrating the relationship between cardiac index and oxygen (O_2) extraction. Four typical examples are given: hyperkinetic state (A), anemia (B), low cardiac output state (C), and profound anesthesia (D).

The difficulty is in evaluating the oxygen requirements (or the oxygen demand) of the body. VO_2 assessment may perhaps be useful to evaluate the caloric need of the critically ill patient.

The calculation of oxygen extraction (oxygen extraction ratio, or O_2ER) is accomplished by determining the ratio of VO_2 to DO_2, or in a simplified way:

$$O_2ER = VO_2/DO_2 = (CaO_2 - CvO_2)/CaO_2$$
$$= (SaO_2 - SvO_2)Hb/SaO_2 \times Hb$$
$$= (SaO_2 - SvO_2)/SaO_2$$

Accordingly, when SaO_2 is close to 100%, in the absence of hypoxemia, O_2ER mirrors SvO_2. Its calculation can be useful in the presence of hypoxemia, when SaO_2 is decreased. Also, the relationship between cardiac output and O_2ER can be helpful to compare the central and the peripheral components of oxygen delivery (Fig. 4.8). This relationship is independent of hemoglobin, so it can be helpful in evaluating the cardiovascular status in the presence of anemia.[25]

Venous Admixture

Venous admixture can be calculated by the Berggren equation:

$$Qs/Qt = (Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2),$$

where Qs is shunt flow, Qt is total pulmonary blood flow, and $Cc'O_2$ represents the capillary oxygen content (assuming an oxygen saturation of 100%). This may help to assess the effects of various interventions (PEEP or other respiratory conditions, administration of vasoactive agents) on pulmonary hemodynamics.

Complications

Complications of pulmonary artery catheterization can be divided into seven categories as listed in Box 4.1. Many of these can be prevented, and most are relatively uncommon.

Complications of the venous access are the same as for the insertion of a central venous catheter. Arrhythmias are common but usually are without major consequence, except in moribund patients. It has been suggested that lidocaine should be given prophylactically in predisposed patients, but this usually is not necessary. Likewise, complete atrioventricular block may develop in patients with left bundle branch block, but this is exceptional. Knot formation will be rare if the catheter is advanced carefully and if its presence in the pulmonary artery is confirmed before further advancement into the right ventricle. In particular, care should be taken not to advance the catheter by more than 30 to 35 cm into the right ventricle. Thrombotic complications have become rare with the development of heparin-coated catheters. The appearance of an infiltrate beyond the tip of the PAC on the chest film should suggest an evolving thrombotic event, which should lead to consideration of the withdrawal of the catheter. Endothelial lesions have been found at autopsy, but their clinical relevance is doubtful. Endocarditis is very rare. Valvular damage may occur as a result of improper handling of the catheter (in particular, its withdrawal with the balloon still inflated). Catheter-related infections remain a risk, but they do not seem to be any more common than with central venous catheters.

Pulmonary artery rupture is the most feared complication; although it is exceptionally rare, it is associated with a high mortality rate. The usual cause is overinflating the balloon in the presence of resistance to inflation, particularly in the presence of preexisting pulmonary artery hypertension. The cardinal sign of rupture is the development of hemoptysis. The reaction to this event should not be to completely pull out the catheter, but rather to withdraw it slightly and then inflate the balloon. If the hemorrhage does not stop, a thoracotomy may be necessary to repair the pulmonary artery.

• BOX 4.1 Complications of Pulmonary Artery Catheter Insertion

- Complicated vascular access (pneumothorax, hematoma)
- Arrhythmias (e.g., heart block, ventricular tachycardia/fibrillation)
- Catheter knotting
- Pulmonary thrombosis and infarction
- Endothelial or valvular damage
- Colonization and bacteremia
- Pulmonary artery rupture

Technical Limitations

Invasive measurements of pressures are based on fluid-filled systems with disposable transducers. The transducer includes a deformable membrane with a Wheatstone bridge modifying the electrical resistance and, correspondingly, the intensity of a current. Reliability is ensured by the excellent linearity between the pressure signal and the electrical signal generated by the transducer, in a range of frequency values largely exceeding the range of frequencies found in the human body.

Reliability is less secure in the intermediary system made of tubes and stopcocks along the extent of the pressure system. These can modify the morphology of the trace, resulting in damping. Motion artifacts can further complicate the tracings. The presence of air bubbles also may alter the signal. Use of fluid-filled catheters to measure pressures provides reliable estimates of mean vascular pressures.

To guarantee reliable measurements, it is essential to have appropriate zeroing, which is accomplished by opening the transducer to atmospheric pressure (taken as the zero value). All pressures must be measured with reference to an arbitrary reference point. This zero reference pressure level should ideally be where

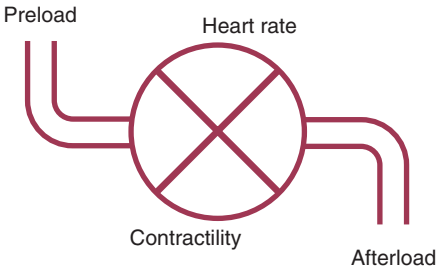
it is least influenced by location on the body. In humans, it is thought to be at the level of the right atrium, so the reference level usually is placed in the midchest (midaxillary) position at the level of the fourth intercostal space. In healthy persons, the CVP referred to that region does not change with supine versus upright position. Obviously, errors in zeroing are relatively more important for measurements of cardiac filling pressures than for arterial pressure measurements, because the errors are quantitatively identical but proportionally greater. One should also ensure the good quality of the trace. Shaking the catheter should result in large pressure variations on the screen. A damped system underestimates systolic pressures. The liquid column should be continuous, without air bubbles in the system. Excessive tubing length, or multiple stopcocks and connectors, may decrease the resonant frequency, resulting in "whipped" traces. Likewise, the presence of bubbles must be carefully avoided. Transient flushing should be followed by an abrupt return of the pressure trace to its actual value.

Applications: Diagnosis Versus Monitoring

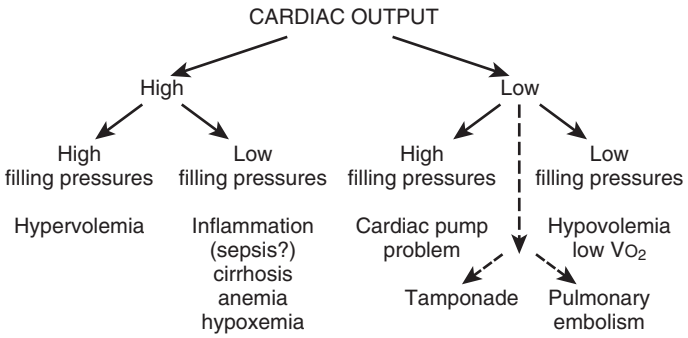
Today the PAC is more useful in guiding therapy rather than in identifying abnormalities; this latter role has largely been taken over by noninvasive, mainly echocardiographic techniques (Table 4.1). In the past, analysis of waveforms was used—for example, the abnormal v waves of mitral regurgitation. Likewise, an increase of all pressures to identical levels should suggest pericardial tamponade. These findings should still alert the clinician to possible abnormalities, but echocardiographic techniques have largely replaced the use of the PAC for identifying valvular disease. The use of echocardiographic techniques for monitoring, however, is hampered by the difficulty of keeping the probe in the esophagus for prolonged periods, and results are very operator dependent.

To illustrate the need to integrate different variables, rather than focusing on just one variable, some suggested applications follow:

- *Interpretation of a cardiac output value.* It is important to consider the four determinants of cardiac output (Fig. 4.9).[26] Interpretation should start by considering the stroke volume (cardiac output divided by heart rate) and relating this to an index of ventricular filling (PAOP) and an index of ventricular afterload (arterial and pulmonary artery pressures); an inotropic agent should be added only when preload and afterload have been optimized.
- *Fluid status.* Low cardiac filling pressures may be normal or reflect hypovolemia. The measurement of cardiac output and SvO_2 will help determine fluid needs. Indeed, hypovolemia typically is associated with a low cardiac output (Fig. 4.10) and a low SvO_2 (Fig. 4.11). By contrast, hypervolemia in the presence of normal cardiac function is manifested by high cardiac filling pressures associated with a relatively high cardiac output and normal or high SvO_2.
- *Hemodynamic versus nonhemodynamic pulmonary edema.* The distinction between hemodynamic and nonhemodynamic types of lung edema no longer requires pulmonary artery catheterization; the clinical history and less invasive (e.g., echocardiographic) measurements usually are sufficient to separate the two.
- *RV dysfunction versus failure.* A reverse gradient between RAP and PAOP (i.e., a higher RAP than PAOP) indicates RV dysfunction or failure and usually is secondary to pulmonary



• **Fig. 4.9** The four determinants of cardiac output.

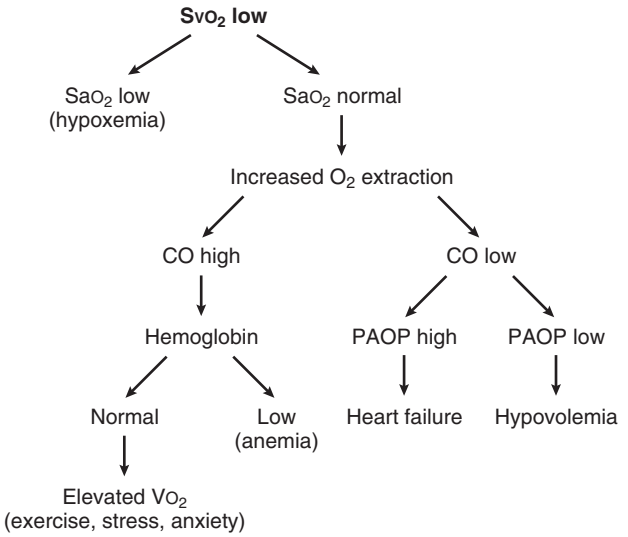


• **Fig. 4.10** Interpretation of cardiac output. Vo_2, Oxygen uptake.

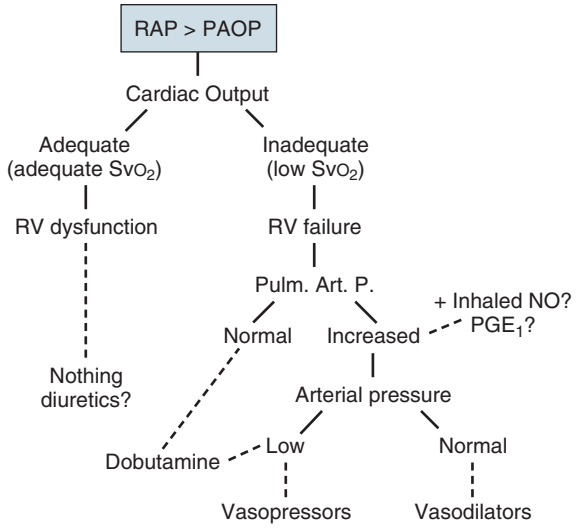
TABLE 4.1 Pulmonary Artery Catheterization Versus Echocardiographic Techniques for Management of Selected Disorders: Relative Value

	PA CATHETERIZATION		ECHOCARDIOGRAPHY	
Disorder	Diagnosis	Monitoring	Diagnosis	Monitoring
Tamponade	+	++	+++	+
Hypovolemia	++	+++	++	+
Valvular disease	+	++	+++	+
Heart failure	++	+++	++	+
Right ventricular failure	++	+++	+++	++
Septic shock	+	+++	+	+

PA, Pulmonary artery.



• **Fig. 4.11** Interpretation of a low SvO_2 (mixed venous oxygen saturation). *CO,* Cardiac output; *PAOP,* pulmonary artery occlusion pressure; *SaO_2,* arterial oxygen saturation; *VO_2,* oxygen uptake.



• **Fig. 4.12** Interpretation of a reversed gradient between the right atrial pressure *(RAP)* and the pulmonary artery occlusion pressure *(PAOP). NO,* Nitric oxide; *PGE_1,* prostaglandin E_1; *RV,* right ventricular; *SvO_2,* mixed venous oxygen saturation.

hypertension, as will be immediately apparent from the measurements of pulmonary artery pressures. RV dysfunction is manifested by RV dilation (and thus a decrease in RVEF) with no limitation on cardiac output. This is the most common situation in patients with acute respiratory distress syndrome, who usually maintain a hyperkinetic state. Rather, RV failure refers to a state in which cardiac output is no longer sustained at adequate levels. These different entities are illustrated in Fig. 4.12.

- *LV dysfunction versus failure.* Here the gradient between PAOP and RAP is higher than the typical 3 to 5 mm Hg. As with the right ventricle, in LV dysfunction the ventricular volumes may increase (so the ejection fraction will decrease), but the cardiac output may be simultaneously preserved; such a situation may exist in septic shock. LV failure is more common and is manifested by a decrease in cardiac output and SvO_2.

Assessing Effects of Interventions

The PAC can be used to monitor the effectiveness of various interventions:

- *Fluid challenge.* A fluid challenge technique is indicated whenever the benefit of fluid administration is in doubt.[6] Ideally, fluid administration results in increases in cardiac output and tissue perfusion without major increases in cardiac filling. An increase in PAOP in the absence of a significant change in cardiac output and SvO_2 indicates that fluid administration will only result in an increased risk of edema and should be discontinued.
- *Inotropic agents.* The use of inotropes aims to increase cardiac output and possibly decrease PAOP. Lack of an increase in cardiac output after administration of a β_1-adrenergic inotropic agent indicates a desensitization of the β-adrenergic receptors and is associated with a worse prognosis.[27]
- *Vasopressors.* The use of pure vasoconstrictors is expected to increase arterial pressure as well as cardiac filling pressures. An excessive increase in cardiac filling pressures with use of such an agent suggests the need for addition of an inotropic agent (e.g., dobutamine).
- *Vasodilators.* The administration of vasodilators may rapidly reduce arterial pressure so that continuous arterial pressure monitoring is usually indicated. Moreover, a reduction in vascular tone in the presence of hypovolemia may reduce venous return and thus cardiac output.

Clinical Indications for Pulmonary Artery Catheter Insertion

The improvement in noninvasive diagnostic techniques means that today the PAC is used primarily for monitoring. Potential indications include the following:

- *Severe circulatory shock.* The PAC can be used to help guide fluid challenges and titrate inotropic agents. Shock caused by hypovolemia (as in polytrauma or with other forms of massive bleeding) does not require insertion of a PAC because management of such patients generally is quite straightforward.
- *RV failure.* The PAC can be used to monitor pulmonary artery pressures, the gradient between RAP and PAOP, cardiac output, and SvO_2.
- *Acute respiratory failure caused by pulmonary edema.* Whether lung edema is hemodynamic or nonhemodynamic, the strategy should be to keep the hydrostatic pressures as low as possible, but this requires measurements of cardiac output and SvO_2 to ensure the systemic circulation is not compromised.
- *Complex fluid management in the presence of impending renal failure.* Sometimes it is difficult to evaluate the fluid status in oliguric patients, in whom hypovolemia may compromise renal function but hypervolemia obviously must be avoided.
- *Dynamic assessment of cardiac function in specific conditions.* The best example is that of the patient who is difficult to wean from mechanical ventilation, possibly owing in part to cardiac dysfunction.

Pulmonary Artery Occlusion Pressure and Partial Occlusion

Partial occlusion of the pulmonary artery in the presence of pulmonary hypertension may be difficult to recognize and can lead to significant overestimation of the PAOP. A useful clue to partial occlusion is occurrence of a substantial increase in the

PAOP without a concomitant change in the pulmonary artery diastolic pressure. If the pulmonary artery diastolic pressure minus the PAOP gradient is normal and the underlying disease process would predict increased pulmonary vascular resistance, partial occlusion should be suspected. Partial occlusion may occur if a catheter is either too proximal or too distal in the pulmonary artery, and appropriate repositioning may be corrective. The best PAOP may be obtained in some circumstances by further advancing the catheter with the balloon fully inflated and at other times by retracting the catheter to the original pulmonary artery position and attempting to occlude with 1.0 to 1.2 mL of air, instead of full inflation. It is imperative never to inflate against resistance.

Does the Use of a Pulmonary Artery Catheter Improve Outcome?

The use of the PAC has been challenged on the basis that it has not been shown to improve outcomes.[28] An improvement in outcome, however, has not been demonstrated with other monitoring techniques either. Moreover, a number of studies have indicated that the use of the PAC can influence therapy.[29] If use of a PAC does not result in better outcomes, important and challenging questions arise about the beneficial effects of many therapeutic interventions in the ICU. Some evidence suggests that the use of the PAC may improve outcomes in the most severely ill subsets of critically ill patients.[30] Errors in measurements from the PAC were identified many years ago,[31] and another consideration is the considerable interobserver variability in interpretation of PAC tracings.[32] Clearly, not all ICU patients need a PAC and insertion should be reserved for complex cases.[33,34] If a PAC is considered necessary, it is important to respect the three successive steps: to take adequate and full measurements; to interpret the results correctly; and to apply the gathered information for the patient's benefit. Unfortunately, potential errors are associated with each step. Some of these issues can be addressed with better teaching and improved basic knowledge of hemodynamics and basic physiology.

Key Points

- No simple guidelines for monitoring are available or applicable in all cases; monitoring should be tailored to each patient's needs.
- Each variable, taken individually, has limitations and is subject to error and difficulty in interpretation. Variables should be combined and integrated to provide a global picture of the clinical situation.
- A monitoring technique cannot improve outcome by itself; each of the three components of monitoring is important with any monitoring technique:
  - Accurate collection of data
  - Interpretation of the data
  - Application of the information obtained
- Cardiac output is an adaptive value that must constantly adjust to the oxygen requirements of the organs.
- Separation of the four determinants of cardiac output—heart rate, contractility, preload, and afterload—is useful to consider the various interventions that can be used to increase it.
- Measurements of mixed venous oxygen saturation are essential to interpret cardiac output measurements.
- The relationship between cardiac filling pressures and volumes is relatively weak. Pressure measurements are important, however, because pressures (rather than volumes) are the primary determinant of edema formation.
- The calculation of derived variables, such as vascular resistances, ventricular work, and oxygen-derived variables, is of limited usefulness.

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Review Questions

1. Invasive arterial pressure measurement is required in all of the following *except*
a. Severe hypotension
b. Severe hypertension
c. Induced hypertension
d. Inotropic therapy
Answer: d. The aim of inotropic therapy is to increase cardiac output and oxygen delivery. It may influence arterial pressure somewhat but not sufficiently to require invasive monitoring (see the Arterial Pressure Measurement section).

2. How do the central venous pressure (CVP) and the right atrial pressure (RAP) correlate with each other?
a. The CVP is slightly higher than the RAP.
b. the CVP is slightly lower than the RAP.
c. The two values are identical.
d. It may vary depending on the respiratory conditions.
Answer: c (see the Measurement of Central Venous Pressure section).

3. A low SvO_2 can be explained by all of these *except*
a. Sedation
b. Anemia
c. Hypovolemia
d. Massive pulmonary embolism
Answer: a. Reduced oxygen demand is characterized by a normal or high SvO_2 (decreased oxygen extraction) (see the Mixed Venous Oxygen Saturation section).

5 Cardiac Pacing

GRANT R. SIMONS

CHAPTER OUTLINE

Electrocardiographic Considerations

Clinical Evaluation of AV Block

Management of Bradycardia and Indications of Temporary Pacing

Cardiac Pacing Techniques
- Esophageal and Transthoracic Pacing
- Transcutaneous Pacing
- Epicardial Pacing
- Transvenous Pacing
- Special Considerations in Temporary Pacing

Common Clinical Scenarios in Which Pacing Should Be Considered
- SN Dysfunction and AV Block
- Electrolyte and Metabolic Derangement
- Medication Side Effects
- Infectious Disease
- After Myocardial Infarction
- Torsades de Pointes

Conditions That Do Not Normally Require Pacing
- Hypothermia
- Hypothyroidism
- Obstructive Sleep Apnea
- Preoperative Considerations
- Seizure
- Spinal Cord Injury and Tracheal Suctioning

Permanent Pacing

Indications for Permanent Pacemaker Implantation
- Pacing Indications for Sinus Node Dysfunction
- Pacing Indications for Acquired AV Block
- Other Permanent Pacing Indications

Complications of Permanent Pacemaker Implantation
- Lead Dislodgement
- Pneumothorax
- Cardiac Perforation
- Bleeding and Hematoma
- Inadvertent Lead Placement in the Left Ventricle
- Arrhythmias
- Thrombosis
- Lead Failure
- Twiddler's Syndrome
- Pacemaker Syndrome
- Infection

Special Considerations in Permanent Pacing
- Intravenous Access
- Magnet Application
- Magnetic Resonance Imaging

Conclusions

Familiarity with the clinical management of patients who require cardiac pacing is essential in the critical care setting. The critical care physician should be proficient in the recognition of pathologic bradycardia and of electrocardiographic patterns that portend it, in temporary pacing, and in the management of patients with previously implanted cardiac rhythm devices. This chapter provides a practical review of these topics.

Electrocardiographic Considerations

Bradycardia may result from either sinus node (SN) dysfunction or atrioventricular (AV) block. Electrocardiographic recognition of SN dysfunction, which can present as sinus bradycardia, sinus pauses, junctional or wide-complex bradycardia without P waves, or postconversion pauses after termination of tachyarrhythmias

such as atrial fibrillation, is relatively straightforward and is not reviewed further here.

Electrocardiographic recognition of AV block is more complex, and proper classification is essential for communication among practitioners and for proper risk stratification and therapy.[1,2] AV block is classified as either first, second, or third degree. First-degree AV block is actually a misnomer, as there is no block, but rather delayed activation of the ventricles after atrial activation; this manifests electrocardiographically as a prolonged PR interval over 200 msec. First-degree AV block itself does not actually cause bradycardia as there is 1:1 AV conduction; however, in some patients it may indicate significant conduction system disease and a risk of progression to a higher degree of AV block and clinically significant bradycardia.

Second-degree AV block presents as *intermittent* failure of AV conduction in the form of nonconducted P waves. In type I second-degree AV block (also known as Mobitz I pattern or Wenckebach), there is a nonconstant PR interval followed by a *single* nonconducted P wave. Most commonly, the PR interval progressively prolongs before the blocked beat, after which there is resumption of a new cycle of gradual PR prolongation until the next blocked P wave. In type II second-degree AV block (also known as Mobitz II pattern), there are intermittent *single* nonconducted P waves with a constant PR interval among conducted beats. Importantly, diagnosis of type II second-degree AV block requires a constant P-P interval.[3]

The electrocardiographic distinction of Mobitz I versus II block, which can be challenging, requires at least two consecutive conducted P waves so that a determination can be made regarding whether there is a nonconstant PR interval prolongation prior to block.[3,4] Thus a third type of second degree AV block is 2:1 AV block, which cannot be classified further as either type I or type II because two consecutive conducted P waves are not present to allow for assessment of whether or not the PR interval is constant. The fourth and final type of second-degree AV block is high-degree AV block (also known as advanced AV block), in which two or more consecutive blocked P waves are present. High-degree AV block is described in terms of the AV ratio—for example, as 3:1 or 4:1 AV block. Significant semantic controversy exists regarding whether 2:1 AV block should be classified as either type I, type II, or advanced AV block[4–6]; however, it is clinically useful to describe it as a separate entity, as discussed below.

Third-degree AV block, which is also referred to as complete heart block, is a pattern in which there is no conduction from the atria to the ventricles. The electrocardiographic hallmark of third-degree AV block is a regular ventricular rate; among patients who are not in atrial fibrillation or flutter, the ventricular rate is faster than the sinus rate. If the ventricular rate is irregular, second-degree AV block is likely and should be strongly considered. Among patients in atrial flutter, it is sometimes challenging to distinguish high-degree AV block from complete heart block.

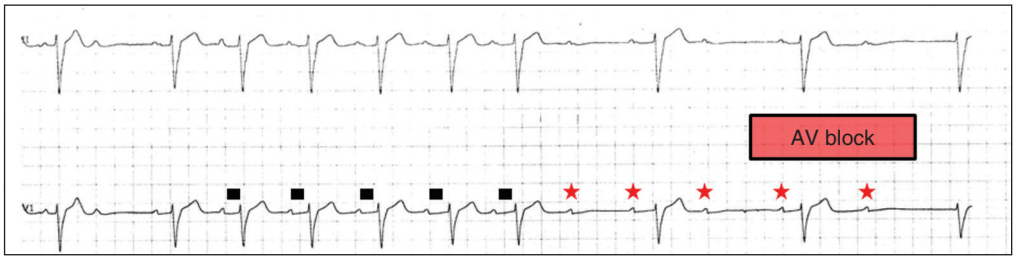
The "level" of AV block—whether within the AV node or below the AV node in the His-Purkinje system—is critical in determining the need for temporary or permanent pacing. A central concept in the assessment of AV block is that *AV nodal block is generally less perilous than block below the AV node (infranodal block)*. This is because AV nodal block is more likely to respond to pharmacologic interventions and because the escape rhythms observed after progression to complete heart block are usually faster and more stable. In contrast, AV block below the AV node, even if intermittent, may portend sudden progression to severe bradycardia or asystole unresponsive to intravenous medications. The pharmacologic responsiveness of the AV node results from its susceptibility to autonomic effects—specifically, parasympatholytic and adrenergic modulation, which is not a characteristic of His-Purkinje tissue. Thus, as a general rule, urgent temporary pacing should be considered for infranodal block, but it is rarely required for block within the AV node.

The most important clinical clue regarding level of block is the QRS width, which is considered to be wide when its duration is 120 msec or greater. Generally speaking, a narrow QRS complex is indicative of block at the level of the AV node, and a wide QRS complex suggests infranodal block. Another important clinical rule is that Mobitz II block is usually infranodal and more ominous than Mobitz I block, which is almost always the result of block at the level of the AV node. Thus a patient with Mobitz II second-degree block is likely to have underlying His-Purkinje disease and a bundle branch block electrocardiographic pattern; this should be recognized as potentially ominous, and there should be a low threshold for temporary pacing, even in the absence of symptoms. On the other hand, a patient with Mobitz I second-degree AV block is much lower risk, and temporary pacing is rarely required, although elective insertion of a permanent pacemaker for alleviation of symptoms may be appropriate. A 2:1 AV block is often "judged by the company it keeps"[5,6]; if Mobitz II infranodal block is also noted, the 2:1 block is likely to share the same mechanism.

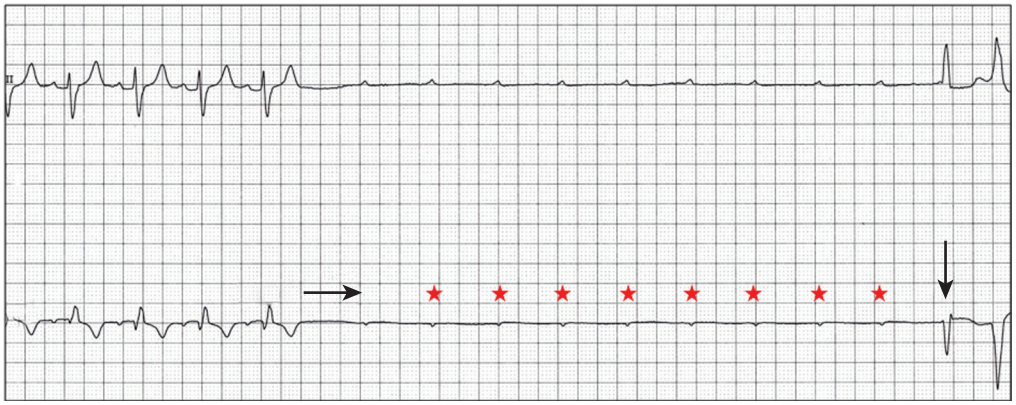
In the case of third-degree AV block, the considerations are similar. Infranodal block is associated with a slow and unreliable escape rhythm arising from the bundle branches or even ventricular myocardium, a wide and often bizarre QRS morphologic pattern, and a heart rate well below 40 beats/min.[7] A significant risk of sudden-onset, pharmacologically unresponsive asystole is present, and urgent intervention is usually required, even in the setting of hemodynamic stability. In contrast, complete heart block with a narrow escape rhythm does not typically require temporary pacing, unless it is medically unresponsive and accompanied by symptoms or significant hypotension. A history of syncope in a patient who presents with advanced second-degree AV block may portend a higher degree of AV block or pause-dependent torsades de pointes, and there should be a very low threshold for temporary pacing.[8]

Clinical Evaluation of AV Block

In the critical care setting, it is crucial to recognize vagally mediated AV block, which is usually clinically benign and rarely requires therapy. Vagally mediated AV block is common and results from causes such as sleep apnea, gastrointestinal distress, coughing, endotracheal suctioning, and sleep. It is frequently observed among asymptomatic young and/or athletic patients. It is due to *extrinsic* enhanced parasympathetic input and is characterized by progressive sinus slowing, progressive PR prolongation, Mobitz type I second-degree AV block immediately before the onset of complete heart block, and/or sinus slowing during the episode (Fig. 5.1). In particular, the finding of concomitant sinus slowing and AV block should be recognized as a *pathognomonic finding* for vagally mediated AV block. In contrast, AV block caused by an *intrinsic* failure of a diseased His-Purkinje system—also termed "paroxysmal" AV block—is characterized by a constant sinus rate, or even sinus acceleration during the episode (Fig. 5.2). Patients with paroxysmal AV block *usually* have a baseline conduction abnormality on their surface 12-lead electrocardiogram—most commonly, right bundle branch block—but this finding is not absolute. The hallmark of paroxysmal AV block is *immediate* transition from apparently normal conduction to complete AV block and ventricular asystole. This



• **Fig. 5.1** Telemetry strip demonstrating vagally mediated complete heart block. There is progressive PR prolongation *(black boxes)* and sinus slowing *(red stars)* just before the development of complete heart block, reflecting parasympathetic innervation of both the sinus and atrioventricular *(AV)* nodes.



• **Fig. 5.2** Telemetry strip demonstrating paroxysmal atrioventricular (AV) block. There is onset of AV block *(horizontal black arrow)* characterized by nonconducted P waves *(red stars)* with associated sinus acceleration, reflecting an intrinsic failure of AV nodal conduction. The nearly 7-second pause is eventually interrupted by a junctional escape complex *(vertical black arrow).*

is often triggered by a pause after a premature atrial or ventricular depolarization, but vagally mediated sinus slowing can have the same effect, complicating the interpretation of these events. Vagally mediated heart block is typically benign, is atropine responsive, and does *not* require temporary pacing. Paroxysmal AV block can be fatal and requires urgent temporary pacing until a permanent pacemaker can be placed.[9]

Management of Bradycardia and Indications of Temporary Pacing

Decisions regarding the need for temporary cardiac pacing are often required in the critical care setting. This decision-making process is in fact more central to critical care medicine than decisions regarding permanent pacing, which are commonly rendered by cardiology or cardiac electrophysiology consultants. Temporary pacing is indicated for hemodynamically significant or otherwise clinically significant bradycardia caused by either SN dysfunction or AV block that is not easily treated medically, for clinical syndromes that are likely to progress to severe bradycardia, and for rhythms that can serve as triggers for malignant ventricular tachyarrhythmias.

Pharmacologic intervention is a useful alternative to temporary pacing, particularly in cases of reversible bradycardia. Medical therapy to reduce vagal tone (e.g., atropine) or to increase sympathetic tone (e.g., dopamine, isoproterenol) may be sufficient in sinus bradycardia and in many cases of AV block. However, although the sinus node and the AV node are usually amenable to these autonomic interventions, the His-Purkinje system is generally not similarly responsive, as discussed previously. Block within the His-Purkinje system, which manifests as second- and third-degree block with a wide QRS complex and/or Mobitz II block, has a substantial likelihood of progression to severe bradycardia that is unresponsive to medical therapy; therefore immediate pacing is usually indicated.

The determination of whether bradycardia is clinically significant involves consideration of multiple parameters, including blood pressure, urine output, renal function, cardiac or other organ ischemia, congestive heart failure, and mental status. When these parameters are significantly deranged as a result of bradycardia, and pharmacologic intervention is not effective or practical, temporary pacing is indicated. It is not uncommon for temporary pacing indications to be reversible and not require subsequent permanent pacing after therapy. On the other hand, in many cases the underlying cause remains, and permanent pacemaker insertion is required before discontinuation of temporary pacing, which has served as a temporizing measure. Occasionally, there is clinical certainty that pathologic bradycardia is irreversible, and depending on staff and facility availability, referral for immediate permanent pacemaker insertion is appropriate in lieu of temporary pacing. Of note, with the exception of surgically placed epicardial electrodes, temporary atrial pacing is not feasible. Therefore temporary pacing is hemodynamically less advantageous than permanent dual-chamber pacing among patients with intact sinus node function caused by a lack of AV synchrony.

Cardiac Pacing Techniques

Esophageal and Transthoracic Pacing

For reasons of efficacy and patient comfort, esophageal pacing has fallen in disfavor in lieu of transcutaneous and transvenous pacing techniques. Transthoracic pacing with direct, percutaneous placement of a needle into the heart is obsolete.

Esophageal pacing and recording are of historical interest. The esophagus lies immediately posterior to the left atrium, and an esophageal pill electrode was historically used for diagnostic purposes. Esophageal recording easily identifies atrial activity, which can be useful in the differentiation of ventricular tachycardia from supraventricular tachycardia with aberrant conduction.[10] The presence of AV dissociation is virtually pathognomonic for ventricular tachycardia, but atrial activity is often difficult to recognize on the 12-lead electrocardiogram, particularly with fast, wide-complex arrhythmias. Nevertheless, straightforward algorithms allow for the rapid and relatively accurate electrocardiographic diagnosis of wide-complex rhythms, often regardless of whether atrial activity is apparent on the 12-lead electrocardiogram.[11,12]

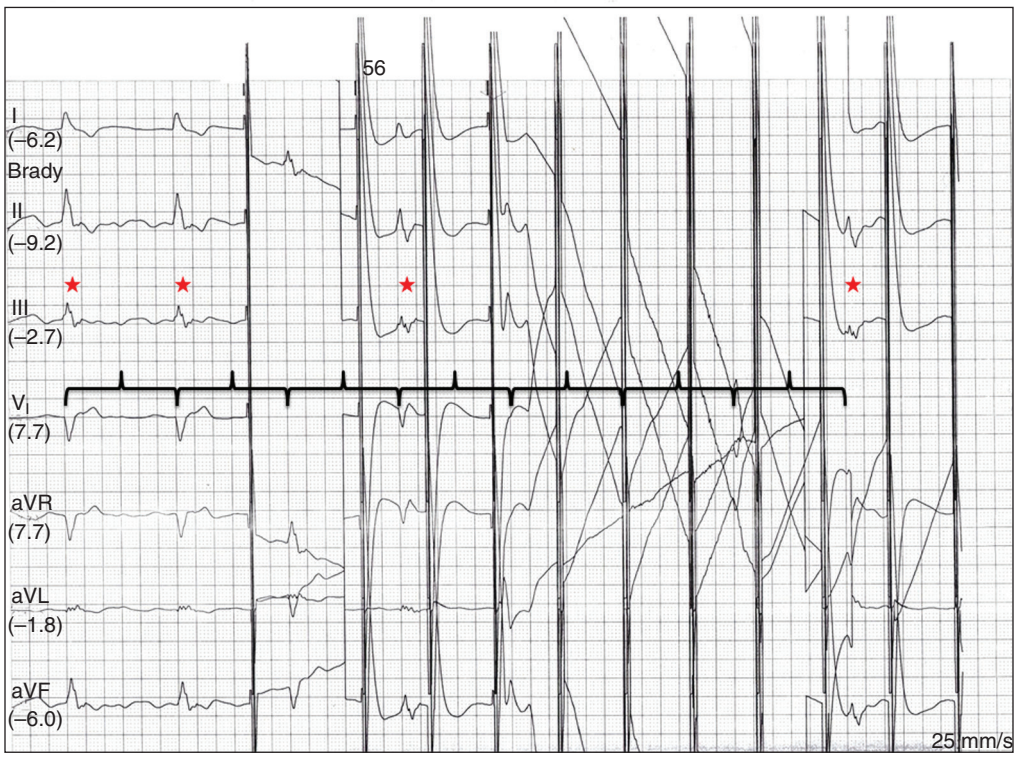
Transcutaneous Pacing

Background

First described by Paul Zoll in 1952 for the management of Stokes-Adams attacks, transcutaneous pacing involves the delivery of pacing stimuli though cutaneous patch electrodes.[13] It is the least technically challenging means of temporary pacing, and it can be initiated very rapidly. Most importantly, it does not introduce the risks associated with vascular access and transvenous pacing. The initial system required the subcutaneous insertion of 21-gauge needles and was limited by high pacing thresholds and significant pain. The technology has evolved over time, but transcutaneous pacing is still painful and generally requires the administration of sedation or analgesics. It is best tolerated in deeply anesthetized or unconscious patients, and it is most appropriate in situations in which pacing is required only briefly or intermittently, or as a bridging measure for placement of a transvenous system. Capture may be difficult to assess electrocardiographically because of saturation artifact from pacing stimuli, particularly if pacing outputs are high (Fig. 5.3).[14]

Methods

Commercially available external defibrillators have both pacing *and* defibrillating capability. The skin should be cleaned thoroughly with alcohol, but preferably not shaved, because the pain associated with pacing is typically localized to small abrasions and local salt deposits on the skin.[15] The patch electrodes should be arranged in an anteroposterior position with one patch over the mid-dorsal spine at the left paravertebral position, and the other over the point of maximal impulse. If abrasions are present, the patches can be positioned over an adjacent area of intact skin. The external generator should be turned on at the lowest pacing output and at a rate higher than the measured heart rate, and then increased in a stepwise fashion until reliable capture is observed on telemetry. It can be difficult to distinguish pacing artifact from capture, but



• **Fig. 5.3** Telemetry strip demonstrating ineffective transcutaneous pacing. There is an underlying junctional rhythm *(red stars)* that "marches through" the pacing artifact without any change in rate or rhythm, proving that transcutaneous pacing fails to capture the myocardium. The pacing artifact saturates the tracing and makes interpretation quite difficult.

the presence of a QRS complex and T wave—which represent cardiac depolarization and repolarization—is confirmatory. Capture can also be confirmed by the presence of a palpable or measurable pulse matching the paced rate. When in doubt, observation of the waveform of an arterial line or pulse oximeter is extremely helpful for confirmation of capture. The pacing output should be set slightly above capture threshold to minimize pacing artifact, pain, and risk of proarrhythmia.

Capture thresholds are predictably higher than with endocardial pacing, but most patients will capture at a pacing output of 40 to 70 mA. The capture threshold is proportional to the size of the patch electrode owing to the relationship between electrode size and current density—that is, larger electrodes require higher output for capture.[16] Higher impedance electrodes are preferred for pacing, but standard patch electrodes are more practical in daily practice. Hypoxia, acidosis, and prolonged periods of asystole may increase the pacing threshold.[17]

The pacing rate is dictated by the underlying rhythm and clinical indication. Pacing for a patient with complete heart block and hemodynamic instability should be at a rate of 60 to 90 beats/min until transvenous pacing can be established. Pacing for a patient with prolonged postconversion pauses or only intermittent heart block should be at a backup rate of 40 beats/min to minimize pacing. In general, the lowest possible rate should be chosen owing to patient discomfort.

Epicardial Pacing

Background

Most patients in the postcardiac surgery critical care setting have epicardial pacing wires. Eventual permanent pacing is required in roughly 2% of coronary artery bypass grafting and up to 7.7% of valve surgery cases,[18–20] but transient sinus node dysfunction (SND), fascicular block, bundle branch block, and AV block are common within the first few days after surgery.[21] Epicardial pacing offers a safe and well-tolerated "bridge" to recovery, avoiding the need for transcutaneous and transvenous pacing. It also allows for prevention, diagnosis, and management of postoperative atrial arrhythmias, and the optimization of hemodynamics in the critical care setting.

Methods

Epicardial wires are typically placed on the anterior right atrium and right ventricle at the conclusion of open heart surgery, then threaded through the right and left subcostal areas for attachment to an external pulse generator. Most surgeons routinely implant both atrial and ventricular leads because AV synchrony and native AV conduction is preferred whenever possible, particularly in patients with preexisting systolic dysfunction.[22,23]

Pacing and sensing thresholds typically deteriorate rapidly over 3 to 5 days owing to local inflammation,[24] and should be checked on a daily basis to ensure adequate safety margins, particularly in patients who are pacemaker-dependent. Thresholds below 5 mA are generally considered to be excellent, and thresholds above 10 mA warrant concern regarding an impending rapid rise in threshold and resultant inability to capture at the maximal external pulse generator output, which is 25 mA for most commercially available models. Of note, high outputs may only further exacerbate the local inflammation that produces high pacing thresholds.[25] Alternate locations—including the basal and lateral left ventricle—may be associated with more favorable pacing thresholds and cardiac performance.[26]

Prevention of Atrial Arrhythmias

Atrial fibrillation complicates 20% to 50% of cardiac surgery cases, resulting in increased length of stay, increased hospital costs, and higher morbidity and mortality rates.[27] The administration of β-adrenergic blockers and amiodarone constitutes first-line therapy, and there are data supporting the use of atrial pacing to prevent atrial fibrillation in the postoperative setting.[28,29] One small, prospective study demonstrated a 17% absolute risk reduction of postoperative atrial fibrillation through the use of "overdrive" atrial pacing (AAI mode at a minimum of 80 beats/min) for 24 hours on the second postoperative day, but longer-term follow-up was not reported in the study.[30] More recently, biatrial epicardial pacing has been demonstrated to be of potential benefit in the prevention of postoperative atrial fibrillation.[31] Overall, trials of epicardial pacing after cardiac surgery have been small and heterogeneous in design, but meta-analyses suggest an absolute reduction of 10% of postoperative atrial fibrillation with overdrive atrial pacing.[32,33] The beneficial effect of atrial pacing is probably synergistic with preventative pharmacologic intervention.

Treatment of Atrial Arrhythmias

Rapid, "burst" atrial pacing can be easily performed at the bedside using a standard external pulse generator. Typical atrial flutter and other macro-reentrant arrhythmias that involve the right atrium are often susceptible to pace termination owing to depolarization of the "excitable gap" of the flutter circuit. Pace termination is performed by pacing the atrium at a rate slightly faster than the arrhythmia and at a sufficiently high pacing output for atrial capture. One can begin pacing at 10 mA and 10 to 20 beats/min faster than the atrial rate for 5 to 10 seconds, but these parameters can be adjusted if initial attempts are unsuccessful. Because rapid ventricular pacing can easily precipitate ventricular fibrillation, it is essential to confirm that the epicardial system is connected appropriately before any pacing attempt, and to first test at a low rate to rule out incidental ventricular capture. Burst pacing may cause atrial flutter to degenerate into atrial fibrillation, which is often associated with a slower and better-tolerated heart rate.

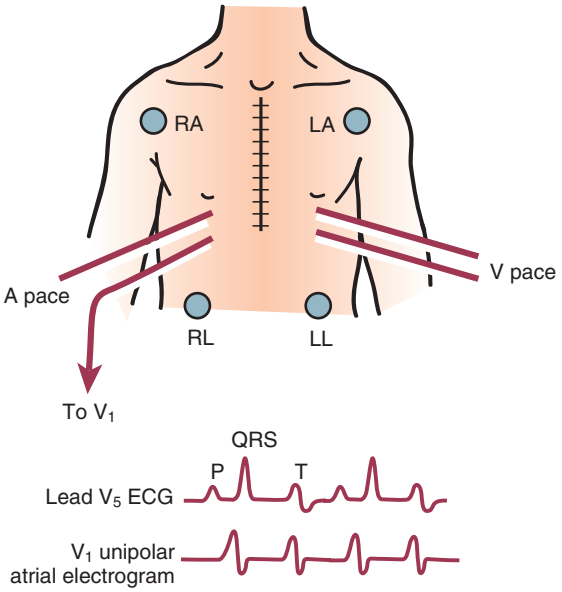
Diagnosis of Wide-Complex Arrhythmias

Atrial activity can be directly recorded by connecting the pin of an atrial epicardial wire to precordial lead V_1 of the 12-lead electrocardiogram, elucidating the mechanism of a tachycardia (Fig. 5.4). As discussed previously in the overview of esophageal recording, the presence of ventriculoatrial dissociation is diagnostic of ventricular tachycardia. AV association with an atrial:ventricular (A:V) ratio of 2:1 or higher is usually diagnostic of atrial tachycardia. Of note, the presence of a 1 : 1 ventriculoatrial relationship does not discriminate between tachycardia mechanisms because ventricular tachycardia may have 1 : 1 ventriculoatrial retrograde conduction.

Risks

Some centers argue against the routine placement of epicardial wires because of their cost and potential risk, but their use remains nearly ubiquitous. The frequency of complications is far less than 1%, but case reports have described the inadvertent laceration of saphenous vein grafts,[34,35] right atrium,[36] and right ventricular outflow tract[37] with development of either pericardial tamponade or hemothorax after wire removal, and infection attributed to

abandonment and bacterial colonization of the wires.[38,39] Epicardial wires should be removed with gentle traction, and their occasional abandonment generally does not constitute a risk to the patient. To minimize risks associated with pericardial bleeding, they should be removed in a monitored setting after discontinuation of anticoagulation therapy.



• **Fig. 5.4** Temporary atrial pacing wires used for arrhythmia diagnosis. Epicardial pacing wires can be used for arrhythmia diagnosis in postoperative coronary artery bypass graft patients when P waves cannot be clearly visualized on surface electrocardiography. One of the epicardial atrial wires is clipped to lead V_1 on the standard electrocardiogram machine. The unipolar atrial electrogram now appears on lead V_1 referenced to surface lead V_5 in this figure, demonstrating two P waves for every QRS complex, making the diagnosis of atrial flutter. *ECG,* Electrocardiogram; *LA,* left atrium; *LL,* left leg; *RA,* right arm; *RL,* right leg.

Transvenous Pacing

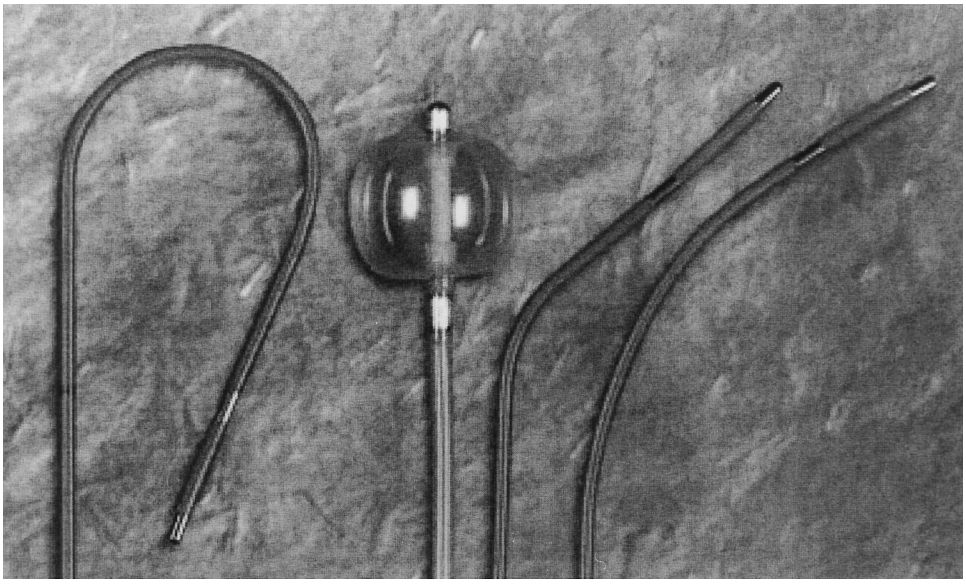
Background

Cardiac pacing with an endocardial electrode was first introduced in 1959 and quickly supplanted transcutaneous pacing as the method of choice for temporary pacing.[40] Transvenous pacing is more reliable and more comfortable than transcutaneous pacing, but it also takes more time to initiate and introduces procedural risk.

Methods

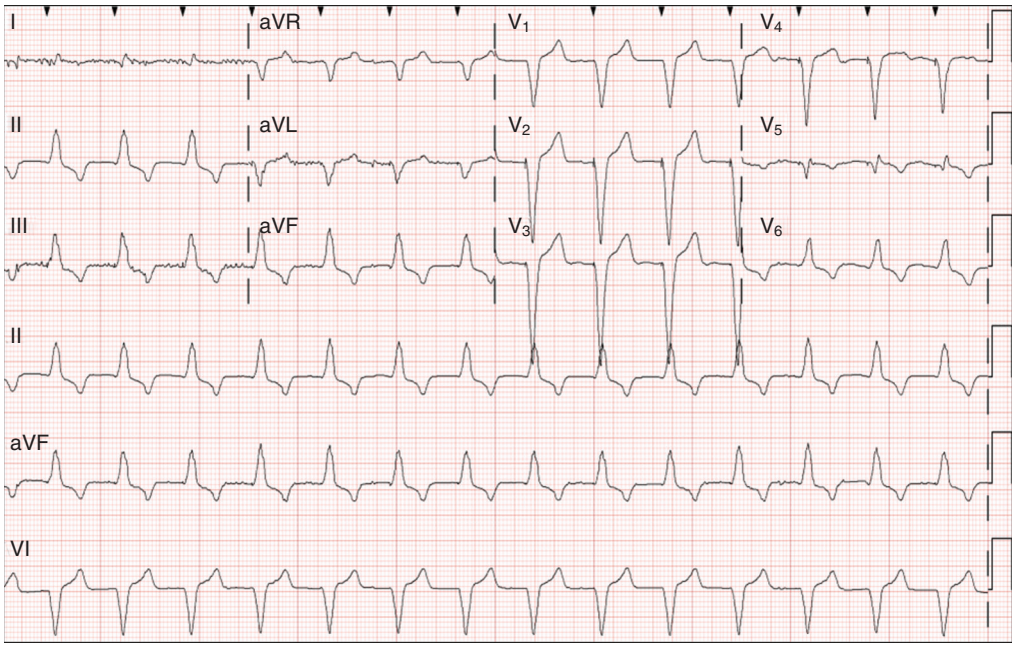
The internal jugular, subclavian, or femoral venous route can be used, but the internal jugular vein is generally the preferred approach. One subclavian vein should be reserved as a potential site for permanent pacemaker insertion, and the femoral vein carries a higher risk of infection, impedes patient movement, and requires fluoroscopic guidance. A variety of catheters are commercially available, the selection of which depends on operator preference, patient characteristics, and the availability of fluoroscopy (Fig. 5.5). Fluoroscopic imaging should be used routinely in patients with significant tricuspid regurgitation owing to the potential difficulty of catheter advancement across the tricuspid annulus. Fluoroscopic guidance should also be considered in patients with preexisting left bundle branch block owing to the potential for catheter-induced complete heart block as the result of mechanical trauma of the right bundle branch.[41]

Fluoroscopy simplifies catheter placement, but it may be unavailable, or a patient may simply be too unstable to transport to the catheterization laboratory. If portable fluoroscopy is unavailable, the procedure is best performed "blindly" at the bedside using a balloon-tipped catheter. Placement can be facilitated by electrocardiographic guidance, with or without pacing. If positioning is performed *with* pacing, the pacing catheter should be attached to an external pulse generator and set to pace at a rate slightly faster than the patient's intrinsic rate and at an intermediate pacing output (5–10 mA). After venous sheath placement, the catheter is then advanced slowly until ventricular capture is observed. Of

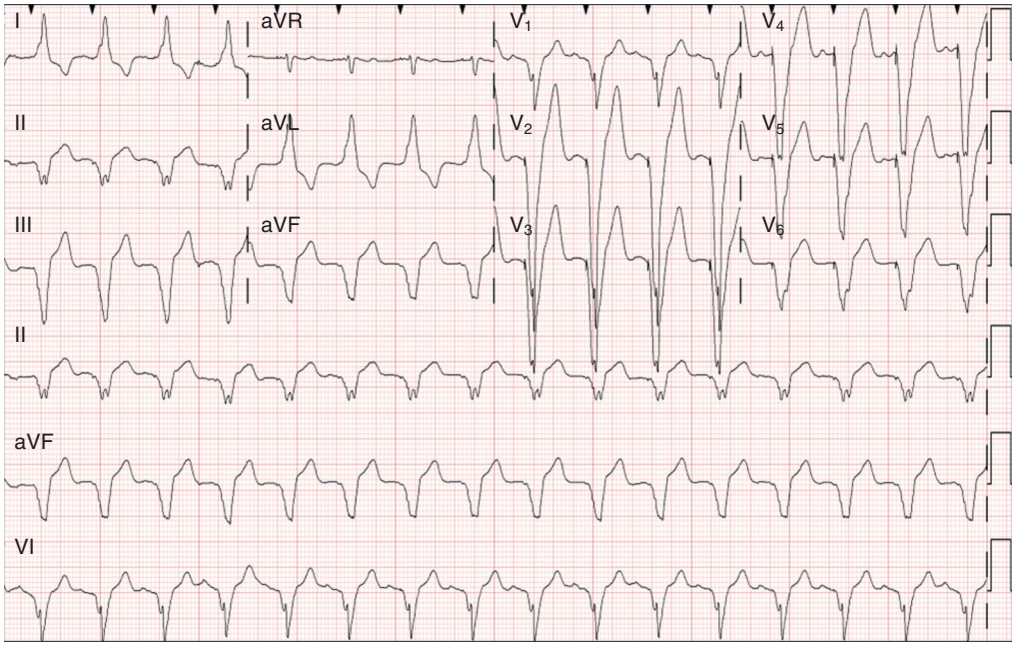


• **Fig. 5.5** Temporary bipolar pacing catheters. From *left to right,* atrial J, semifloating balloon-tipped, and two ventricular catheters with different curves. (Courtesy Daig Corporation/St. Jude Medical, Minneapolis, MN.)

note, right phrenic nerve capture and/or right atrial capture is sometimes incidentally observed as the catheter advances past these structures. Catheter contact and position can be assessed by examination of the paced QRS morphologic appearance: a left bundle branch block (LBBB) morphologic pattern with positive QRS complexes in leads II, III, and aVF (inferior frontal axis) suggests catheter position in the right ventricular outflow tract (Fig. 5.6), whereas an LBBB morphologic pattern with negative QRS complex in leads II, III, and aVF (superior frontal axis) suggests catheter position in the right ventricular apex (Fig. 5.7). If in the outflow tract, gentle withdrawal of the catheter will allow it to fall to a more inferior position and further advancement will guide it toward the apex. Deflating the balloon, then very gently advancing the catheter an additional 1 to 2 mm to wedge it in between the trabeculae of the right ventricle, can improve catheter stability.



• **Fig. 5.6** Paced morphologic pattern from right ventricular outflow tract. A paced QRS with a "left bundle branch block" morphologic pattern and "inferior" axis (positive QRS complexes in II, III, and aVF) suggests a pacing catheter position in the right ventricular outflow tract.

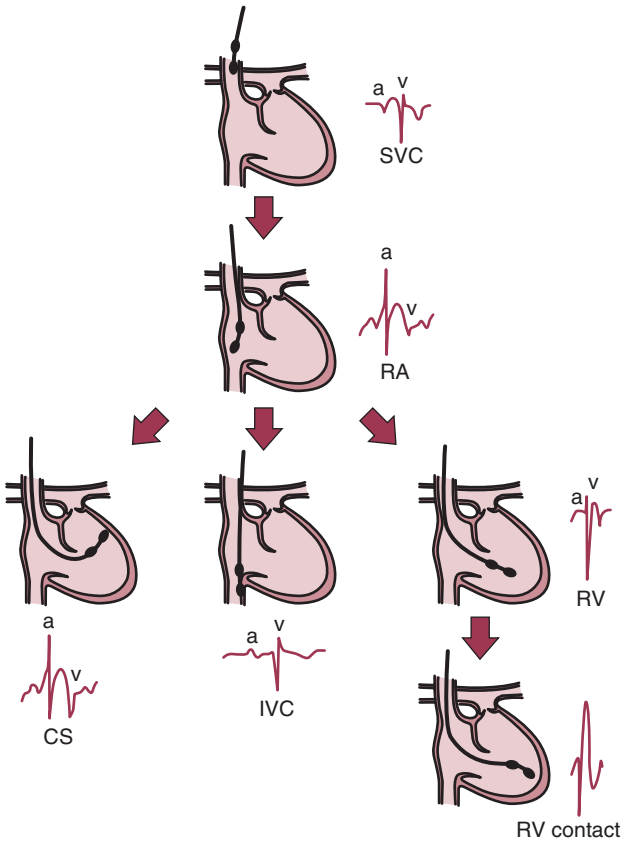


• **Fig. 5.7** Paced morphologic pattern from right ventricular apex. A paced QRS complex with a "left bundle branch block" morphologic pattern and "superior" axis (negative QRS complexes in II, III, and aVF) suggests a pacing catheter position at the right ventricular apex.

If positioning is performed *without* pacing, a pattern of ST-segment elevation on the local electrocardiogram indicates endocardial contact (Fig. 5.8).[42] The latter technique may be preferable in patients with complete heart block because even a brief period of overdrive pacing can extinguish a ventricular escape rhythm, resulting in immediate pacemaker dependency; therefore transcutaneous pacing patches should be in place and available for use. If the pacing catheter has been advanced more than 40 cm without evidence of capture, it may have looped within the right atrium or passed through the right atrium into the inferior vena cava. Either way, the catheter should be withdrawn with the balloon deflated and then advanced again after inflating the balloon. A sterile sleeve should always be placed over the catheter at the time of introduction so that subsequent repositioning can be performed aseptically.

Once good contact has been established, the pacing threshold can be tested by pacing at a rate above the underlying heart rate while reducing pacing output until loss of capture is noted on the monitor. R-wave sensing is assessed by setting the temporary pacemaker at a rate below the underlying heart rate and slowly *increasing* the sensitivity until undersensing is noted, in the form of inappropriate pacing spikes. Ideally, the pacing threshold should be below 2 mA and sensing should be greater than 5 mV. The system is set to a submaximal output several times the capture threshold, and a sensitivity of 20% to 30% of the measured R waves. If there is no underlying rhythm, the sensitivity can be set very high or to the asynchronous mode.

To prevent inadvertent dislodgment during manipulation of the external pulse generator, the pacemaker should be sutured to the patient's skin with a redundant loop in two locations. A new battery should be placed in the external pacemaker box. All connections between the catheter, cables, and pacemaker box should tightened and checked regularly for possible loosening. A chest radiograph should be performed immediately to rule out pneumothorax and to document catheter position.



• **Fig. 5.8** Electrogram guidance to place a temporary transvenous pacing lead. The end of the electrode is connected to an electrocardiogram to guide positioning. The electrogram appearances within the superior vena cava *(SVC)*, right atrium *(RA)*, inferior vena cava *(IVC),* and right ventricle *(RV)* are illustrated. When in contact with the RV, the electrogram demonstrates an injury current with ST-segment elevation. *CS,* Coronary sinus.

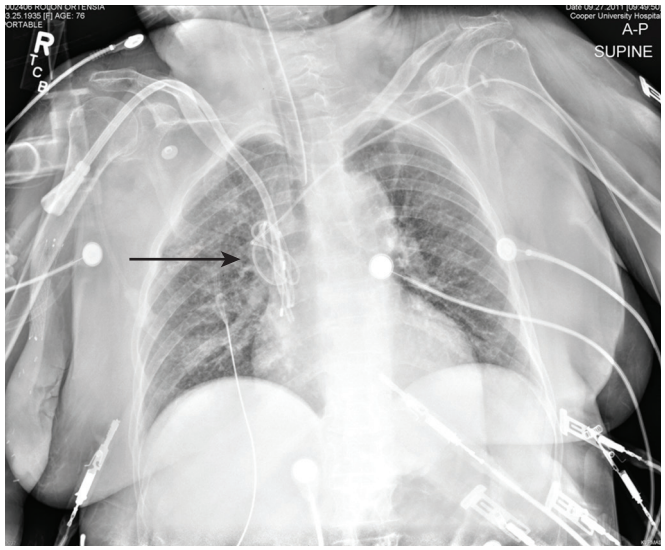
Special Considerations in Temporary Pacing

Contraindications

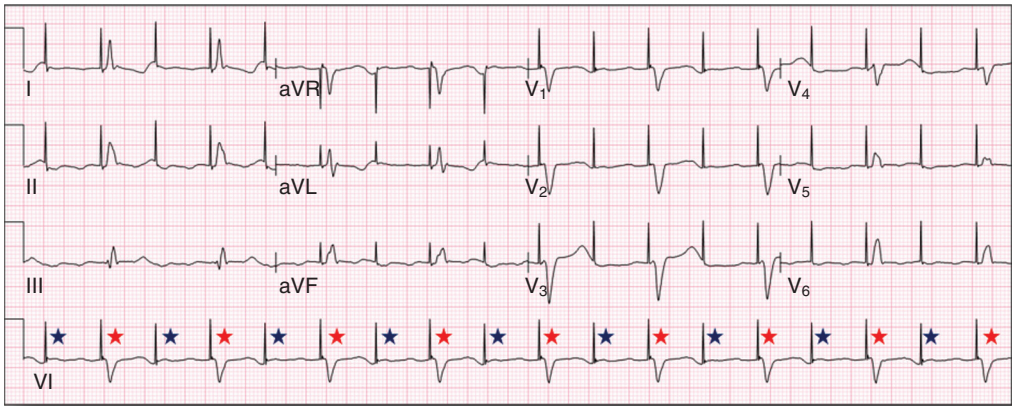
Transvenous pacing should not be attempted in patients with a known superior vena cava stenosis, and any resistance encountered during advancement of an intracardiac catheter should prompt the use of fluoroscopy (Fig. 5.9). Similarly, the presence of a mechanical tricuspid valve is an absolute contraindication owing to the potential for irreversible catheter entrapment.[43] Patients with a significant coagulopathy or an ongoing need for anticoagulation may be better served with transcutaneous pacing, if at all possible. If transvenous pacing is necessary, it should be performed under fluoroscopic guidance to minimize the risk of cardiac perforation. Femoral access may be preferable in these circumstances, particularly if the need for transvenous pacing is expected to be short-lived.

Sensitivity and Threshold Testing

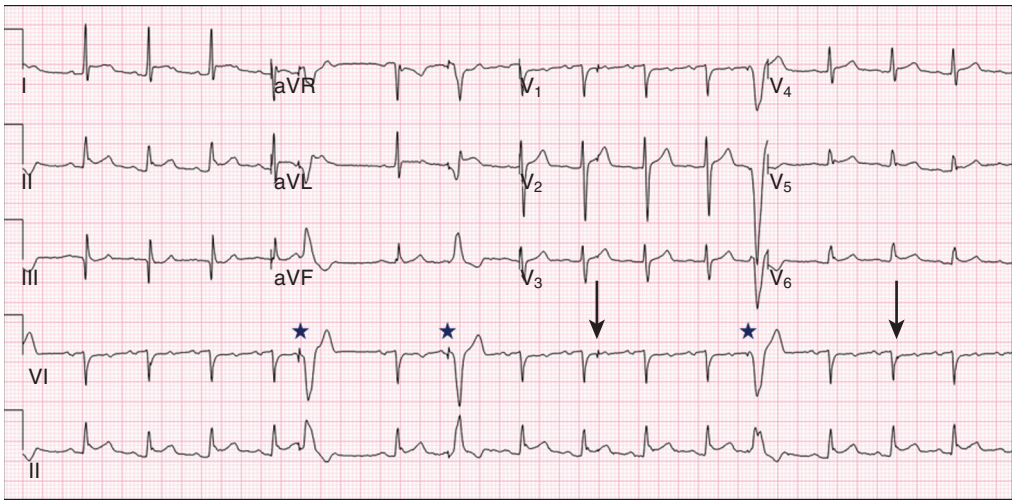
Owing to the inherent instability of a balloon-tipped catheter, sensing and pacing thresholds must be checked at least on a daily basis. Failure to sense can result in inappropriate pacing and precipitate polymorphic ventricular arrhythmias in rare circumstances.[44] Failure to capture in a pacemaker-dependent patient has obviously deleterious consequences, and it is imperative that the device be programmed with an adequate safety margin, typically at least two times the measured threshold. Failure to capture can be easily recognized on the 12-lead electrocardiogram



• **Fig. 5.9** Superior vena cava (SVC) stenosis. There is extensive entanglement of a temporary pacing catheter at the site of an SVC stenosis *(black arrow).* Any resistance encountered during catheter advancement should prompt the use of fluoroscopy.



• **Fig. 5.10** A 12-lead electrocardiogram demonstrating both capture *(red stars)* and failure to capture *(black stars)*. Failure to capture can be easily recognized by the presence of a pacing artifact without a subsequent QRS complex or T wave.



• **Fig. 5.11** A 12-lead electrocardiogram demonstrating failure to sense. There is indiscriminate delivery of a pacing artifact, independent of the underlying heart rate and rhythm *(black stars)*. Pacing intermittently fails to capture when falling within the refractory period of the ventricular myocardium *(black arrows)*.

or telemetry monitor by the presence of a pacing artifact without a subsequent QRS complex or T wave (Fig. 5.10). Failure to sense can be easily recognized by the inappropriate delivery of pacing spikes (Fig. 5.11).

Infection

Prevention of catheter-based infections is always important, but even more so in a patient who may ultimately require a permanent cardiac implantable electronic device. If a temporary pacemaker has been placed in emergent conditions, empiric coverage with a first- or second-generation cephalosporin is reasonable to minimize the likelihood of infection, particularly if femoral access has been chosen.

Timing of Reimplantation

The timing depends on a number of factors, including (1) the stability of the temporary pacing system; (2) the pacing indication; and (3) ongoing contraindications to permanent pacemaker implantation. In some circumstances—for example, in the setting of bloodstream infection—a prolonged period of transvenous pacing is required. Permanent, active fixation pacing leads with retractable screws can be inserted through a venous sheath and then attached to a permanent pulse generator on the patient's skin[45,46] (Fig. 5.12). This technique is highly favored for long-duration temporary pacing because it allows for ambulation and normal activity without concerns regarding lead dislodgement. In patients with recurrent ventricular tachyarrhythmias, a permanent defibrillator lead can be attached to an externalized defibrillator in the same fashion.[47] Permanent leads are more maneuverable than temporary leads, and the use of preformed stylets can facilitate delivery of leads to the right atrium, if atrial pacing is desired. If AV synchrony is desired and SN function is normal, a VDD lead with atrial sensing and ventricular pacing capability can be placed.[48]

Common Clinical Scenarios in Which Pacing Should Be Considered

SN Dysfunction and AV Block

As discussed earlier, the diagnosis of SN dysfunction is fairly straightforward, and electrocardiographic classification of AV

• **Fig. 5.12** Use of an active fixation permanent pacemaker lead for long-term temporary pacing. The lead was placed through a right axillary vein sheath and attached to an externalized permanent pacemaker generator. This allowed for normal patient activity and a low risk of lead dislodgment.

block is more challenging. Temporary pacing is indicated for hemodynamically significant or symptomatic bradycardia caused by SN dysfunction or AV block not known to be due to a promptly reversible cause. The relative risks and benefits of pacing and the overall clinical status of the patient should be taken into account. When there is clinical certainty that permanent pacing will be required and the patient is relatively stable, referral for expedited permanent pacemaker insertion should be considered instead.

Electrolyte and Metabolic Derangement

Hyperkalemia can precipitate complete AV block and can also elevate pacing thresholds in permanent pacemaker systems.[49–51] A progressive increase in extracellular potassium raises the resting membrane potential of cardiac myocytes, inactivating voltage-gated sodium channels that depend on a sufficiently negative resting membrane potential for normal function. The effect is more pronounced in the atrium and ventricle than within the specialized conduction system, explaining why the characteristic changes in the P wave, QRS complex, and T wave typically precede SN and AV nodal dysfunction: "peaked" T waves and QT shortening (potassium level 5.5 mEq/L); PR prolongation and QRS widening (potassium level 6.5 mEq/L); a "sinoventricular" rhythm caused by the apparent absence of atrial activity (potassium level 8–9 mEq/L); and lastly, a "sine wave" pattern owing to merging of the QRS and T wave that predicts impending cardiac arrest (potassium level 10 mEq/L).[52] Nevertheless, the 12-lead electrocardiogram may be entirely normal in cases of pronounced hyperkalemia, and AV block may occur in the absence of other electrocardiographic findings.[53–56] Therefore a routine metabolic evaluation is indicated in all patients with new conduction abnormalities.

The initial management of hyperkalemia-induced heart block is medical. If 12-lead electrocardiographic findings are pathognomonic for hyperkalemia, empiric treatment is appropriate while laboratory studies are pending. The administration of calcium chloride or calcium gluconate acutely antagonizes the electrical effects of potassium, partially restoring normal SN automaticity and conduction velocity. The effect is short-lived, however, and does nothing to correct extracellular potassium levels. Insulin, albuterol, and catecholamines reduce extracellular potassium through activation of the Na^+/K^+-ATPase pump, and sodium polystyrene sulfonate (Kayexalate) facilitates its gastrointestinal excretion. Dialysis is the most definitive treatment but requires peritoneal or vascular access. Temporary pacing may be helpful, but prohibitively high capture thresholds may be problematic. In patients with preexisting cardiac rhythm devices, pacing outputs can be increased if there is intermittent failure to capture.

Case reports and animal studies suggest a link between metabolic acidosis and heart block, and metabolic acidosis frequently accompanies hyperkalemia in the setting of chronic kidney disease.[57] The administration of sodium bicarbonate indirectly lowers extracellular potassium because of its effect on extracellular pH; this may improve responsiveness to vasopressors in emergent situations.[58]

Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia have not been implicated as precipitants of bradycardia.

Medication Side Effects

A number of medications can cause severe sinus bradycardia, AV block, or both. β-Adrenergic blockers and nondihydropyridine calcium channel blockers are both negatively chronotropic, dromotropic, and inotropic, and their administration can result in significant bradycardia and hypotension, particularly in overdose. The hallmark of digitalis toxicity is the appearance of concomitant AV block and enhanced atrial or ventricular automaticity; it may present with high-degree or complete AV block. Amiodarone, dronedarone, and sotalol—class III antiarrhythmic drugs with mixed antiarrhythmic effects—frequently cause bradycardia owing to negative SN or AV conduction effects. Some studies suggest that drug-induced AV block—particularly at therapeutic levels—is a predictor of future conduction disorders.[59]

Clearly, the initial treatment is discontinuation of the offending medication(s). Directed therapy may occasionally be useful as well, but the evidence is largely anecdotal. β-Adrenergic blocker toxicity may respond to glucagon, and calcium channel blocker toxicity may respond to calcium or glucagon in refractory cases.[60–64] Vasopressors are occasionally necessary because of the vasodilatory and negative inotropic effects of these drugs. Digoxin toxicity can be treated with digoxin antibody fragments (Digibind).[65] If hemodynamic instability persists in the setting of severe bradycardia, temporary pacing is indicated. β-Adrenergic blockers and calcium channel blockers can increase pacing thresholds in permanent devices; if failure to capture is noted in a patient with suspected overdose of these agents, a temporary increase in pacing output may solve the problem.[66]

Infectious Disease

Lyme disease is the most common tick-borne illness in North America.[67] Erythema migrans is sufficient for diagnosis, but most patients cannot recall a tick exposure or rash.[68] The diagnosis of Lyme carditis requires serologic testing for confirmation, and *Borrelia burgdorferi* immunoglobulin M and G antibodies are positive in the vast majority of patients with the disease.[69] Regardless of patient history, the diagnosis of Lyme carditis should always be considered in a patient presenting with heart block in an endemic area, particularly during warmer months. Typically, Lyme carditis affects the AV node; progression from first- to third-degree AV block and back to normal conduction may be noted; resolution of complete heart block can take from several days to several weeks.[70] Temporary pacing is occasionally necessary because of hemodynamic instability. Third-degree AV block in Lyme carditis is associated with a stable junctional escape rhythm, but more diffuse involvement of the His-Purkinje system with a slower, more unstable escape is rarely noted.[71] It is essential for the clinician to always consider Lyme disease as a cause for AV block for two reasons. First, because this etiology is reversible, proper diagnosis prevents inappropriate permanent pacemaker insertion. Second, failure to treat Lyme disease at this otherwise asymptomatic stage allows for further unrecognized progression to fully disseminated Lyme disease and systemic organ involvement.[72]

Infective endocarditis can be complicated by a broad spectrum of conduction disturbances, including first-degree AV block, bundle branch block, and complete heart block. Any new conduction deficit suggests perivalvular abscess because of the proximity of the compact AV node and bundle branches to the membranous septum.[73,74] Conduction disturbances most commonly complicate aortic valve endocarditis, but the tricuspid valve and mitral valve are also susceptible.[75–77] Perivalvular abscess and heart block are indications for surgical repair.[78] Serial 12-lead electrocardiography should be performed in all patients with endocarditis, and temporary pacing should be strongly considered for any progressive conduction disturbance, including a significant increase in the PR interval.

Lymphocytic and giant cell myocarditis are typically associated with acute systolic dysfunction, but they can also be complicated by severe electrical abnormalities, including complete heart block. Lymphocytic myocarditis carries a more favorable prognosis than giant cell myocarditis, but permanent pacemaker dependency is possible with either condition.[79]

After Myocardial Infarction

Official guidelines for temporary and permanent pacing after ST-elevation and non-ST-elevation myocardial infarction (NSTEMI) were last updated in 2013 and 2014, respectively,[80,81] and permanent pacemaker indications after myocardial infarction were last updated in 2012.[82] The most recent guideline updates include a stronger focus on infarct location as a diagnostic consideration. Recommendations for temporary pacing are largely based on expert opinion, in addition to case reports, case series, and published summaries from before the reperfusion era.

The interventional cardiologist frequently assesses the need for temporary pacing at the time of percutaneous intervention, but familiarity with official guidelines and an understanding of the risk of progression are critical in the appropriate management of the patient after myocardial infarction. It is important to remember that bradycardia-induced hypotension and decreased cardiac output may exacerbate myocardial ischemia and limit reperfusion, and therefore heart rate support in the periinfarct setting should always be considered.

The culprit artery has prognostic implications. Complete heart block complicating anterior wall myocardial infarction—usually involving the proximal left anterior descending artery—is due to necrosis of the interventricular septum and irreversible damage to the His-Purkinje conduction system. In contrast, complete heart block in inferior wall infarction—usually involving the proximal right coronary artery (RCA)—is usually vagally mediated and atropine sensitive in the first hours of infarction.[83] Local accumulation of adenosine in the days after infarction may lead to longer-duration, atropine-insensitive AV block, but permanent pacing is rarely indicated.[84] Because the RCA supplies the sinoatrial nodal artery in 90% of cases, a proximal RCA infarction may also be complicated by sinus bradycardia, sinoatrial exit block, and sinus arrest; these, too, are typically transient in nature and atropine responsive.

In the case of both NSTEMI and ST-elevation myocardial infarction (STEMI), temporary pacing is indicated for asystole or for symptomatic or hemodynamically significant bradycardia unresponsive to medical therapy, which is usually limited to atropine because of concerns regarding pressor-induced myocardial ischemia. Overdrive pacing is also always indicated to prevent recurrence of bradycardia-induced ventricular tachycardia. Inferior NSTEMI is often associated with sinus bradycardia, which is usually treated medically, and with first-degree AV block, which does not require therapy. Transient high-degree AV block with a narrow QRS is also often seen after inferior NSTEMI, but this does not generally require pacing. However, new second- or third-degree AV block or bundle branch block after *anterior* NSTEMI is more ominous because of correlation with a larger amount of conduction system involvement, which portends a risk of progression to asystole. Prophylactic temporary pacing is therefore indicated for anterior NSTEMI associated with high-degree AV block, new bundle branch block, or bifascicular block. Of course, when the location of NSTEMI is unclear, the clinician should err on the side of caution and treat as if the infarct is anterior.

The most recent guideline update for STEMI has reduced the number of recommendations for transvenous pacing. Whereas temporary transvenous pacing was previously recommended for STEMI complicated by new bifascicular block or bundle branch block *and* concomitant Mobitz type II second-degree AV block, regardless of the culprit artery, and for alternating bundle branch block, regardless of the status of AV conduction,[85] the more recent guidelines stress STEMI location as an important diagnostic consideration. In the case of inferior/posterior STEMI, conservative management is recommended for transient second- or third-degree AV block, with application of prophylactic trancutaneous pacing pads. For anterior or lateral myocardial infarction, temporary pacing is recommended for even transient second- or third-degree AV block, new bundle branch block, or bifascicular block. The updated guidelines also indicate that either transcutaneous pacing or transvenous pacing can be chosen in these situations, which is less stringent than the prior edition.

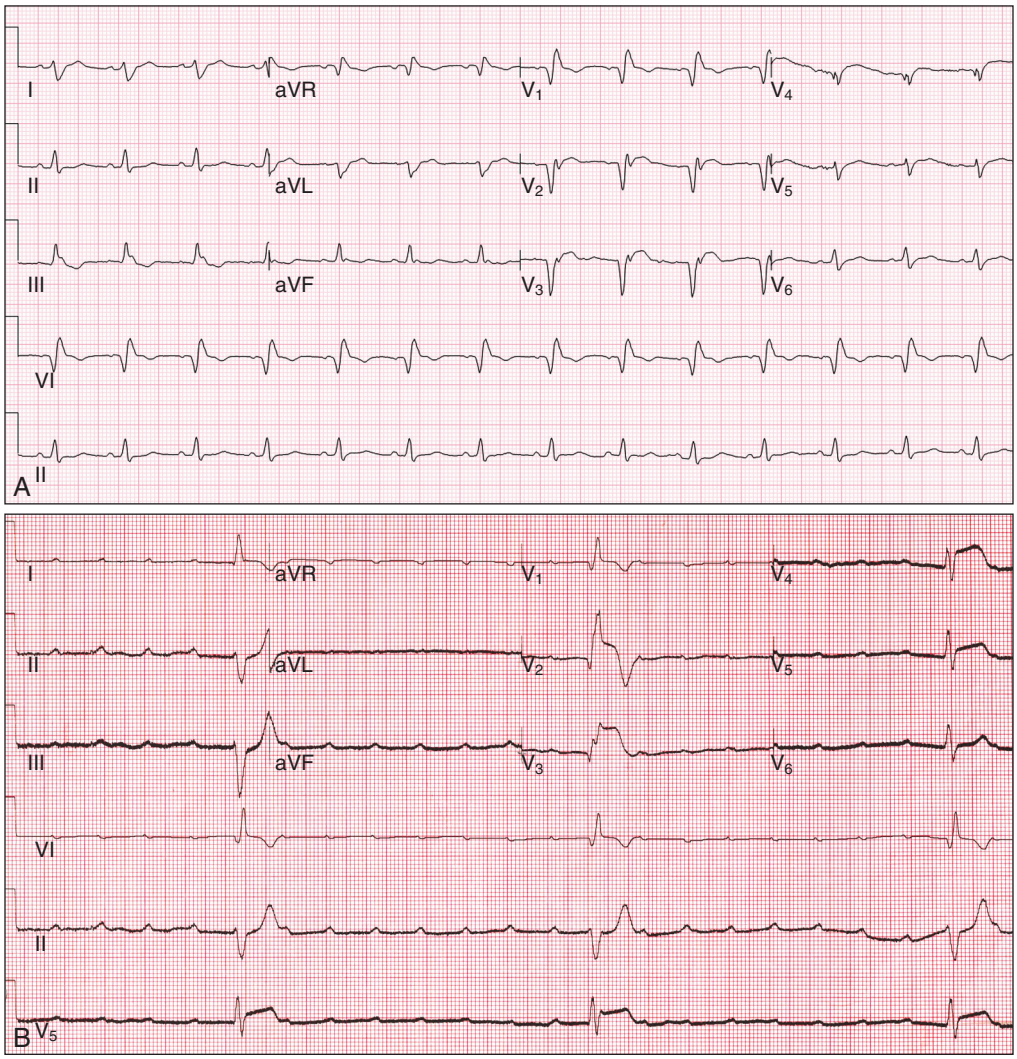
However, the critical care physician should be well versed in the significance of His-Purkinje abnormalities during the periinfarct setting, and it is good clinical practice to place prophylactic transcutaneous pacing pads in high-risk settings. In particular, alternating bundle branch block—right bundle branch block alternating with left bundle branch block, or right bundle branch block with alternating left anterior and posterior fascicular block—is a marker of severe His-Purkinje disease. Bifascicular block with

right bundle branch block and left posterior fascicular block carries a very poor prognosis with a high risk of progression to complete heart block (Fig. 5.13).[86,87] Any of these findings—or new or not previously known bundle branch block or intraventricular conduction delay—should be noted, and transcutaneous pacing should be readily available because of the risk of progression to clinically significant second- or third-degree AV block.

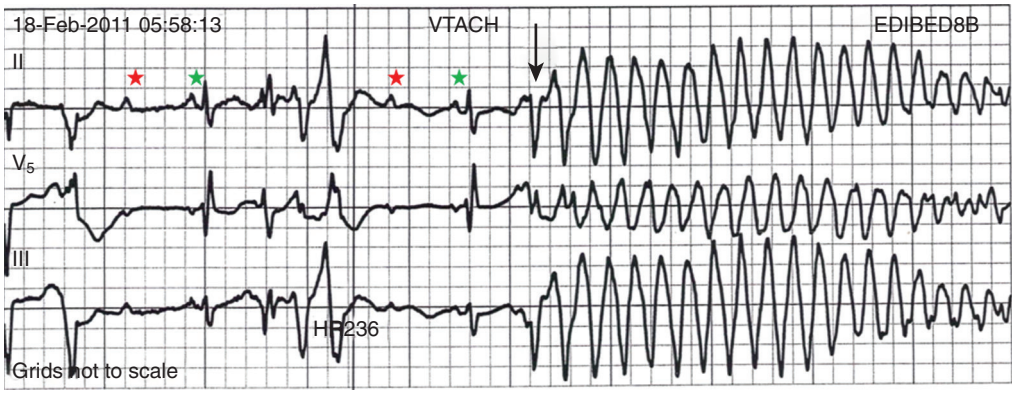
Torsades de Pointes

Torsades de pointes is a syndrome of *bradycardia-induced ventricular tachycardia* whose diagnosis requires the three elements of polymorphic ventricular tachycardia (typically with the appearance of "twisting" around the electrocardiographic baseline), a prolonged QT interval, and pause-dependent initiation of tachycardia, usually during the compensatory pause following a premature ventricular depolarization.[88–90] Not all cases of bradycardia-induced, or pause-dependent, ventricular tachycardia meet all three criteria, but pacing still plays a prominent role in management. Although ventricular tachycardia in torsades de pointes is usually nonsustained, it can rarely degenerate into ventricular fibrillation. The underlying QT prolongation can be either congenital or acquired, the latter of which is by far more common in the critical care setting and most often is due to either administration of a culprit drug or severe electrolyte disturbance.

The most important considerations in the management of torsades de pointes are appropriate recognition of the problem, correction of the underlying cause(s), and avoidance of QT-prolonging drugs that can further exacerbate the problem. Although this arrhythmia is polymorphic by definition, not all polymorphic ventricular arrhythmias are due to torsades de pointes. Polymorphic ventricular tachycardia may complicate acute coronary syndrome, but it is typically associated with a suggestive clinical history and ST-segment deviation. Temporary or permanent pacemaker



• **Fig. 5.13** Bifascicular block after acute, left anterior descending coronary artery infarction. A, A 12-lead electrocardiogram demonstrating sinus rhythm with normal atrioventricular (AV) nodal conduction, but right bundle branch block and left posterior fascicular block. There are also pathologic Q waves in leads V_1 to V_4, consistent with an anterior wall infarction caused by occlusion of a proximal left anterior descending artery. B, A 12-lead electrocardiogram of the same patient, 1 week later. There is now high-grade AV block with a right bundle branch block and left anterior fascicular block, owing to necrosis of the His-Purkinje system that has left only the left posterior fascicle capable of conduction.



• **Fig. 5.14** Telemetry strip demonstrating torsades de pointes. The rhythm is sinus with both conducted *(green stars)* and nonconducted *(red stars)* P waves. Premature ventricular complexes emerge from a dramatically prolonged QT-U complex *(black arrow),* eventually initiating polymorphic ventricular tachycardia.

malfunction with ventricular undersensing can lead to "R on T" pacing, and certain pacemaker settings that minimize ventricular pacing can predispose to "long-short" sequences and polymorphic ventricular arrhythmias as well.[91–94] If ventricular tachycardia is reliably initiated with pacing, pacemaker reprogramming may resolve the problem; electrophysiology consultation should be sought immediately.

The administration of intravenous magnesium sulfate (1–2 g over 5–10 minutes) and correction of hypokalemia is acutely effective in many patients.[95] If ineffective, isoproterenol (1–4 μg/min) can accelerate the heart rate and shorten the QT, but this should be avoided in long QT syndrome—particularly long QT type 1—because of the potential for proarrhythmia owing to the underlying ionic channel defect, in which catecholamines paradoxically prolong repolarization. Similarly, amiodarone should not be given for torsades; this is a common error, which can exacerbate QT prolongation. If an antiarrhythmic medication is essential, lidocaine is a reasonable alternative.

Temporary pacing is indicated for patients in whom electrolyte supplementation and pharmacologic augmentation of the heart rate fail, or for patients with severe AV conduction disturbances that predispose to long-short initiation sequences. Temporary pacing at an increased rate shortens the action potential and QT interval but also truncates the post–premature ventricular contraction pauses that typically trigger an episode (Fig. 5.14).[96] Typically, pacing at a rate of 90 to 100 beats/min is sufficient to suppress ventricular ectopy and/or avoid post–premature ventricular contraction pauses, but rates as fast as 140 beats/min may be necessary.[97] Patients with previously implanted cardiac rhythm devices should undergo bedside device reprogramming to achieve the same effect. In patients with normal AV nodal conduction, atrial pacing is preferred.

Conditions That Do Not Normally Require Pacing

Hypothermia

Hypothermia can produce dramatic electrocardiographic abnormalities—PR prolongation, QRS widening, and QT prolongation, in addition to both atrial and ventricular arrhythmias—and familiarity with this condition is increasingly important in the critical care setting owing to the widespread adoption of therapeutic hypothermia in survivors of cardiac arrest.[98–100] Moderate (32°C–33.9°C) hypothermia causes a reduction in cardiac output that is mediated by sinus bradycardia, but this is accompanied by an increase in myocardial contractility and proportional decrease in basal metabolism. No specific treatment is needed, and attempts to increase the heart rate with drug or temporary pacing are counterproductive.[101] Deep hypothermia (<30°C) is associated with an increased risk of atrial and ventricular arrhythmias, reduced responsiveness to electrical and pharmacologic cardioversion, and increased sensitivity to mechanical manipulation.[102] Resuscitation of severely hypothermic patients with transcutaneous pacing has been reported,[103] but the near-immediate initiation of ventricular fibrillation by transvenous pacing has also been described.[104] The role of temporary pacing—whether transcutaneous or transvenous—is limited and should be reserved for extreme situations of hemodynamic and electrical instability. The primary treatment is rewarming.

Hypothyroidism

Severe hypothyroidism is most commonly seen in the elderly and is often precipitated by infections. Case reports have established that severe hypothyroidism and myxedema coma can cause not only SN dysfunction but also a range of AV conduction abnormalities, including complete heart block. The symptoms of hypothyroidism can be vague, and the electrocardiographic manifestations—P-wave flattening, low QRS voltage and intraventricular conduction delays, QT prolongation, and T-wave flattening or inversion—are nonspecific. Thyroid hormone replacement, which is occasionally administered intravenously in severe cases of myxedema, can quickly normalize conduction but may take up to several weeks in some patients.[105–107] Patients who present with new conduction abnormalities—particularly the elderly and infirm—should be routinely screened for hypothyroidism. Temporary pacing is rarely needed in cases of advanced AV block. Thyroid hormone supplementation is usually curative.

Obstructive Sleep Apnea

Obstructive sleep apnea has been associated with cyclic patterns of SN and AV nodal conduction disturbances, occasionally resulting in prolonged periods of asystole during sleep.[108] In general, nocturnal arrhythmias are less clinically relevant than those during the day,

and the need for intervention should be taken in the context of the clinical situation. The finding on telemetry of profound sinus pauses or long-duration AV block during sleep should always generate a suspicion for sleep apnea, and patients should be evaluated accordingly.

Atropine has been shown to abolish cyclic variation and nocturnal bradycardia, suggesting that autonomic influences play a role.[109] One study suggested that atrial overdrive pacing reduces the number of central and obstructive apneic episodes,[110] but subsequent studies have shown no benefit, and pacing does *not* currently play a role in the chronic management of this disorder.[111–113] Continuous positive airway pressure, which is the therapy of choice for sleep apnea and associated bradycardia, abolishes conduction disturbances in the majority of patients, suggesting that hypoxia plays a role in the pathophysiology of the condition.[114]

Preoperative Considerations

Preexisting His-Purkinje disease—complete right or left bundle branch block, or bifascicular block, for example—does *not* routinely require temporary pacing before surgery. Patients with complete heart block, regardless of whether junctional or ventricular escape complexes are present, should be considered for temporary pacing during surgery owing to the potentially suppressive effects of general anesthesia on sympathetic tone and on a reliable escape mechanism. Patients with preexisting left bundle branch block who require Swan-Ganz catheterization have a small risk of procedurally related complete heart block caused by catheter-induced right bundle branch block.[41] In these situations, right-sided heart catheterization should be performed under fluoroscopy, and transcutaneous pacing should be immediately available. The presence of an "rS" complex in lead V_1 may reflect left-to-right septal activation and left bundle branch *delay*, rather than complete left bundle branch block; the risk of catheter-induced heart block may be lower in these circumstances.[115]

Seizure

Severe sinus bradycardia and prolonged periods of asystole complicate less than 0.4% of seizures.[116] "Ictal bradycardia" is likely vagally mediated, but there is disagreement within the epilepsy community about its potential contribution to sudden death.[117,118] Although the majority of episodes terminate spontaneously, some patients are ultimately referred for pacemaker implantation. In the critical care setting, simultaneous electrocardiographic and encephalographic monitoring can be quite helpful to rule out a primary bradycardic etiology when clinical features suggest prodromal seizure activity. Recently simultaneous video-electroencephalographic monitoring and tilt table testing has been introduced to distinguish between primary epilepsy and secondary seizures caused by bradycardia.[119] The most appropriate management of ictal bradycardia—including the potential need for temporary pacing—is unclear.

Spinal Cord Injury and Tracheal Suctioning

Severe cervical injury is nearly universally associated with sinus bradycardia, sinus pauses, and hypotension in the days after injury, but these changes typically resolve within 2 to 6 weeks.[120] Temporary or permanent pacing is almost never required in this situation and should be reserved for intractable cases where long pauses are clearly clinically significant. Endotracheal intubation, tracheal suctioning, and repositioning can precipitate prolonged, vagally mediated pauses, presumably caused by impairment of the sympathetic nervous system input during periods of increased parasympathetic tone. There have been case reports of asystolic cardiac arrest during tracheal suctioning; supplemental oxygen therapy was at least partially effective in preventing further episodes, suggesting that hypoxia played a role.[121] The administration of atropine, theophylline, aminophylline, and isoproterenol—individually or in combination—may attenuate these pauses, but their administration may be ineffective in the short term and cumbersome in the long term. There is no consensus on the issue, but some authors advocate placement of a permanent pacemaker in patients with medically refractory, profound pauses who require prolonged mechanical ventilation owing to the unpredictable nature of these events.[122] Temporary pacing can be considered on a case-by-case basis, but it is important to recognize that the primary underlying problem is autonomic in nature.

Permanent Pacing

As discussed previously, decisions made in the critical care setting regarding pacing primarily involve a decision whether or not urgent temporary pacing is indicated, and decisions regarding permanent pacemaker implantation are generally made in collaboration with cardiology and/or cardiac electrophysiology consultants. However, familiarity with indications for permanent pacemaker insertion is useful in cases where it may be appropriate and feasible to forgo temporary pacing in favor of expeditious permanent pacemaker insertion. This is certainly worth consideration when bradycardia is not due to a reversible or transient cause, as avoidance of temporary pacing minimizes overall procedural risk and length of stay. More importantly, expertise in the management of patients with previously implanted pacemakers, including management of pacemaker insertion complications, is essential.

Indications for Permanent Pacemaker Implantation

Indications for permanent pacemaker insertion are reviewed briefly. The American College of Cardiology Foundation, the American Heart Association, and the Heart Rhythm Society have jointly engaged in the production of guidelines for cardiac implantable electronic device implantation, with publication of updated guidelines in 2012.[82] These recommendations are primarily evidence-based, and this publication includes an extensive review of the literature on the topic. As with other guideline documents, recommendations are classified as class I, II, or III as follows:

- Class I: Benefit $\ggg$ Risk; the procedure/treatment *should* be performed/administered.
- Class II: Conditions for which there is conflicting evidence or divergence of opinion about the usefulness/efficacy of the procedure.
  - Class IIa: Benefit $\gg$ Risk; *it is reasonable* to perform the procedure/administer treatment, although additional studies with focused objectives are still needed.
  - Class IIb: Benefit $\geq$ Risk; the procedure/treatment *may be considered*, although additional studies with broad objectives are needed or additional registry data would be helpful.
- Class III: Risk $\geq$ Benefit; the procedure/treatment should *not* be performed/administered because it is not helpful and may be harmful.

The level of evidence or weight of evidence to support these recommendations is ranked as follows:

- Level of evidence A: Data are derived from multiple randomized clinical trials or meta-analyses.
- Level of evidence B: Data are derived from a single randomized trial or nonrandomized studies.
- Level of evidence C: Data represent the consensus opinion of experts, case studies, or standard of care.

Indications for permanent pacemaker implantation can be divided into the following categories: (1) pacing for bradycardia owing to SN and AV node dysfunction; (2) pacing for special conditions, such as carotid sinus hypersensitivity, neurocardiogenic syncope, and cardiac transplantation; (3) pacing for prevention and treatment of arrhythmias; and (4) pacing for hemodynamic indications, including cardiac resynchronization therapy (CRT) and hypertrophic cardiomyopathy. As SN and AV node dysfunction are the most common indications for permanent pacemaker implantation and are the most commonly encountered problems that require pacing in the intensive care setting, these indications are the main focus of this section.

Pacing Indications for Sinus Node Dysfunction

SND is the most common cause of bradyarrhythmias in clinical practice. The typical age at the time of diagnosis of SND appears to be in the seventh or eighth decade of life, with a mean or median age of 71 to 74 years in randomized clinical trials evaluating pacemaker therapy.[123–125] However, clinical manifestations of SND may occur at any age and may be secondary to several potential causes, including destruction of the SN, ischemia, infarction, infiltrative disease, surgical trauma, autonomic dysfunction, or endocrinologic abnormalities.[82,126]

Clinical manifestations of SND are diverse, and symptoms may include fatigue, reduced exercise tolerance, dyspnea on exertion, presyncope, lightheadedness, dizziness, or syncope. In the absence of any clearly reversible cause of bradycardia, the only effective long-term treatment for symptomatic bradycardia in patients with SND is permanent pacing. Of note, AV block may also occur in patients with SND, and 20% of patients with SND have some degree of AV block.[125] In addition, after permanent pacemaker implantation for SND, the risk of developing AV block within 5 years of follow-up is up to 35%.[127–130] Society guidelines stress the importance of *symptoms* in the decision-making process; a permanent pacemaker is rarely indicated in asymptomatic SND.

Pacing Indications for Acquired AV Block

Electrocardiographic classification of AV block, and considerations regarding level of AV block, have been discussed previously. Acquired AV block is most often due to aging or related to calcification of the conduction system. Ischemic heart disease, myocardial infarction, and traumatic surgical causes (such as cardiac valve surgery) are other common causes. Less common causes of AV block include infection (syphilis, Lyme disease, endocarditis), infiltrative disease (sarcoidosis, malignancy), neuromuscular disease, or medications (β-blockers, calcium channel blockers, digoxin, or membrane-active antiarrhythmic agents).

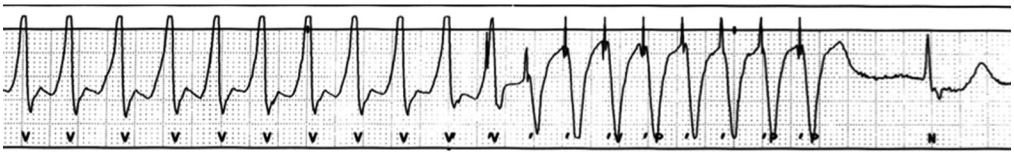
Patients with AV block may be asymptomatic, or they may have symptoms that vary from mild lightheadedness, dizziness, shortness of breath, or fatigue to presyncope and loss of consciousness. The decision regarding permanent pacemaker implantation should take into account whether or not symptoms are attributable to bradycardia, as well as the cause and "level" of AV block. Completely reversible causes of AV block, such as electrolyte disturbances or Lyme disease, should be excluded. Permanent pacing is usually indicated for acquired complete block without reversible causes. The reader is directed to the 2012 guidelines update for a more in-depth understanding of indications for permanent pacemaker insertion.[82]

Other Permanent Pacing Indications

In specific situations, permanent pacing may also be clinically indicated in some patients with carotid sinus hypersensitivity, neurocardiogenic syncope, or obstructive hypertrophic cardiomyopathy and after cardiac transplantation.[82] Historically, antitachycardia pacemakers were occasionally used to treat recurrent supraventricular arrhythmias, but they are rarely used in contemporary practice with the availability of catheter ablation therapy. Pace termination of ventricular tachycardia is frequently used for the treatment of monomorphic ventricular tachycardia as part of implantable cardioverter-defibrillator therapy; it can also be used to terminate frequent arrhythmia episodes using a temporary transvenous pacing system in the intensive care setting (Fig. 5.15).

Pacing may be useful in the prevention of pause-dependent, polymorphic ventricular tachycardia as well (see Fig. 5.14). Permanent pacing is indicated for pause-dependent ventricular tachycardia, with or without QT prolongation (class I indication, level of evidence C), and is reasonable for high-risk patients with congenital long QT syndrome (class IIb indication, level of evidence B). Atrial-based pacing (AAI or DDD mode) is considered the preferred pacing mode for prevention of polymorphic ventricular tachycardia associated with the congenital long QT syndrome.

Pacing the left ventricle can improve hemodynamics in patients with dilated cardiomyopathy and bundle branch block by altering the ventricular activation sequence, narrowing the QRS complex, and influencing regional contractility, and is particularly effective in patients with left bundle branch block. This therapy, for which congestive heart failure rather than bradycardia is an indication, is referred to as cardiac resynchronization therapy (CRT) or "biventricular pacing" and is beyond the scope of this chapter. The 2012 guidelines update addresses indications for CRT.[131]



• **Fig. 5.15** Telemetry strip demonstrating antitachycardia pacing. Pacing is delivered at a rate that is slightly faster than the underlying ventricular tachycardia, ultimately terminating the arrhythmia.

Complications of Permanent Pacemaker Implantation

Although pacemaker implantation is a well-established procedure with a low risk of major complications in experienced hands, physicians working in the critical care setting must be aware of complications that may require rapid recognition and therapy. Common complications include lead dislodgment, pneumothorax, hematoma, perforation with or without cardiac tamponade, and infection. Less frequent complications, including arrhythmias, thrombosis, inadvertent placement of a lead within the left ventricle, twiddler's syndrome, and pacemaker syndrome, are also discussed.

The most common complications after pacemaker implantation include bleeding, lead failure, and pneumothorax.[131] Higher complication rates are noted with less experienced operators.[131,132] Elderly patients (≥75 years) are also at increased risk of early postoperative complications.[133] Body mass index, congestive heart failure, use of anticoagulants, and passive atrial fixation leads are also independent predictors for development of short-term (within 2 months) pacemaker complications.[134]

Lead Dislodgment

The incidence of lead dislodgment noted in clinical trials is 1.8% to 2.6%.[125,135,136] Lead dislodgment rates depend on multiple factors including lead fixation mechanism issues and operator experience. Active fixation (or "screw-in") mechanisms have reduced the frequency of this complication. Typically, lead dislodgment rates should be below 3% with contemporary technology. Lead complications in general are more likely to occur with inexperienced operators.[132]

Lead dislodgment may lead to increased capture thresholds, loss of capture (see Fig. 5.10), or loss of sensing (see Fig. 5.11). When a change in lead position is detectable by chest radiograph, this is referred to as "macro-dislodgment." However, loss of capture or undersensing can also be seen with "micro-dislodgment" of leads, where there is no radiographically detectable change in lead position. In some cases of micro-dislodgment, intermittent undersensing of intrinsic complexes or a change in pacing threshold may be corrected by reprogramming the pacemaker sensitivity or output. However, large changes in lead position typically require lead revision. Intermittent motion of the cardiac lead may also result in increased ventricular ectopy, with a premature ventricular contraction morphologic pattern that is similar to the morphologic pattern of the paced complex.

Pneumothorax

Venous access may be obtained through subclavian or axillary puncture, as well as direct cephalic vein cut-down. Complications related to venous entry include bleeding, arterial injury caused by inadvertent arterial puncture, pneumothorax, hemothorax, thrombosis, air embolism, arteriovenous fistula, and brachial plexus injury. The risk of pneumothorax related to subclavian venous puncture is 1% to 2%[125,135]; this risk may be reduced by contrast venography before venipuncture.

Pneumothorax typically presents early after the procedure, usually within 24 hours. Symptoms include chest pain, shortness of breath, or respiratory distress, which may be associated with hypotension or hypoxemia. Patients may also be asymptomatic. Chest radiography is typically performed shortly after the implantation procedure to document baseline lead placement and exclude pneumothorax, even in asymptomatic patients. Small pneumothoraces can be managed conservatively with high-flow oxygen and serial chest radiography. Chest tube insertion should be considered in cases involving more than 10% of the pleural space and always in cases of hemodynamic compromise, hypoxia, or continued expansion of the pneumothorax.

Cardiac Perforation

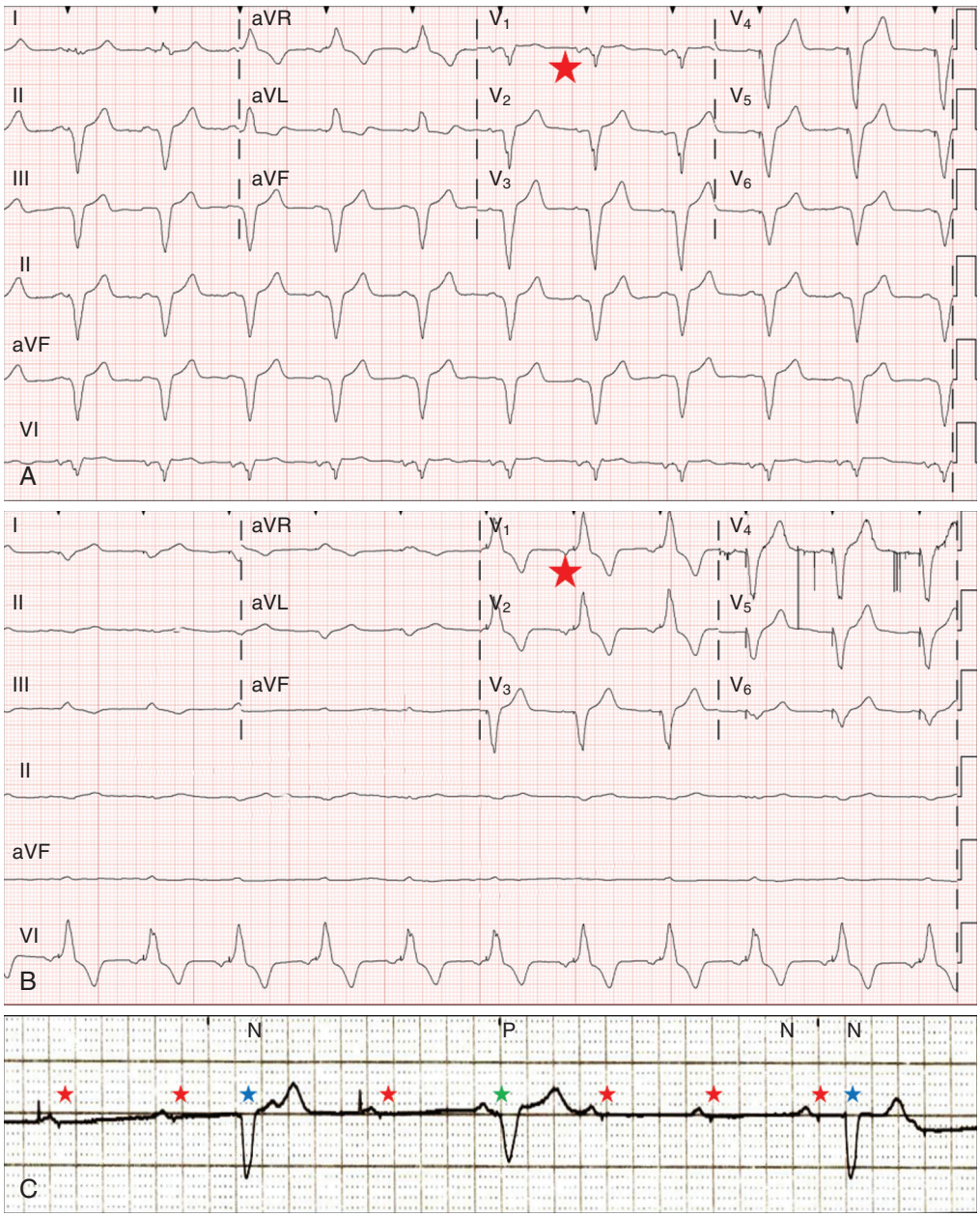
Cardiac perforation has been reported to occur in less than 1% of patients undergoing permanent pacemaker implantation.[135] The risk may be higher in elderly patients, particularly elderly women, or those requiring anticoagulation. Perforation may not be initially detected, as some patients are asymptomatic. Alternatively, patients may report chest pain or shortness of breath. Lightheadedness or syncope may also occur and can be associated with hemodynamic compromise in patients who develop cardiac tamponade owing to a large pericardial effusion.

Signs of perforation may include pacemaker undersensing, increased pacemaker lead impedance, increased pacing threshold, loss of capture, or any combination thereof. Depending on the location of the perforation, diaphragmatic pacing or pericardial rub may also be noted. A change in the paced morphologic features from left bundle branch block to right bundle branch block in a patient with a single, right ventricular lead (Fig. 5.16A and B) is highly suggestive of a lead perforation and should be investigated further. Chest radiography may reveal extension of the lead tip beyond the typical border of the right ventricle (Fig. 5.17). If loss of capture occurs in a pacemaker-dependent patient (see Fig. 5.16C), higher pacing outputs may temporarily stabilize the situation, as long as the lead maintains some degree of contact with the ventricular myocardium. This is not a long-term solution but may obviate the need for transcutaneous or temporary transvenous pacing. Urgent pericardiocentesis may be required if cardiac tamponade is present. Lead repositioning requires consideration of whether a lead tip is beyond the myocardial wall, as removal may leave a defect, causing renewed pericardial bleeding; in such cases, cardiac surgical consultation is essential.

Bleeding and Hematoma

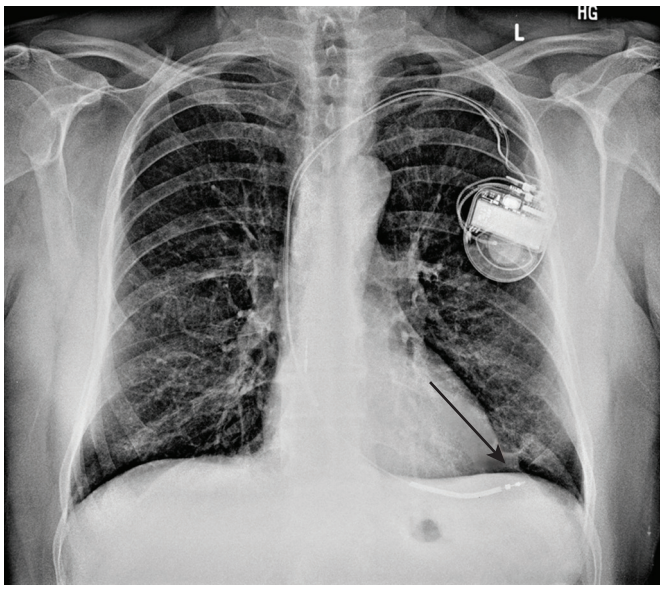
Hematoma is a common complication of pacemaker implantation, with an increased risk among patients receiving anticoagulation. Although not life-threatening, a large hematoma can be quite painful, result in significant blood loss, and increase the risk of infection.[137,138] In most cases, hematomata can be managed conservatively with observation and analgesia alone. Placement of a tight pressure dressing over the site, immobilization of the ipsilateral arm with a sling, and temporary discontinuation of anticoagulation are often effective. However, in some cases, hematomata may become large and very painful, with oozing or drainage from the site (Fig. 5.18). When concomitant infection cannot be excluded, open wound exploration in a sterile operative setting should be considered. Needle aspiration of a hematoma should *never* be attempted at the bedside because this increases the risk of infection.

Precautions should be taken to reduce the risk of bleeding preoperatively and postoperatively. As with any surgical procedure, the risk of bleeding associated with device implantation must be weighed against the risk of interruption of anticoagulation. In recent years, there has been a dramatic shift from official guidelines



• **Fig. 5.16** Lead perforation. A, A 12-lead electrocardiogram demonstrating sinus rhythm with synchronous ventricular pacing in a patient who had just undergone dual-chamber pacemaker placement. The paced morphologic pattern demonstrates a "left bundle branch block" appearance in lead V_1 *(red star)* with a leftward axis, consistent with normal lead position. B, A 12-lead electrocardiogram in the same patient demonstrating a "right bundle branch block" morphologic pattern in lead V_1 *(red star)* with a rightward axis, suggestive of lead perforation through the interventricular septum. C, Telemetry strip showing intermittent loss of ventricular capture shortly thereafter, caused by progressive migration of the lead tip. There are sinus P waves with ventricular capture *(green stars)* and failure to capture *(red stars)* with pauses truncated by ventricular escape complexes *(blue stars).* The patient required emergent lead revision.

recommending "bridging" anticoagulation with heparin products in patients with mechanical valves, atrial fibrillation, and venous thromboembolic disease deemed to be at high risk for thromboembolism[139] to evidence-based recognition that continuation of oral anticoagulation may be safer than "bridging" with unfractionated and low–molecular-weight heparin in most patients.[140–145] Most electrophysiologists now implant pacemakers and defibrillators in fully anticoagulated patients.[146] A patient with a compelling indication for anticoagulation may be better served by early initiation of warfarin, rather than a prolonged interruption of anticoagulation in the perioperative period. However, most operators perform pacemaker implantation if the international normalized ratio is in excess of 3.0. A growing body of literature suggests device insertions can also be performed safely in patients taking novel oral anticoagulants,[147] but randomized data are not yet available. Because there is significant variability in practice patterns, communication



• **Fig. 5.17** Lead perforation. The lead tip extends to the lateral border of the cardiac silhouette, well beyond the typical border of the right ventricle *(black arrow).*

• **Fig. 5.18** Hematoma. The edges of the hematoma at the site of pacemaker implantation are marked to follow the size and exclude continued expansion. A more erythematous area is noted on the medial lower edge of the hematoma. This may require drainage when large, tense, and painful, particularly if there is a need for early anticoagulation or if infection cannot be excluded.

with the physician implanting the device with regard to anticoagulation management is strongly recommended rather than routine discontinuation of anticoagulation in patients awaiting pacemaker or defibrillator insertion.

Patients who have undergone device insertion or revision should not receive unfractionated or low–molecular-weight heparin for *at least* 6 hours after completion of the procedure, and low–molecular-weight heparin should be avoided in patients with significant renal insufficiency.[148] Dual antiplatelet therapy also increases the risk of pocket hematoma,[149,150] but these agents are not commonly held. Thrombocytopenia and anemia are relative contraindications to device implantation, but a platelet count less than 50,000/μL and hemoglobin less than 7.0 g/dL are usually considered to be absolute contraindications for many implanters. Hematologic evaluation is recommended and transfusions may be necessary when pacemaker therapy is urgently required.

Inadvertent Lead Placement in the Left Ventricle

Very rarely, a ventricular lead may be errantly placed within the left ventricle. This may occur if the physician implanting the device inadvertently uses the subclavian artery for access, or if the pacing lead passes through a patent foramen ovale or atrial septal defect into the left atrium (Fig. 5.19). Twelve-lead electrocardiography typically shows a right bundle branch block morphologic pattern in lead V_1 during ventricular pacing, and lateral chest radiography demonstrates an abnormally posterior lead position. Left ventricular access introduces significant risk of arterial thromboembolism and should be corrected immediately. If identified early after implantation, the lead should be easy to reposition. A decision between lifelong anticoagulation versus advanced extraction techniques is required for chronically implanted left ventricular leads.

Arrhythmias

The most common arrhythmias occurring after pacemaker implantation are ventricular ectopic beats, particularly in the very early postoperative period. These ventricular premature beats typically have a QRS morphologic appearance similar to the paced complexes. Ectopy often subsides within the first 24 hours, rarely requiring intervention. However, a change in lead position should be excluded by chest radiograph and bedside pacemaker analysis.

Thrombosis

Subclavian or axillary venous thrombosis may be detected early or late after implantation and can be either asymptomatic or associated with upper extremity swelling and pain. This is typically managed with elevation and anticoagulation with heparin and then warfarin. More severe presentations of thrombosis, including superior vena cava syndrome or venous thromboembolic complications, are very rare.

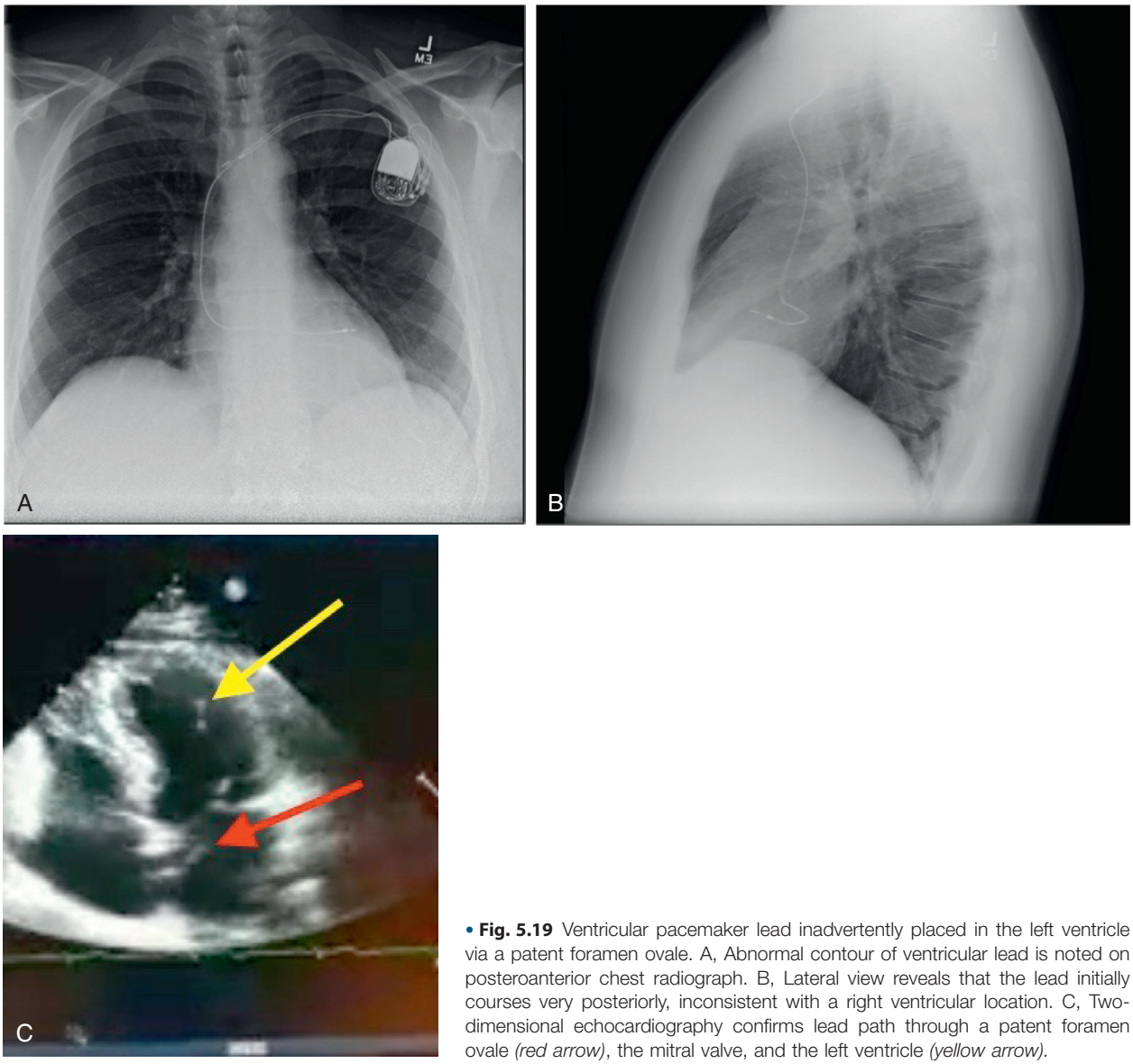
Lead Failure

Lead failure is typically due to fracture or insulation break, usually occurring long after initial implantation. Lead damage most often occurs close to the puncture site in the infraclavicular region (Fig. 5.20). Damage to the insulation may also occur at a site beneath the pulse generator owing to abrasion, or the damage may be the result of a suture being placed directly on the lead itself, in lieu of a suture sleeve. External trauma may also lead to lead damage and fracture.

Signs of insulation breaks include undersensing and reduced pacing lead impedance. Lead fractures may lead to high pacing lead impedance and loss of capture. Lead revision is indicated for lead fractures or insulation failure. Lead fracture typically requires replacement, but a localized insulation breach can often be repaired operatively using a silicone repair kit.

Twiddler's Syndrome

Some patients may manipulate the pacemaker pulse generator, leading to dislodgment or fracture leads. This is called "twiddler's syndrome." Telemetry or electrocardiographic findings may include



• **Fig. 5.19** Ventricular pacemaker lead inadvertently placed in the left ventricle via a patent foramen ovale. A, Abnormal contour of ventricular lead is noted on posteroanterior chest radiograph. B, Lateral view reveals that the lead initially courses very posteriorly, inconsistent with a right ventricular location. C, Two-dimensional echocardiography confirms lead path through a patent foramen ovale *(red arrow)*, the mitral valve, and the left ventricle *(yellow arrow).*

loss of capture and/or sensing. In addition to demonstrating lead dislodgment, the twisted leads within the pacemaker pocket may also be visualized on chest radiograph (Fig. 5.21A). Suturing the pulse generator to the chest wall, using a submuscular pocket, and use of a mesh pouch to stabilize the generator may all help reduce motion of the pulse generator, although patients should always be instructed to avoid manipulation of the pocket. The operative appearance of the leads at the time of pacemaker lead revision is illustrated in Fig. 5.21B.

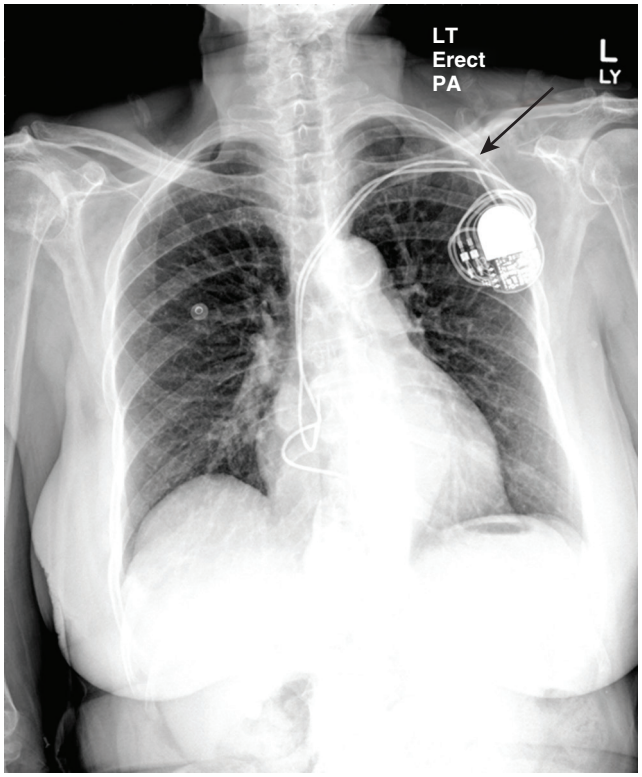
Pacemaker Syndrome

"Pacemaker syndrome" refers to a constellation of symptoms, such as fatigue, chest discomfort, dyspnea, cough, confusion, presyncope, or syncope, which are related to adverse hemodynamic effects resulting from loss of AV synchrony in patients who receive ventricular pacing. A significant drop in blood pressure may occur, and the diagnosis may be elusive in some cases unless specifically considered and confirmed by bedside evaluation. This can be corrected by reprogramming from the VVI mode to the DDD mode or AAI mode (in patients with intact AV conduction) or upgrading to a dual-chamber pacemaker, if a single-chamber ventricular device was implanted in a patient with sinus rhythm.

Infection

Care should be taken to avoid implantation of a permanent pacemaker in a patient with active infection, as this will increase the risk for device infection. Any active infection is a relative contraindication to permanent pacemaker implantation, although active bacteremia or fungemia are absolute contraindications. A fever or rising leukocytosis within the prior 24 hours should delay device implantation until a thorough investigation can be performed. Temporary pacing is appropriate in this setting, although that, too, has been associated with an increased risk of infection.[151] Patient characteristics also contribute to the risk of infection, and all modifiable risks should be optimized before device implantation. There are limited data on the efficacy of postoperative antibiotic administration, but most physicians who implant devices empirically continue antibiotics for 24 hours after the procedure.

Preoperative antibiotic administration has been shown to reduce the risk of device-related infection.[137] There is no standard regimen, but most practitioners administer a penicillin or first- or second-generation cephalosporin for coverage of staphylococcus.[152] Patients with a history of methicillin-resistant *Staphylococcus aureus* colonization or infection, recurrent or prolonged hospitalizations, or either a penicillin or cephalosporin allergy should be administered vancomycin. Patients with a history of vancomycin-resistant enterococcus require infectious disease consultation.



• **Fig. 5.20** Lead fracture. Chest radiograph demonstrating unequivocal fracture of an atrial pacing lead *(black arrow)*.

Pacemaker infection may be superficial or deep, with an incidence of less than 2% after initial implantation procedures, although it is be higher after generator replacement or lead revisions.[125,153–155] Infections vary in severity from superficial infection at the incision with a local stitch abscess to a pocket infection or systemic infection with bacteremia. Erosion of the pacemaker pulse generator or leads may result from infection.

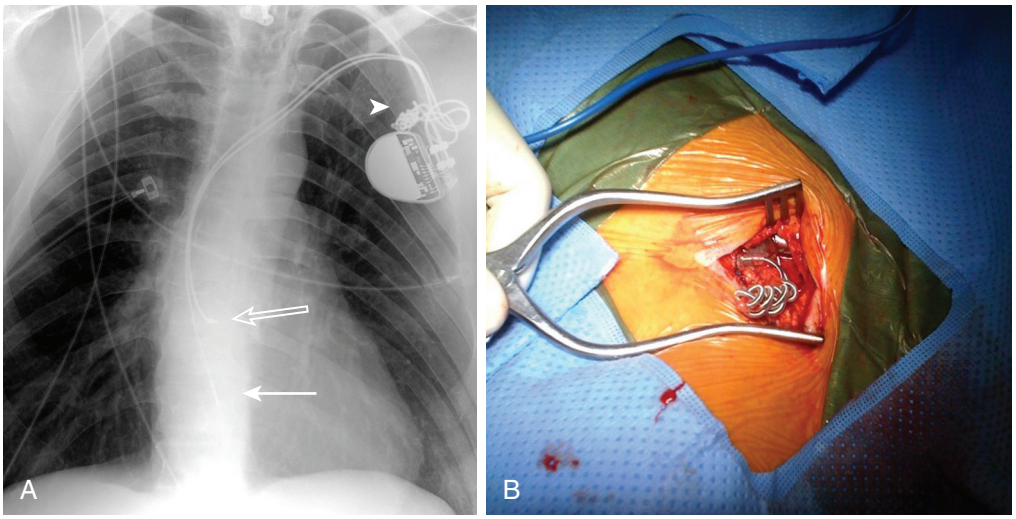
Superficial skin infections or stitch abscesses may be treated and cured with antibiotic therapy. However, lead-associated endocarditis is a more serious complication and is associated with a high mortality rate. Systemic infections with bacteremia and endocarditis require device and lead extraction. Vegetations may develop on the pacemaker lead itself and become large, requiring extraction and removal of the pacing system for cure (Fig. 5.22). Infections may occur many months after device implantation, and hematogenous spread of organisms from a distant site may be a contributing factor. The most common organisms responsible for cardiac implantable electronic device infections are *S. aureus* (often methicillin-resistant) and coagulase-negative staphylococci followed by streptococci, enterococci, and gram-negative rods.[156,157]

Special Considerations in Permanent Pacing

Intravenous Access

The vast majority of permanent device implants use the cephalic, axillary, or subclavian vein. Implants using the internal jugular and femoral vein are exceedingly rare. Devices are generally implanted on the nondominant side for reasons of patient convenience, but implants are usually less technically challenging on the left side. Devices should not be placed ipsilateral to the site of an arteriovenous fistula or graft because of the short-term risk of vein thrombosis and long-term risk of venous stenosis, both of which can compromise hemodialysis access flow.

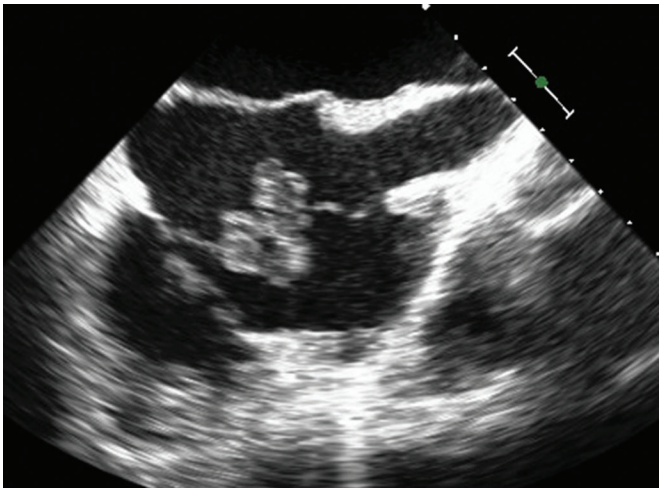
If at all possible, the nondominant subclavian access should be preserved in the critical care patient who may require permanent device implantation. If temporary central venous access is required, the internal jugular vein should be used whenever possible; if subclavian access is necessary, the critical care physician should



• **Fig. 5.21** Pacemaker lead dislodgment caused by twiddler's syndrome. A, Chest radiograph illustrating dislodgment of the atrial *(outlined arrow)* and ventricular leads *(arrowhead)* as well as significant lead entanglement in the vicinity of the pulse generator *(solid arrow)* in a patient with twiddler's syndrome. B, Photograph taken at the time of lead revision, demonstrating significant entanglement of the leads.

first establish that the contralateral infraclavicular site is available and feasible for use during subsequent device implantation, and it should be "reserved" for that use.

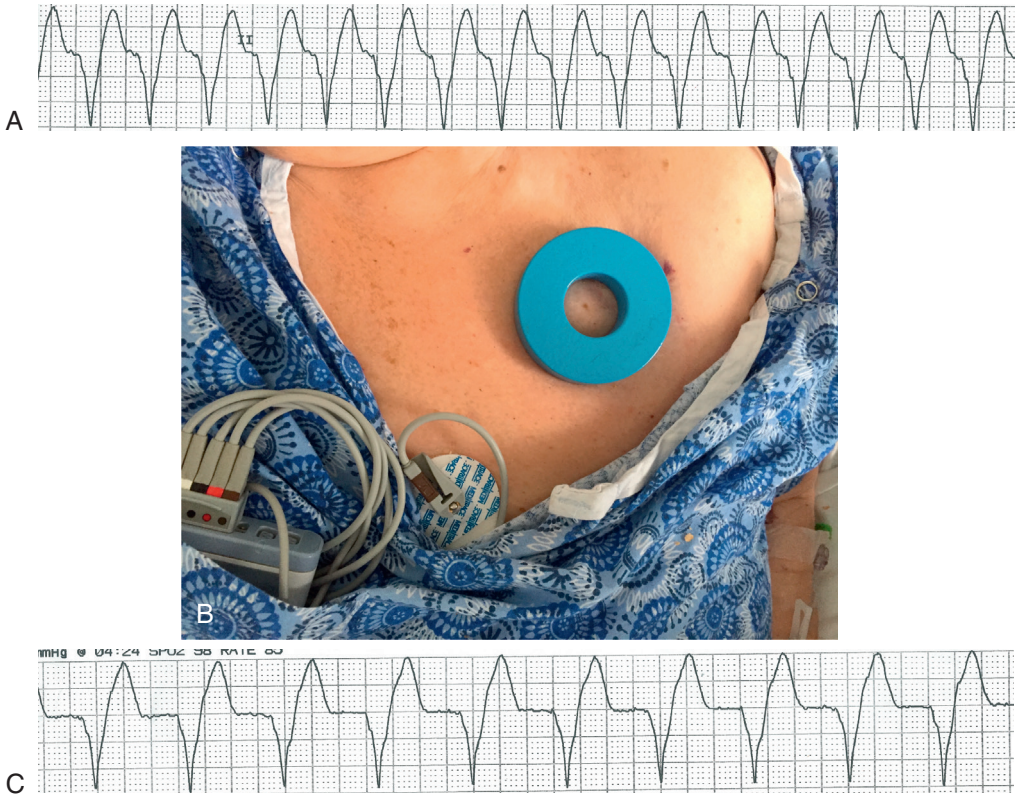
Peripherally inserted central catheter lines (i.e., peripherally inserted central catheters) should be avoided ipsilateral to the side of the future permanent implant because of risk for venous thrombosis. Intraprocedural peripheral venography is not mandatory but can be helpful in very thin patients with a higher risk of pneumothorax and patients with signs of venous occlusion. It is therefore preferable to have an 18- or 20-gauge peripheral intravenous catheter in the upper extremity ipsilateral to the planned implantation site. Telemetry electrode placement over the planned surgical site should be avoided to preserve skin integrity. Finally, repeated preoperative skin cleansing with chlorhexidine-gluconate alcohol wipes the night before and the morning of implant procedures, a technique widely used in cardiac and noncardiac surgery, is a reasonable intevention to lower the risk of device infections.[158,159]



• **Fig. 5.22** Endocarditis. The echocardiographic appearance of a large vegetation attached to an atrial lead.

Magnet Application

Magnet application over a permanent pacemaker results in asynchronous pacing, such that regularized pacing stimuli are delivered *regardless* of the underlying rhythm.[160] Various magnet rates, generally between 60 and 100 beats/min, are characteristic of each pacemaker manufacturer. In contrast, a magnet placed over an implantable cardioverter-defibrillator suspends detection of ventricular arrhythmias, *but it does not change pacemaker function*. In the critical care setting, magnet application over a permanent pacemaker can be used to confirm capture, evaluate the morphologic appearance of the paced complex, increase the pacing rate, stop inappropriate rapid tracking of atrial arrhythmias, and terminate pacemaker-mediated tachycardia (Fig. 5.23). Prolonged periods of magnet-induced asynchronous pacing should be avoided in the critical care setting, when concomitant metabolic and electrolyte derangement may increase the risk of proarrhythmia from R on T pacing; reprogramming of the pacemaker should be performed as soon as possible so that the magnet can be removed. Among defibrillator patients who experience inappropriate shocks, magnet application may be lifesaving.



• **Fig. 5.23** Use of an external magnet for asynchronous pacing. A, Telemetry reveals upper rate behavior of a dual-chamber pacemaker owing to tracking of atrial arrhythmia. B, "Doughnut" magnet placed on skin overlying pacemaker generator. C, Resultant asynchronous pacing at 85 ppm.

Magnetic Resonance Imaging

Critically ill patients with previously implanted permanent pacemakers and defibrillators sometimes require magnetic resonance imaging (MRI) scanning. The vast majority of implanted devices are not approved for MRI scanning because of the potential for lead heating, changes in device and/or lead function, and myocardial stimulation with proarrhythmia.[161,162] Pacemaker-dependent patients with implantable defibrillators pose a particularly high set of risks. Since 2011, the U.S. Food and Drug Administration has approved several MRI-conditional permanent pacemakers and defibrillators, and many radiology departments have developed protocols for MRI scanning of patients with these devices. Interestingly, recent data suggest that the overall risk of MRI scanning may be overstated, even for patients with non–MRI-conditional devices, particularly at 1.5 T or below.[163,164] This is a rapidly changing field in which significant controversy exists.

Based on expert opinion, patients with new device implants (<6 weeks old), abandoned leads, passive fixation leads, or epicardial leads are ineligible for MRI outside highly specialized centers, regardless of the clinical indication.[165] Patients with temporary pacemakers are also ineligible because of similar concerns for lead heating, dislodgment, and external interference. If a patient with a non–MRI-conditional cardiac implantable electric device absolutely requires MRI scanning, close coordination with electrophysiology and radiology consultants is mandatory to minimize risk via assessment of system components and abandoned leads, appropriate monitoring during the scan, and device reprogramming before and after the MRI procedure.[166,167] In selected patients with no other alternatives, lead and pulse generator extraction may be an option.[167]

Conclusions

Many critically ill patients develop bradyarrhythmias or have previously implanted permanent pacemakers already in place. Pacing may relieve symptoms, improve quality of life, or provide lifesaving therapy. Therefore it is essential that critical care physicians are adept at arrhythmia recognition, at urgent delivery of temporary pacing, and at basic device troubleshooting. Temporary pacing is particularly useful in the critical care setting and can be performed using a variety of techniques, including transcutaneous, transvenous, and epicardial approaches.

Key Points

- Bradyarrhythmias may be caused by either intrinsic dysfunction of the SN or AV conduction system, or they may be due to a response of normal tissues to extrinsic factors.
- Transcutaneous pacing is most appropriate in situations in which pacing is required only briefly or intermittently, or as a bridging measure for placement of a transvenous system.
- Complete heart block with a narrow-complex escape rhythm does not typically require temporary pacing, unless it is accompanied by hypotension.
- Complete heart block with a wide-complex escape rhythm usually requires temporary pacing, even if the patient is hemodynamically stable.
- Temporary pacing should be avoided in severely hypothermic patients because of the potential risk of catheter-induced ventricular fibrillation.
- If there is an anticipated need for permanent pacing, the nondominant infraclavicular area and subclavian vein should be preserved for device placement.
- Permanent pacemakers are frequently implanted without interruption of therapeutic anticoagulation because the outcomes are better than "bridging" with parenteral agents.
- It is imperative that the critical care physician recognize the electrocardiographic and radiographic signs of lead dislodgment and perforation.

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Review Questions

1. A 40-year-old man with no significant medical history presents to the emergency department with a 3-day history of mild fatigue. He denies recreational drug use and states that he is "in great shape" because he is an avid rock climber and backpacker. He reveals that his air conditioner broke during the current heat wave, and he has not been consuming adequate fluids. He is found to be volume depleted. His blood pressure is 100/60 mm Hg. His electrocardiogram reveals complete heart block with a ventricular rate of 40 beats/min and a narrow QRS complex. He is admitted for observation. Which of the following statements is correct?

a. Intravenous fluids are likely to reverse his dehydration-induced electrocardiographic abnormality.

b. A transvenous pacer should be placed and positioned in the right ventricular apex.

c. Serologic tests should be performed.

d. Electrophysiology consultation should be obtained for scheduling of permanent pacemaker insertion.

Answer: c. This clinical presentation—a young patient, active in the outdoors, during the summer months—is highly suggestive of Lyme disease complicated by carditis and complete heart block. This is a reversible condition, generally with a stable and narrow-complex escape, which generally does not require permanent pacing. The presence of volume depletion is incidental. Temporary pacing is indicated only for significant symptoms or hemodynamic instability. Blood samples for Lyme titers should be drawn, and infectious disease consultation should be obtained. The treatment is observation and antibiotics.

2. A 67-year-old woman has a permanent pacemaker implanted for high-degree AV block secondary to sarcoidosis. Several years after implantation, she has a syncopal event and telemetry while in hospital shows intermittent high-degree AV block with a ventricular rate of 30 beats/min. On telemetry, there are pacing spikes with no evidence for ventricular capture. Which of the following statements is correct?

a. Lead failure caused by insulation break is a possible explanation for pacing failure.

b. Sensitivity should be lowered and the pacemaker should be left in place.

c. This is a typical presentation of pacemaker-associated endocarditis.

d. Magnet application to the pacemaker will fix this problem.

Answer: a. Lead failure typically occurs years after initial implantation and most often occurs close to the puncture site of initial insertion. Lead failure is typically due to fracture or insulation break. Signs of insulation break include sensing abnormalities, failure to capture, and reduced pacing lead impedance. Lead failure is an indication for a lead revision procedure, as opposed to changing the programmed sensitivity. Endocarditis is one of the worst complications (albeit very rare) associated with permanent pacemakers. It presents in typical fashion, with signs and symptoms of bacteremia. The application of a magnet over a permanent pacemaker results in asynchronous pacing, such that pacing stimuli are delivered regardless of the underlying rhythm; because there is already failure to capture, asynchronous pacing will not be of benefit.

3. A 32-year-old man is brought to the emergency department after being found unconscious in the park during a cold winter night. His vital signs are significant for a heart rate of 30 beats/min, blood pressure of 85/30 mm Hg, and a rectal temperature of 30.2°C. Which of the following is correct?

a. A transvenous pacer should be placed immediately with the threshold turned up as high as possible.

b. Transcutaneous pacing should be undertaken immediately, with the pacing rate set as high as possible until blood pressure stabilizes.

c. The role for electrical pacing in this situation is limited, and the primary treatment should focus on rewarming.

d. There is no danger to attempting electrical pacing.

Answer: c. This patient is suffering from life-threatening hypothermia caused by environmental exposure. Hypothermia is known to produce dramatic electrocardiographic conduction abnormalities, eventually leading to mechanical abnormalities as well. Hypothermia can cause bradycardia, PR interval and QT interval prolongation, widening of the QRS complex, and ventricular arrhythmias. Treatment should be focused on rewarming as severe/deep hypothermia is associated with decreased responsiveness to electrical stimuli, and the potential to cause ventricular arrhythmias exists with attempting temporary pacing.

4. Immediately after successful placement of a transvenous temporary pacemaker in a patient, failure to pace occurs, resulting in asystole. All of the following are emergently indicated *except*

a. Cardiopulmonary resuscitation.

b. Placing the patient in the right lateral decubitus position.

c. Increasing current output to the highest possible setting.

d. Beginning transcutaneous pacing.

Answer: b. Emergency measures in the asystolic patient with pacing failure include (1) performing cardiopulmonary resuscitation; (2) increasing current output to highest setting possible; (3) checking and tightening all connections; (4) placing the patient in the left (not right) lateral decubitus position; (5) reversing polarity (if epicardial wires); and (5) establishing other means of heart rate support (i.e., transcutaneous pacing) or giving pharmacologic agents (i.e., atropine, isoproterenol).

6

Pericardial Tamponade: Clinical Presentation, Diagnosis, and Catheter-Based Therapies

TILAK K.R. PASALA, VLADIMIR JELNIN, AND CARLOS E. RUIZ

CHAPTER OUTLINE

Clinical Presentation
Diagnosis
- History
- Physical Examination
- Electrocardiography
- Echocardiography
- Other Imaging Studies
- Catheter-Based Diagnosis

Catheter-Based Therapies
Pericardiocentesis
Post-Pericardial Drain
Percutaneous Balloon Pericardiotomy
Surgical Drainage of Pericardium

Pericardial tamponade (PT) is a life-threatening condition caused by accumulation of fluid in the pericardial sac that causes critical cardiac compression. There is an impaired filling of the cardiac chambers, leading to a drop in the cardiac output. The spectrum of hemodynamic compromise in PT varies from mild to critical with varying prognosis. Without immediate intervention, critical PT can lead to cardiac arrest and death. For a timely recognition and intervention in PT, critical care physicians should have a thorough understanding of the pericardial anatomy, pathophysiology of PT, clinical presentation and differential diagnosis, understanding of imaging modalities, and knowledge of catheter-based interventions.

Clinical Presentation

The pericardium is a sac that contains the heart and includes the outer fibrous sac and the serosal component. The outer fibrous layer continues as the adventitia of the great vessels superiorly and is attached to the central tendon of the diaphragm inferiorly.[1] The pericardial cavity is enclosed by the serosal component, which forms the outer parietal (along with fibrous component) and inner visceral pericardium. The visceral pericardium reflects and becomes continuous with the parietal pericardium ensheathing the arteries and veins at the base of the heart. The reflections form the transverse sinus behind the great vessels and the oblique sinus behind the left atrium separated by the pulmonary veins and inferior vena cava. Pericardial fluid (normally 15–50 mL) is contained between the visceral and parietal pericardium that helps in lubrication and equalizes pressures between pericardial chamber and heart chambers. The accumulation of pericardial fluid beyond the pericardial reserve volume (dependent on the compliance of pericardium) causes elevation of the intrapericardial pressure, leading to PT. Equalization of the diastolic cardiac chamber pressures is seen. The cardiac chambers collapse, which restricts diastolic filling and results in low cardiac output.

PT varies in presentation. The presentation is dependent on the rate of accumulation of pericardial effusion and underlying cause (Box 6.1). Some patients are asymptomatic when accumulation of pericardial effusion is slow and chronic. With the chronic accumulation of fluid, pericardium stretches and becomes more compliant. A compliant pericardium can accommodate as much as 1 L of fluid without hemodynamic compromise. Clinical manifestations occur when a critical threshold of intrapericardial pressure is reached. In the cases of acute pericardial effusion where normal pericardium with lower distensibility is present, this threshold is reached at a lower volume (as low as 100 mL) of pericardial effusion (see Fig. 24.1). PT clinically manifests as dyspnea, tachycardia (acute bradycardia owing to vagal response), tachypnea, hypotension, elevated systemic venous pressure, pulsus paradoxus (PP) (exaggerated inspiratory decrease in arterial blood pressure >10 mm Hg). Clinical PT represents a later stage in the spectrum of hemodynamic compromise. Most patients show abnormalities on echocardiography and catheter laboratory hemodynamic measurements before overt clinical PT is seen.[2] Hypotension may be a late manifestation as the blood pressure is maintained by adrenergic response and vasoconstriction balancing the decreased stroke volume. After a critical threshold is reached, hypotension can be sudden and potentially fatal without intervention. Hence, it is important to have a high clinical suspicion for early recognition and prompt intervention of PT.

• BOX 6.1 Etiology of Pericardial Tamponade

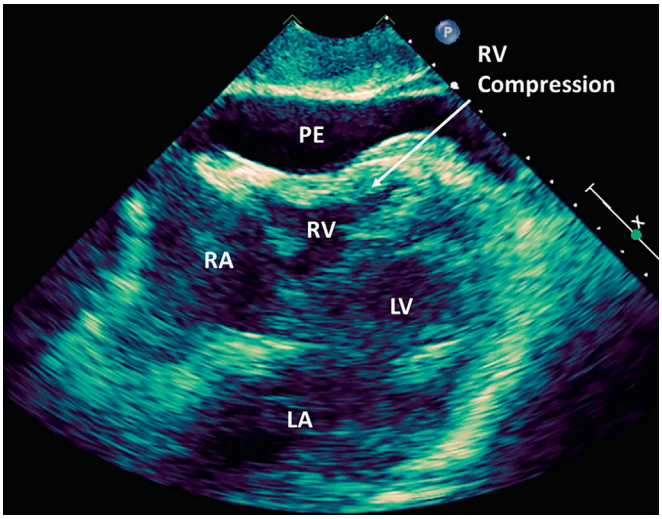
Neoplasm/Malignancy

Pericarditis (any process that causes pericarditis and pericardial effusion)

- Infectious: viral (enteroviruses, herpesviruses, and so on), bacterial (*Mycobacterium tuberculosis, Coxiella burnetii,* and so on); fungal (*Histoplasma* spp.)
- Neoplastic: secondary tumors common (lung and breast cancer)
- Autoimmune: systemic lupus erythematosus, Behçet syndrome, sarcoidosis, inflammatory bowel disease
- Metabolic: uremia
- Drugs: phenytoin, doxorubicin, cyclophosphamide, and so on

Iatrogenic (After Invasive Cardiac Procedures or Surgery)

Infectious diseases
Anticoagulation
Connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
After acute myocardial infarction
Idiopathic



• Fig. 6.1 Cardiac tamponade on echocardiography**.** Echo shows large pericardial effusion which is compressing the right ventricle. *LA,* Left atrium; *LV,* left ventricle; *PE,* pericardial effusion; *RA,* right atrium; *RV,* right ventricle.

Diagnosis

An early and prompt diagnosis is crucial. The combination of clinical signs and imaging modalities can usually clinch the diagnosis.

History

Patients can express various symptoms depending on the etiology of PT, chronicity, comorbidities, and stability of the patient's condition. The symptoms can range from chest pain, dyspnea, cough or dysphagia (with mass effect on the esophagus), fatigue, presyncope or syncope (reduced cardiac output), and even oliguria and edema if chronically present. Patients with iatrogenic catheter- or wire-related injury may report chest pain or shoulder pain as the result of pericardial irritation. Other atypical symptoms can include nausea, sweating, anxiety, and so on. Additionally, a good review of systems can point toward the etiology of the pericardial effusion. For example, patients with malignant or systemic disease may have weight loss and anorexia.

Physical Examination

Patients may be in distress and have tachycardia. The classic Beck's triad of jugular venous distention, decreased arterial pressure, and small quiet heart (owing to fluid accumulation around the heart) may be present. Jugular venous distention may be an early finding that increases as the tamponade worsens. However, this may be absent in patients with localized effusions or hypovolemia. There is blunting of the y descent (produced by early ventricular filling and lowering of atrial pressure) owing to compression on the right side of the heart throughout the cardiac cycle. Although a prominent x descent (produced by atrial relaxation and systolic descent of tricuspid valve during ventricular systole) is seen in tamponade, it can also be seen in constrictive pericarditis and restrictive cardiomyopathy. A drop in pulse pressure owing to a decrease in stroke volume during inspiration can be felt on palpation and arterial monitoring. PP, which is a fall in arterial systolic pressure by 10 mm Hg during normal inspiration, can be seen in PT. The mechanism of PP is ventricular interdependence where the left ventricular filling is impaired by the increase in right ventricular filling during inspiration. PP is not specific to tamponade and can be present in conditions that cause respiratory variation in ventricular filling, such as hypovolemic shock, acute massive pulmonary embolism, constrictive pericarditis, and so on. Heart sounds are muffled with large pericardial effusion. Pericardial rub may be present.

Electrocardiography

Although electrocardiography is not specific, low voltages can be seen. Another finding is an electrical alternans, which is a beat-to-beat alternation in voltage caused by a wide swinging of the heart in large effusions changing the direction of the electrical vectors.

Echocardiography

Echocardiography is the first-line imaging modality for diagnosing PT and follow-up (Fig. 6.1). Two-dimensional echocardiography allows quick assessment of the size of effusion; delineation of the size and distribution of the effusion, including loculated effusions; and helps assess the success of pericardiocentesis. The echocardiogram also can provide a reasonable estimate of the total volume of the effusion. A circumferential effusion greater than 1 cm in width is considered large[1] (>500 mL). Moderate effusions (100–500 mL) are usually circumferential but less than 1 cm, whereas small effusions (<100 mL) are usually localized posterior to the left ventricle and measure less than 1 cm. Classification criteria differ significantly among various echocardiographers and institutions. The typical echocardiographic signs of PT are listed in Box 6.2.

Other Imaging Studies

The chest x-ray film may show enlarged cardiac silhouette with large pericardial effusions that have accumulated chronically. It

• BOX 6.2 Two-Dimensional and Doppler Echocardiographic Features of Pericardial Tamponade

Key features
- Presence of pericardial effusion
- Dilated inferior vena cava
- Abnormal hepatic veins flow (blunting or reversal of diastolic flows in expiration)
- Reduced left ventricular end-diastolic and end-systolic dimensions
- Doppler evidence of reduced stroke volume and cardiac output

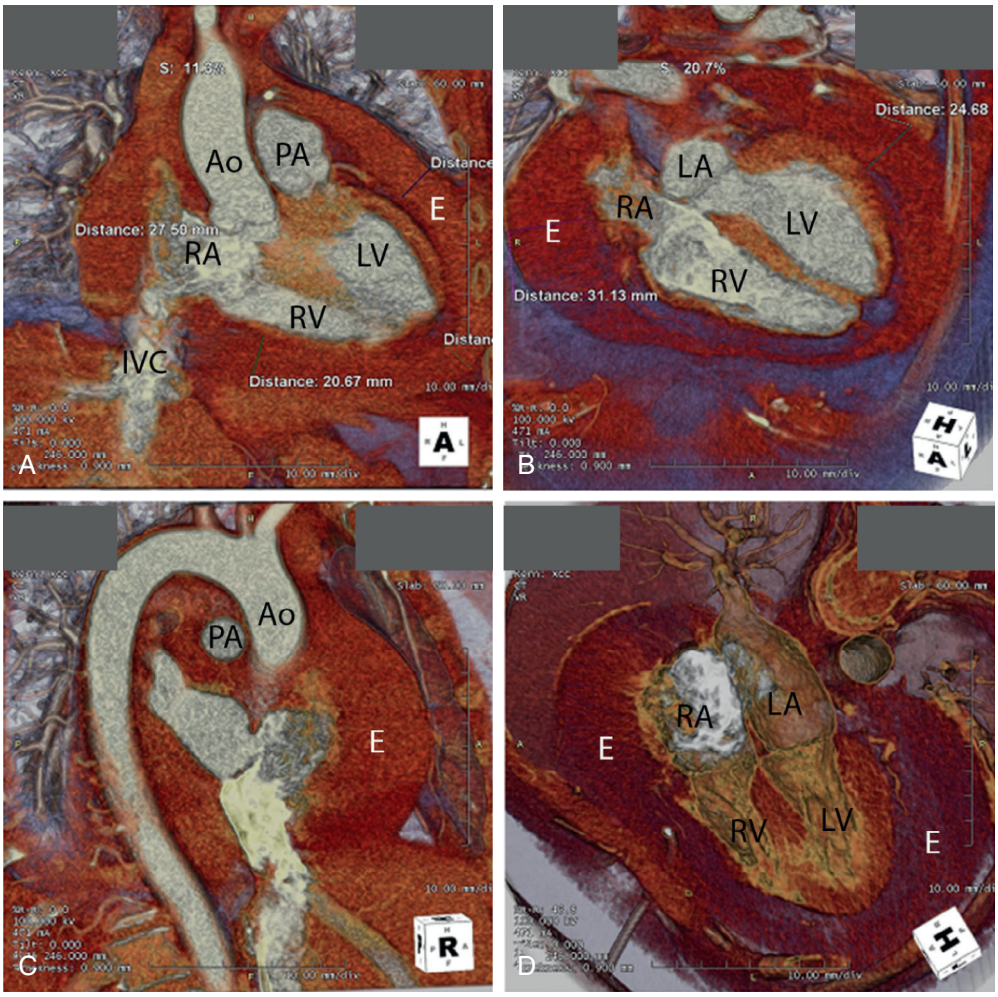
Additional features
- Right heart chamber collapse
- Inspiratory bounce of interventricular septum toward left ventricle
- Variation in mitral inflow (The maximal peak mitral E-wave inflow drop occurs with the first beat of inspiration and the first beat of expiration, usually exceeding more than 30% respiratory variation.)
- Variation in tricuspid flow (The maximal tricuspid E-wave inflow drop occurs on the first beat of expiration at the same time as the hepatic vein atrial reversal and usually exceeds more than 60% respiratory variation.)

may not be possible to distinguish tamponade from pericardial effusion without tamponade.

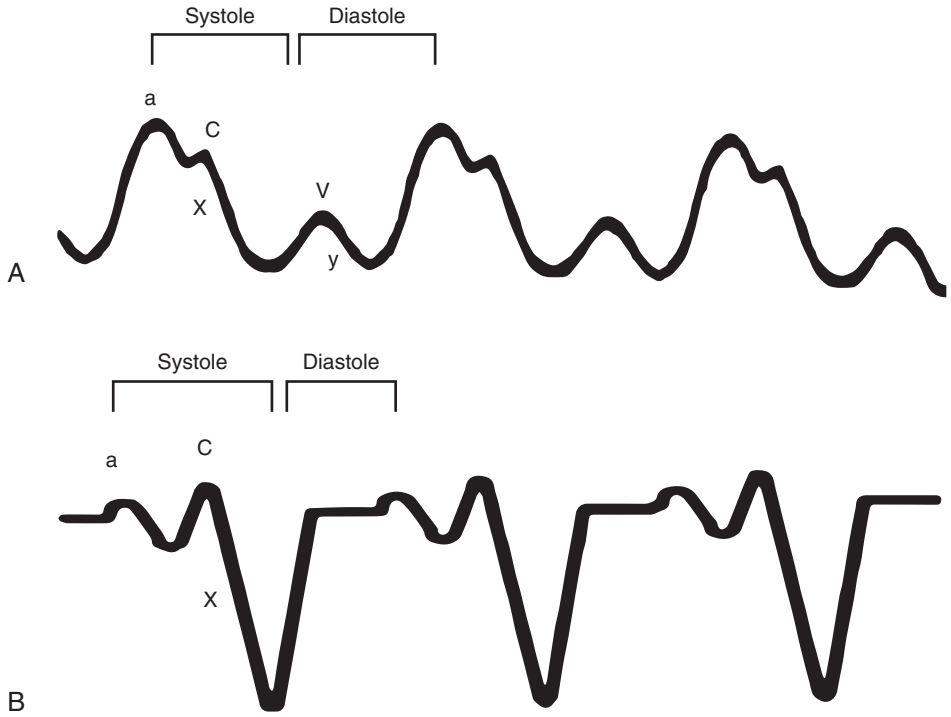
Computed tomography (CT) scanning can be used in instances in which loculated or complex effusions are suspected (Fig. 6.2). It may help in determining if percutaneous versus surgical drainage is feasible. Some of the signs seen on CT may include flattened heart, compressed coronary sinus, septal bowing, and increase in the size of superior vena cava/inferior vena cava. Cardiovascular magnetic resonance imaging can characterize tissues based on signal intensity.

Catheter-Based Diagnosis

Catheter-based hemodynamic assessment is rarely used when echocardiography is readily available (Box 6.3). There is an absence of the y descent on the central venous pressure waveform that can occur relatively early (Fig. 6.3). As tamponade progresses, there is equalization of pressures on the left and right sides of the heart with the pericardial pressure.



• Fig. 6.2 Cardiac computed tomography three-dimensional reconstruction: volume-rendering technique showing large pericardial effusion from different views. A, Straight anteroposterior view with cut plain through the aortic root; C, modified sagittal view; B and D, windows simulating echocardiographic modifications of four chambers view. *Ao,* Ascending aorta; *E,* pericardial effusion; *IVC,* inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle.



• **Fig. 6.3** Central venous pressure (CVP) waveform in cardiac tamponade. A, Normal CVP waveform during systole and diastole is shown. B, There is absence of y descent because of restricted right ventricular filling. (From Carmona P, Mateo E, Casanovas I, et al. Management of cardiac tamponade after cardiac surgery. *J Cardiothoracic Vasc Anesth.* 2012;26:302–311.)

• BOX 6.3 Hemodynamic Features Seen on Heart Catheterization During Pericardial Tamponade

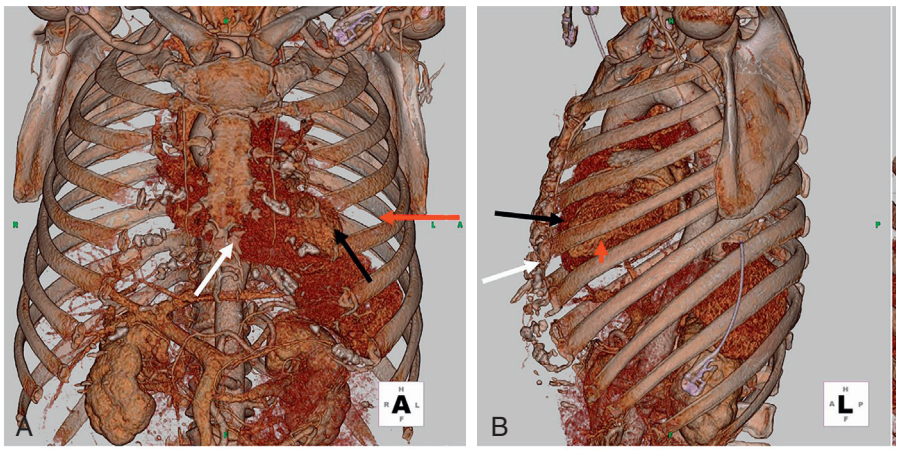
Key features
- Elevated atrial pressures
- Blunted or absent y descent and preservation of x descent
- Equalization of diastolic pressures
- Reduced cardiac output and stroke volume
- Alterations in systolic ejection period or pulse pressure (pulsus paradoxus)

Catheter-Based Therapies

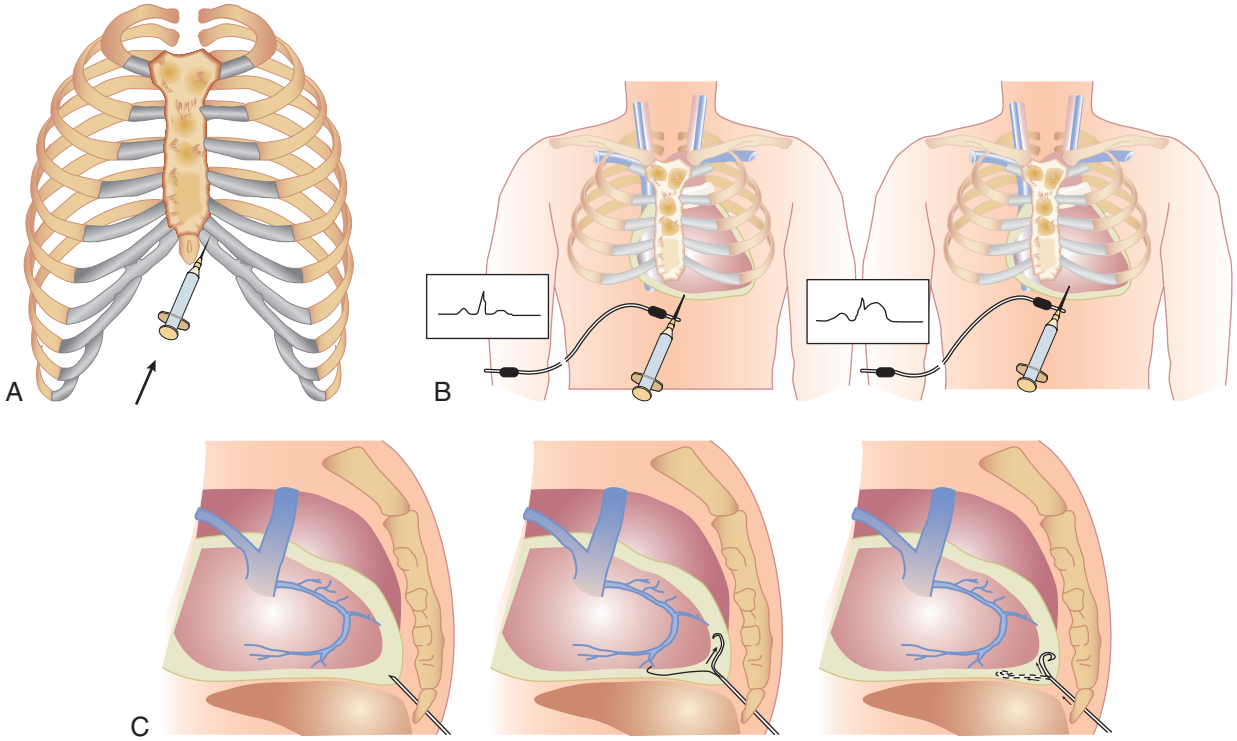
Prompt treatment of PT is crucial for survival and therapy should not be delayed once PT is diagnosed. Decompression of the pericardium can be achieved with pericardiocentesis (removal of pericardial fluid usually with a needle), and usually a catheter drain is placed for continuous and complete drainage of fluid. Surgical approaches to PT include (1) chest tube placement via a subxiphoid approach, thoracotomy, or sternotomy, and (2) a pericardial window where a small portion of pericardium is excised, allowing fluid to drain freely. The pericardial window provides a long-term solution for recurrent pericardial effusion but is invasive. Additionally, recurrence of pericardial effusion/tamponade can occur as the result of reorganization of pericardial space caused by adhesions. Catheter-based pericardiotomy, which is the percutaneous balloon dilation of the pericardium, is underused but can achieve results similar to pericardial window in expert hands.[3]

Pericardiocentesis

The site of pericardiocentesis should be guided by ultrasound to determine the optimal window. Most commonly a subcostal or subxiphoid approach is used (Fig. 6.4). However, an apical approach may provide the nearest distance. Other approaches include right-sided and lower parasternal approaches. With a subxiphoid approach the left lobe of the liver is situated near the needle track and care should be taken to avoid injury. Similarly, when an intercostal approach puncture is used, the site should be above the ribs to avoid blood vessels that travel inferior to the ribs. Care should be taken to avoid lingual and left pleural injury during an apical approach. Another structure to keep in mind is the left anterior descending artery. Echocardiography-guided pericardiocentesis has shown high procedural success with low risk of complications in a large series of patients from the Mayo Clinic.[4] It can be helpful in identifying even difficult loculated effusions. A long micropuncture needle is preferred (Fig. 6.5). A 10- to 20-mL syringe is attached to the needle and advanced with suction. Once the pericardial fluid is withdrawn through the needle, a stiff shaft microwire is passed through the needle. A microcatheter is advanced over the wire. Confirmation of pericardial space can be made by injecting agitated saline solution mixed with blood or Definity (Lantheus Medical Imaging, North Billerica, MA) contrast through the needle or microcatheter. Subsequently a guidewire is inserted through the microcatheter and positioned under fluoroscopy while confirming the guidewire is in the extracardiac space (Fig. 6.6). Then usually a pigtail catheter is advanced over the guidewire (Figs. 6.7 and 6.8). Pericardial fluid is drained with 60-cc syringes until it is dry, subsequently drained by either gravity or hooked to negative pressure.



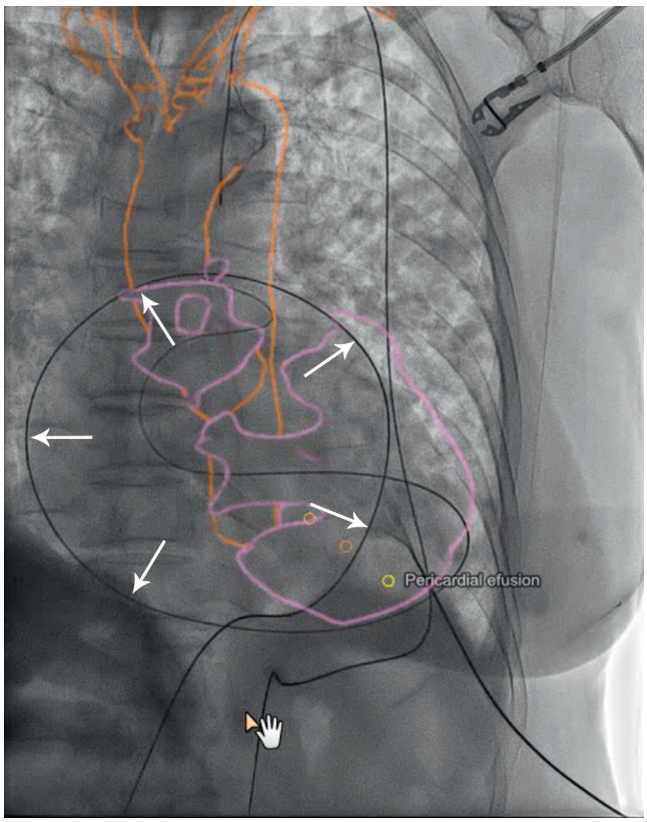
• **Fig. 6.4** Common access sites for pericardial drainage. Cardiac computed tomography angiography volume rendering of the chest used to plan access site for pericardial drainage. The subxiphoid approach *(white arrows)* is the most commonly used access site. Other options include midclavicular apical access *(black arrows)* and axillary access *(red arrows)*.



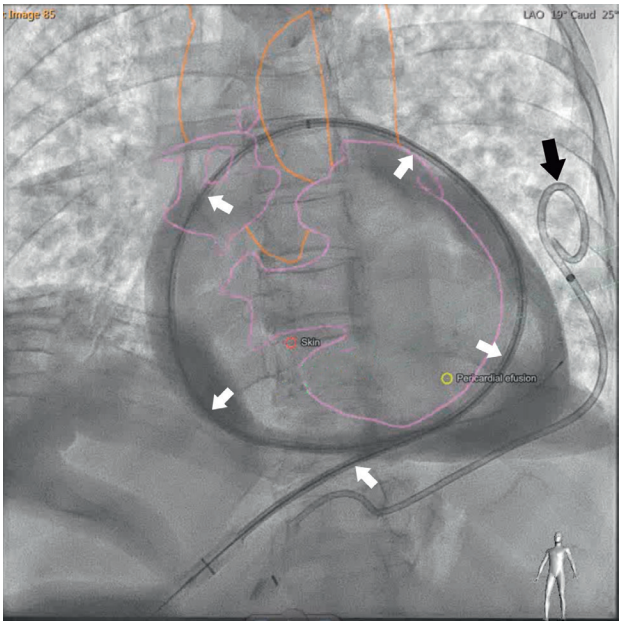
• **Fig. 6.5** Diagrammatic representation of a pericardiocentesis procedure via subxiphoid approach. A, A subxiphoid approach is used. B, A pericardial needle is connected to an electrocardiogram (ECG) lead and is advanced left lateral to the subxiphoid area aiming toward the left shoulder. ST-segment elevation is seen on the ECG lead tracing when the needle touches the epicardium. The needle should be retracted slightly until the ST-segment elevation disappears. C, After the pericardial space is entered with the pericardial needle, a guidewire is introduced in the pericardial space through the needle. The needle is removed, and a catheter is inserted in the pericardial sac over the guidewire (either anteriorly or inferiorly in the pericardial sac).

Post-Pericardial Drain

Depending on the etiology of pericardial effusion, there may be continuous extravasation of fluid into the pericardial space. The drain usually is left in place for 48 to 72 hours until no significant drainage of pericardial fluid is seen (50–100 cc/24 hr). Antibiotics are usually administered. Because the pericardium can cause pain, adequate analgesia should be given in anticipation of pain caused by pericardial irritation. Patients should be watched for recurrent PT; possible causes could be an inability to drain acute accumulation of pericardial fluid or blood, clogging of the pericardial drain that may need heparin flushes, or a repositioned drain. Patients should



• **Fig. 6.6** Guidewire in the pericardial space. A subcostal approach is being used. A long guidewire *(white arrows)* is seen encircling the extracardiac space, confirming that the wire is in the pericardial space.



• **Fig. 6.7** A pericardial drain *(white arrows)* is placed over the guidewire. A pigtail catheter can be placed as well. Additionally, a pleural drain *(black arrow)* is seen in the figure. The outlines of the aorta *(orange color)* and extent of effusion *(purple)* is seen from the overlaid computed tomography (CT) angiography (computed tomography angiography/fluoroscopy fusion was used for this procedure).

be watched for signs suggesting recurrent PT, and an echocardiogram should be obtained as a follow-up to rule out recurrence. Patients whose effusion continues to drain or have signs of recurrence could be considered for open surgical pericardial window or percutaneous balloon pericardiotomy.

Percutaneous Balloon Pericardiotomy

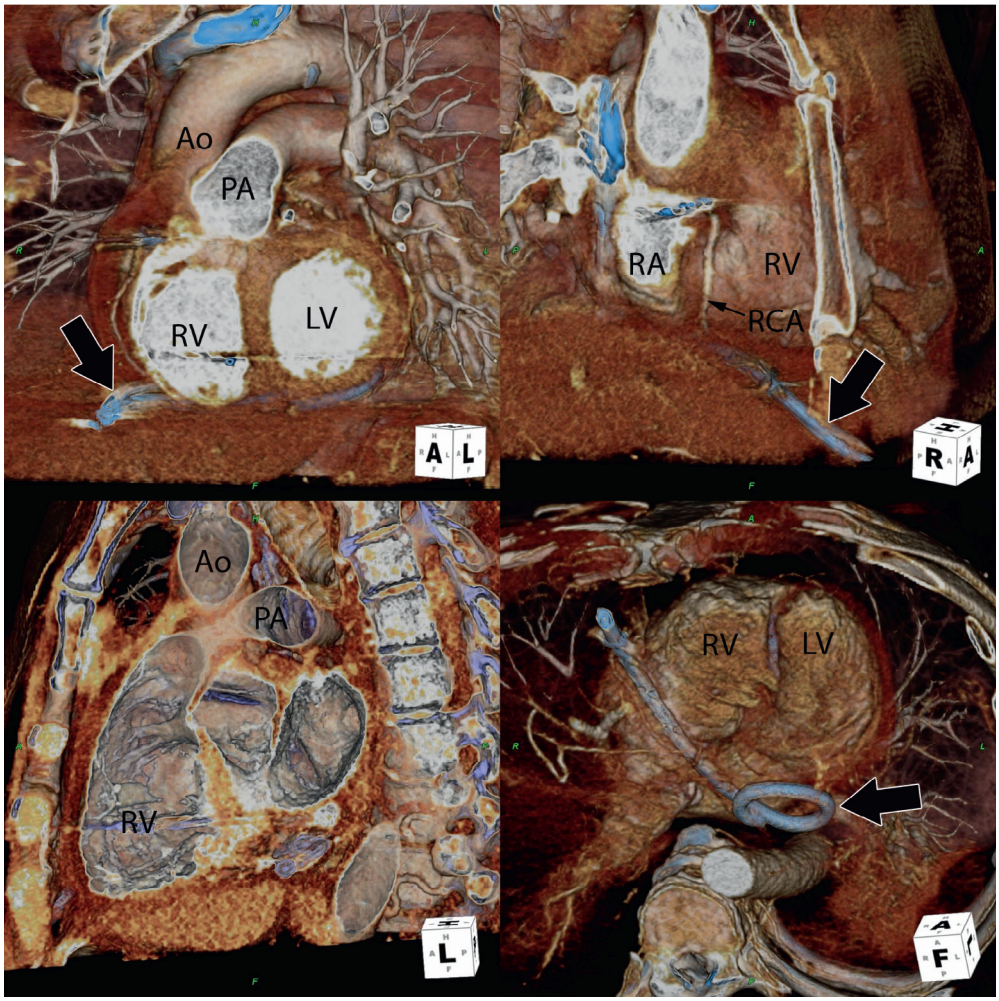
Percutaneous balloon pericardiotomy (PBP) is a procedure in which a pericardial window is created percutaneously using balloon inflation of the pericardium. This can be performed with the patient under conscious sedation and is relatively safe. In patients with persistent drainage or malignant pleural effusion, PBP can be particularly useful. The first human experience with the technique was done by Palacios et al., who performed PBP in eight patients with malignant pericardial effusion and tamponade.[5] They reported 100% success with no immediate complications. No recurrence was noted up to 6 months. In other literature, ~85% success is reported.[6]

The most common route is the subxiphoid approach. After accessing the pericardial space via the technique previously described, contrast dye is injected into the pericardial space (Fig. 6.9).

We used CT angiography fluoroscopy fusion imaging (superimposing relevant cardiac structures processed from cardiac CT angiography over fluoroscopy) in this example. The cardiac structures are segmented and color coded to identify each structure. Subsequently, this information is translated over the fluoroscopy, which helps in the orientation of the three-dimensional anatomy on fluoroscopy. A preshaped stiff guidewire is advanced through the needle or preferably a pigtail catheter. If pigtail catheter is used, it is removed and over-the-wire predilation of the skin is performed to accommodate the balloon. The skin, tract, and the pericardium are predilated to allow for the passage of the balloon. A 20-mm balloon is chosen to dilate the pericardium. The balloon is advanced beyond the skin and using contrast as a guide the balloon is positioned at the site of pericardium (Fig. 6.9C). Usually two to four inflations, until the waist of the balloon disappears, are performed to achieve adequate result. A major complication after the procedure is large pleural effusion that occurs frequently in large effusions. Here in our example, a pleural drain is placed at the time of procedure (see Fig. 6.9D). After the PBP, frequently a pericardial drain is left in place. Closure and recurrence can occur and one should monitor after the procedure with echocardiography.

Surgical Drainage of Pericardium

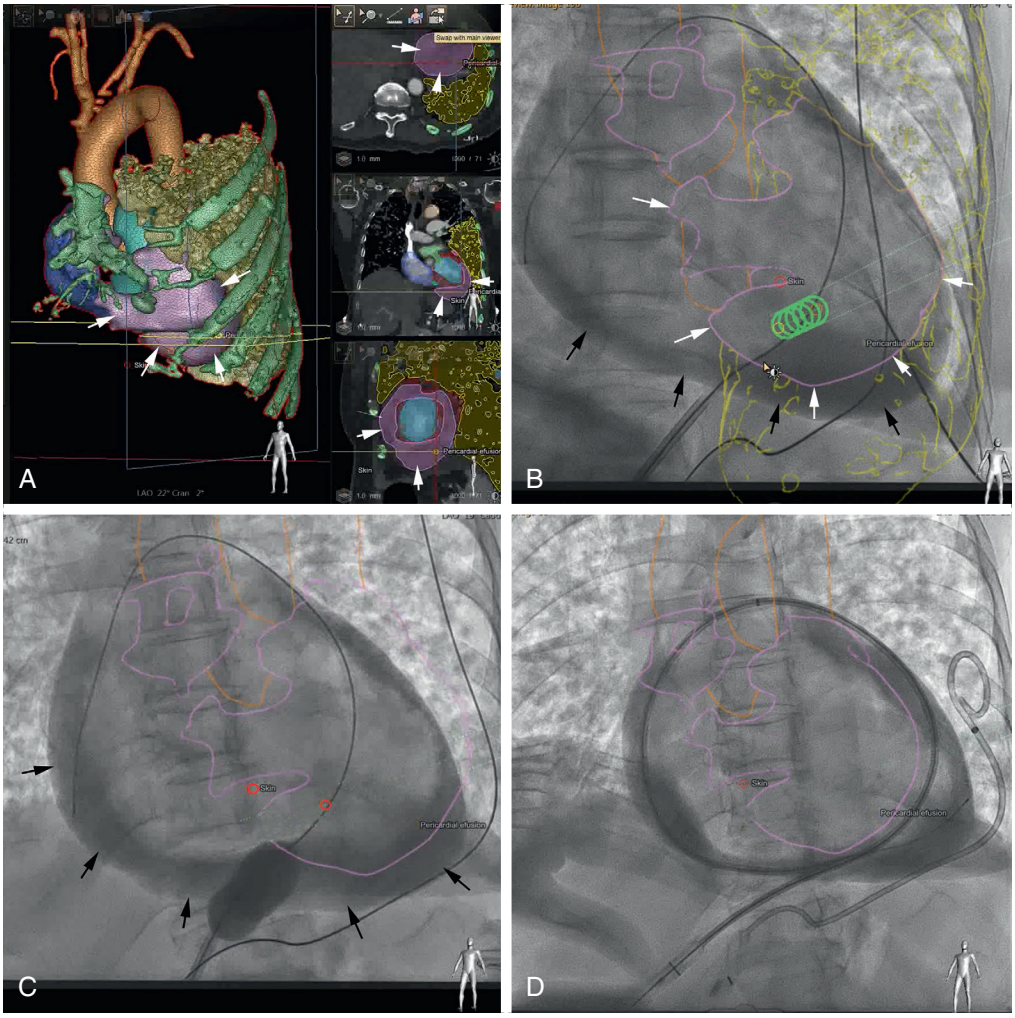
Surgical drainage of the pericardium is highly effective in the removal of pericardial fluid, for uncluttering of loculations, and improving hemodynamic compromise. Surgical pericardiotomy and pericardiectomy (pericardial window) can be achieved by subxiphoid incision or video-assisted thoracoscopic pericardiectomy.[7] Catheter pericardiocentesis remains the treatment of choice in most patients and should be the preferred surgical approach.[8] Surgical drainage has the advantage when pericardial biopsies are needed or pericardiectomy needs to be performed. In addition, surgery may have additional advantages in the case of extensive loculated effusion and reaccumulation of pericardial fluid after catheter drainage. The drawbacks of surgery are that it is more invasive, often requires general anesthesia, and is not emergently available. Surgical drainage should be reserved for PT related to trauma, recurrent malignant effusion, and loculated purulent pericardial effusion.



• **Fig. 6.8** Cardiac computed tomography three-dimensional reconstruction (volume rendering technique) after pericardial drain shows a pigtail catheter *(black arrow)* placed via subcostal, subxiphoid approach in the inferior border of the heart. *Ao,* Ascending aorta; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RCA,* right coronary artery; *RV,* right ventricle.

Key Points

- Patients with PT vary in presentation. It can range from asymptomatic tamponade to tamponade associated with shock and death.
- PT is associated with pericardial effusion increasing intrapericardial pressure beyond a threshold, causing pressure on the heart chambers that leads to restricted ventricular filling that causes decreased cardiac output.
- Echocardiography remains the mainstay of imaging modality to identify pericardial effusion, signs of PT. Typical features may not always be present and precede clinical manifestation of tamponade.
- Pericardiocentesis can be lifesaving and can be performed via various anatomical approaches. If available, echocardiographic or fluoroscopic guidance should be used.
- Percutaneous balloon pericardiotomy is an alternative therapy to surgical pericardial window and can be performed safely with training and imaging guidance.
- Recurrence of tamponade can occur and patients undergoing catheter-based procedures should be closely monitored clinically and with echocardiography.



• **Fig. 6.9** Percutaneous balloon pericardiotomy with computed tomography angiography–fluoroscopic fusion imaging.

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Review Questions

1. Confirmation of the needle in the pericardial space is usually done by
- **a.** Injecting conjecting contrast dye into the pericardial space under fluoroscopy.
- **b.** Drawing back bloody fluid into the syringe.
- **c.** Injecting agitated saline solution mixed with blood or Definity contrast under echocardiographic guidance.
- **d.** Passing the wire through the needle and checking the path of the wire on fluoroscopy.

Answer: c. Confirmation of microneedle placement in the pericardial space is usually done by injecting Definity (Lantheus Medical Imaging, North Billerica, MA) contrast, which is a perflutren lipid microsphere injectable suspension that is an ultrasound contrast agent. It should be noted that cardiopulmonary adverse events (1.1%) can occur with this agent and patients should be monitored for 30 minutes after administration.

2. Care should be taken to avoid which structure while performing pericardiocentesis via apical approach?
- **a.** Left circumflex artery
- **b.** Left lobe of liver
- **c.** Left anterior descending artery
- **d.** Left phrenic nerve

Answer: c. The left anterior descending artery travels anteriorly in the interventricular groove and supplies the anterior wall and apex of the left ventricle. It can be injured via the apical approach. When it is available, echocardiographic guidance should be used and the advance of the needle should be avoided once the fluid is withdrawn into the syringe.

3. What is the common major complication that occurs after percutaneous balloon pericardiotomy for large pericardial effusion?
- **a.** Pericarditis
- **b.** Left phrenic nerve injury
- **c.** Pleural effusion
- **d.** Right coronary artery injury

Answer: c. Pleural effusion is commonly seen after percutaneous balloon pericardiotomy. The pleural drain is routinely placed at the time of the procedure along with a pericardial drain.

7

Percutaneous Assist Devices

JOHN ADAM REICH, NAVIN K. KAPUR, AND MARK B. ANDERSON

CHAPTER OUTLINE

Intraaortic Balloon Pump Counterpulsation
- Introduction and History
- Physiology
- Placement Removal and Troubleshooting
- Indications/Contraindications
- Complications

Active Mechanical Circulatory Systems
- Introduction
- Physiology

Impella and Tandem Heart
- Left Sided Impellas
- High Risk PCI
- Impella RP
- Tandem Heart
- Complications

Extracorporeal Membrane Oxygenation
- History
- ECMO Configurations
- Hemodynamics and Left Ventricular Venting Strategies
- Pulmonary Indications and Clinical Outcomes
- Cardiac Indications and Clinical Outcomes
- Advanced Heart Failure and Cardiogenic Shock
- Right Heart Failure
- Complications

Cardiac assist technology has matured over more than a half century. The first practical device to enter routine clinical use, the intraaortic balloon pump (IABP), revolutionized the management of acute heart failure, and saw an ever-expanding variety of uses, including as an adjunctive tool to protect the heart during heart surgery and percutaneous interventions. It was also a test platform for learning the limitations of cardiac assist, including complications related to vascular access, and forced physicians to deal with a variety of practical and ethical limitations. A host of mechanical pumps initially required surgical placement, but with increasing miniaturization and better understanding of means to deal with hemolysis, thrombosis, energy delivery, and infection control, percutaneous ventricular assist devices (VADs) are now becoming dominant. A burgeoning list of high-level clinical trials, most published since the last edition of this textbook, have contributed substantially to appreciation of the role of these technologies in heart failure and as adjunctive therapy in surgical and percutaneous interventions. IABP has continuing utility and cost-effectiveness, but in a number of settings it appears clearly inferior to VADs such as the Impella device (Abiomed, Danvers, MA), TandemHeart (TandemLife, Pittsburgh, PA), and extracorporeal membrane oxygenation (ECMO). This chapter focuses largely on these four temporary support technologies (Table 7.1).

Intraaortic Balloon Pump Counterpulsation

Introduction and History

The first percutaneously placed cardiac assist device was the IABP, which displaces blood from the descending aorta during diastole and results in altered myocardial mechanics during systole. By raising diastolic perfusion pressure, the IABP has the potential to augment coronary flow. Unlike the majority of more recently developed devices, it provides auxiliary rather than independent support of cardiac output (CO). Although it uses complex software algorithms, it is the simplest of the invasive devices mechanically, the lowest in profile, and is associated with relatively low failure rates. Its advantages include ease of insertion in the cardiac catheterization laboratory (CCL), operating room, or the bedside, and a relatively small footprint, allowing placement in the vasculature with less morbidity than other devices in its class. The CCL has become the primary location of placement while bedside placement in critical care units has declined to the low single-digit percentages.[1,2]

Initial investigations aimed at altering the timing of phases of the cardiac cycle originated with animal experiments conducted by Adrian Kantrowitz in the early 1950s.[3] The focus was initially oriented toward improving coronary blood flow rather than augmentation of CO. Appreciating that coronary flow (particularly in the left coronary circulation) occurs primarily in diastole, the concept was to delay the peak systolic pressure pulse to the diastolic phase of the cardiac cycle.[4] The IABP was introduced in humans in 1967 (Fig. 7.1). Modification over the next decades improved packaging, ease of placement, improvement in timing algorithms, and proliferation of placement in the CCL.

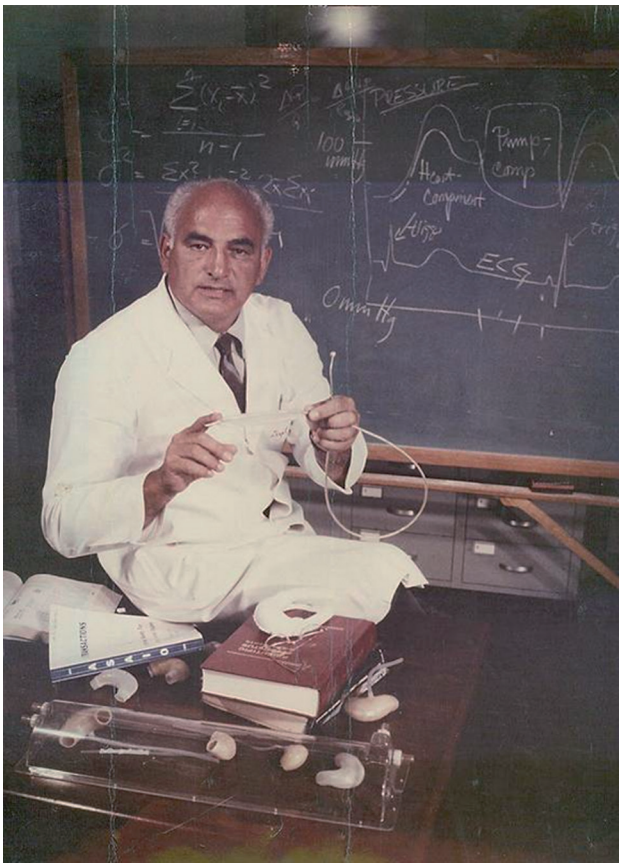
Physiology

The classic concept of intraaortic balloon counterpulsation involves inflation in synchrony with aortic valve closure, at the onset of isovolumic diastole and the appearance of the dicrotic notch, displacing blood comparable to the balloon's volume into the peripheral circulation during diastole. An example of the effects of balloon counterpulsation on systolic and diastolic pressure is seen in Fig. 7.2.

TABLE 7.1 A Comparison of Temporary Mechanical Support Technologies

	IABP	Impella 2.5	Impella CP	Impella 5.0/LD	Impella RP	TH	ECMO
Flow augmentation	0.5–1	1.5–2.5	4	5	4	4	4–7
Size (Fr)	7.5	12	14	21	22	15	17–25
Placement	Percutaneous	Percutaneous	Percutaneous	Open	Percutaneous	Percutaneous	Percutaneous or central
Support	LV	LV	LV	LV	RV	LV, RV, biventricular	RV, LV, biventricular
Type of flow	Pneumatic	Axial	Axial	Axial	Axial	Centrifugal	Centrifugal
Time to initiate	+	++	++	++++	++	++++	+++

Flow augmentations are expressed in liters per minute.
+Signs refer to relative time to initiate support from shortest (+) to longest (++++).
2.5, CP, 5.0/LD, and RP refer to various Impella model brand names.
ECMO, Extracorporeal membrane oxygenation; *IABP*, intraaortic balloon pump; *LV*, left ventricular; *RV*, right ventricular; *TH*, TandemHeart.



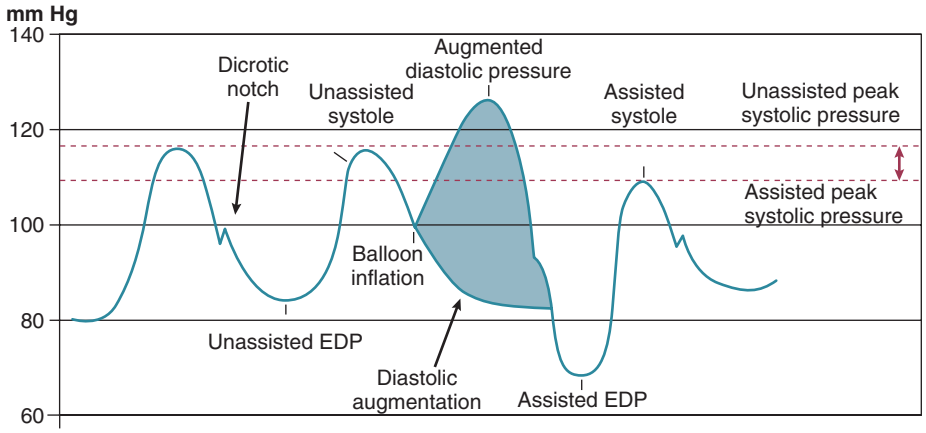
• **Fig. 7.1** Dr. Adrian Kantrowitz with an early model of a working intraaortic balloon pump used in patients circa 1968, the year of the initial human experience with the device. (Photographed by Ralph Morris, *Life Magazine*, licensed by Getty Images, used with permission.)

The "classic" response to IABP lowers systolic blood pressure and augments diastolic pressure. Initial studies showed a 20% decrease in systolic pressure and a 30% increase in diastolic pressure.[5] An important characteristic of IABP, in contrast to most mechanical assist devices, is that it contributes to pulsatile flow, with theoretical benefits to end-organ perfusion beyond any actual change in mean flow or pressures. Because the majority of coronary flow occurs in diastole, an increase in diastolic pressure has the potential to augment coronary flow as well as flow to other end-organs. However, diastolic pressure augmentation can be affected by compliance characteristics of the aorta and vascular bed[6] and increases in diastolic pressure; hence coronary perfusion pressure may not result in an increase in coronary flow because autoregulation modulates this potential. In patients with normal physiology, end-organs capable of autoregulation maintain flow without significant change. Thus experimental and clinical data fail to show change in flow in native coronary arteries[7,8] or in bypass grafts[9] regardless of the severity of coronary stenosis.[10] Although total coronary blood flow may not increase, coronary blood flow velocity has consistently been demonstrated to rise.[11–13] That pulsatile flow may have additional benefit was suggested in a randomized study comparing cardiopulmonary bypass with or without concomitant IABP; multiple parameters of whole-body perfusion were superior in the pulsatile flow setting.[14] In general, augmentation of blood flow appears most likely to occur in patients in profound shock.[11,13,14] Most of the benefits of IABP are related to improvement in hemodynamics with secondary relief of ischemia. Amelioration of ischemia may in turn result in improved left ventricular (LV) function and additional improvement in hemodynamics.

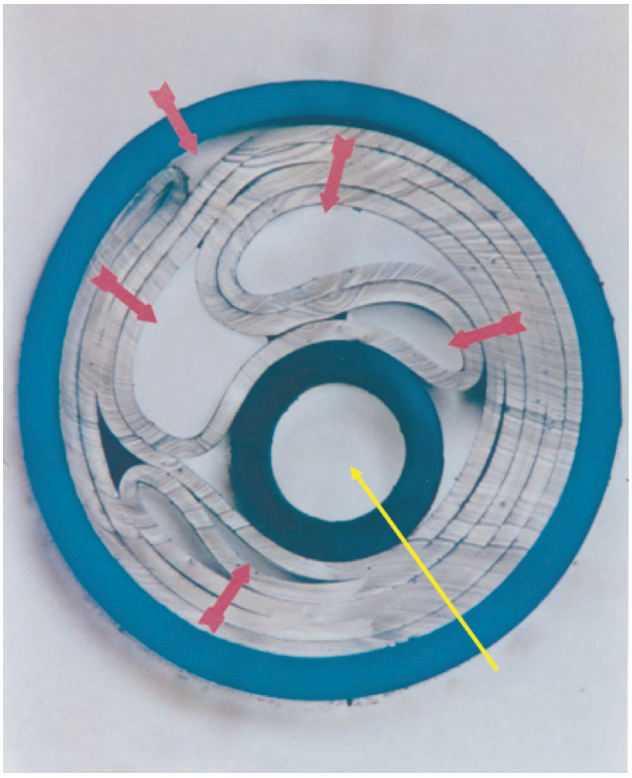
Although the IABP is generally described as both improving myocardial oxygen supply and lowering myocardial oxygen demand, the predominant effect is the latter. This is based on decreased afterload and decreased wall stress with increased stroke volume and CO, particularly in patients with low-output states. In general, the magnitude of hemodynamic response is proportional to the extent of depression of cardiac function.[6] When IABP results in improved end-organ perfusion, as evidenced by signs such as improved urine output, the overall prognosis is generally improved.[5]

Placement Removal and Troubleshooting

With the introduction of a separate guidewire lumen in the early 1980s,[15] the safety of IABP placement improved significantly. Improvements in technology allowed for the introduction of tightly folded balloons prewrapped around the central lumen (Fig. 7.3); previously a cumbersome process that sometimes led to device failure required the operator to wrap the balloon just before insertion. The available IABP catheters range in gas volume from 25



• **Fig. 7.2** Systemic pressure response to an intraaortic balloon pump. The console is set to trigger at 1:2, hence both unassisted and assisted systole and diastole are seen. Note the decrease in systolic pressure with balloon counterpulsation *(double arrow)* and augmentation of diastolic pressure (area under curve in *blue*), thus decreasing afterload and increasing inflow pressure to the coronary and other vascular beds during diastole. *EDP,* End-diastolic pressure. (Courtesy Zoltan G. Turi, MD.)



• **Fig. 7.3** Magnified cross-sectional view of a prefolded intraaortic balloon. This was a significant advance in technology in the early 1980s because it eliminated folding at the bedside, a process that occasionally led to tearing of the balloon membrane and substantially reduced the overall profile of the device at insertion. *Red arrows* point to membrane folds, *yellow* to the central pressure and guidewire lumen. (Courtesy Getinge, Wayne, NJ.)

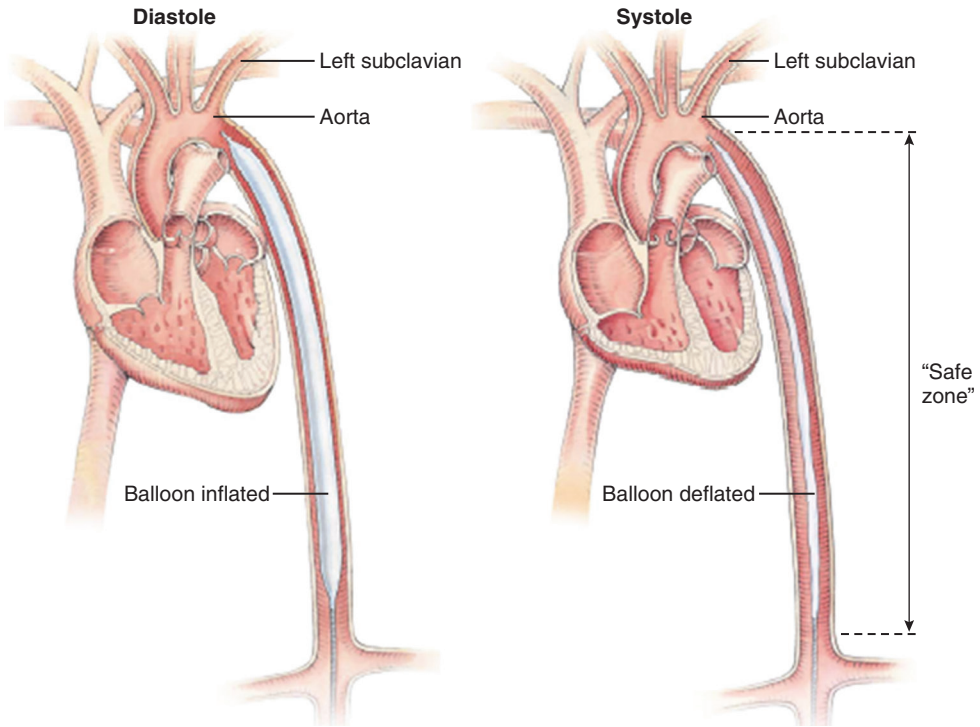
to 50 mL and in shaft lengths from approximately 60 to 72 cm, with the 40-mL balloon used in approximately three-fourths of patients.[16] It is essential to locate the balloon below the origin of the left subclavian artery at the upper margin and above the renal arteries at the lower (a "safe zone"; Fig. 7.4), the tolerances are relatively low.

IABP consoles trigger balloon inflation either from the electrocardiogram (including paced rhythms) or from pressure waveforms, although in some settings, such as during cardiopulmonary bypass, an automatic trigger at a preset rate can be used. Tachyarrhythmias and irregular rhythms have substantial influence on the effectiveness of IABP, the former in part because of the disproportionately shorter diastolic filling of the dicrotic notch.[17] A series of alarms identify leaks in the IABP circuit, high or low pressure, loss of trigger signals, blood in the gas line, low battery, and other anomalies that foreshadow or indicate impending or existing system failures. Fig. 7.5 demonstrates the control panel of a modern IABP console.

The IABP (Fig. 7.6) is designed to be introduced percutaneously through the common femoral artery, which is the method used in 95% to 98% of cases, two-thirds via the right common femoral.[16,18] Every effort should be made to ensure that the femoral puncture is above the femoral bifurcation and below the inguinal ligament. Puncture below the femoral head drastically increases the likelihood of puncture into the femoral bifurcation vessels (77% of femoral bifurcations are at or below the inferior margin of the femoral head[19]), which in turn is associated with acute leg ischemia as the result of vascular obstruction, and pseudoaneurysm formation on balloon removal.

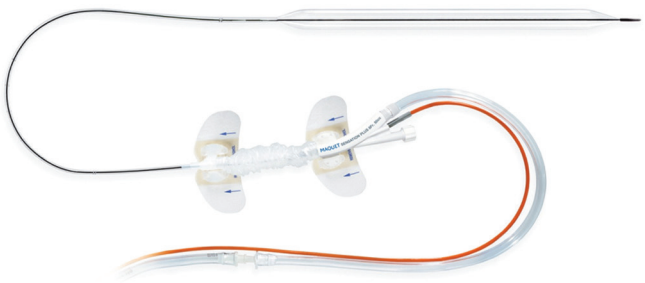
IABP placement is ideally performed with fluoroscopy at the bedside. In the critical care setting, transesophageal echocardiography can be used as a suitable alternative to fluoroscopy for precise balloon placement.[20] Optimal placement of tip of the balloon is 1 to 2 cm inferior to the left subclavian artery origin (see Fig. 7.4), typically near the top of the descending aorta. The distal circulation should be assessed carefully after IABP placement. Distal ischemia is relatively common. Postprocedure and subsequent monitoring of left arm pressures can lead to early diagnosis of inadvertent balloon advancement obstructing left subclavian inflow, a phenomenon to which restless patients who flex their thigh are predisposed.

Alternatives to femoral placement include brachial, subclavian, axillary, iliac, transthoracic, and translumbar. In some cases, distal perfusion in the legs can be preserved by placing an external femorofemoral shunt.[21] Placement in subclavian[22] and axillary arteries[23,24] can be done to aid in allowing ambulation during prolonged use.



• **Fig. 7.4** Location of intraaortic balloon during systole and diastole. Ideally the tip should be a few centimeters distal to the origin of the left subclavian and the proximal portion above the origins of the renal arteries, the "*Safe Zone*." (Adapted from figure courtesy Teleflex Incorporated, Wayne, PA. All rights reserved. Adapted figure courtesy Zoltan G. Turi, MD.)

• **Fig. 7.5** Intraaortic balloon console showing continuous display of electrocardiogram, electrocardiogram, systemic pressure (note diastolic augmentation), and balloon pressures. (Courtesy Getinge, Wayne, NJ.)

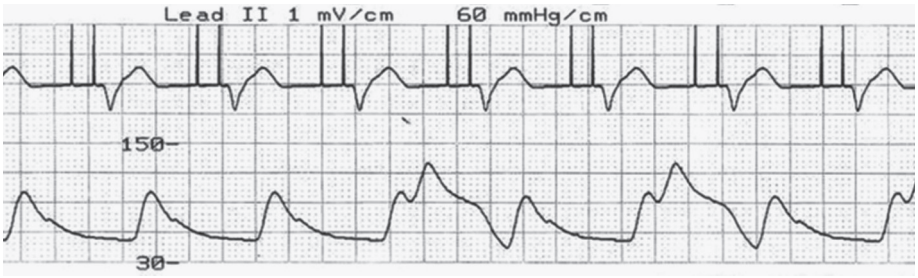


• **Fig. 7.6** A modern intraaortic balloon. A minimal sized central lumen allows advancement over a guidewire. Low-profile balloons such as this one use fiberoptic cable for pressure monitoring because the central lumen is of inadequate size for phasic pressure measurement. (Courtesy Getinge, Wayne, NJ.)

The timing of balloon inflation and deflation is designed to optimize afterload reduction and enhancement of diastolic pressure without interfering with ventricular ejection. Classically, it was considered optimal to inflate at the dicrotic notch, as soon as aortic valve closure occurred, and to deflate near the onset of ventricular depolarization, anticipating the beginning of mechanical systole (Fig. 7.7). Early deflation can result in reversal of both coronary and other end-organ (e.g., cerebral) flow back into the aorta, shunting blood from vital end-organs.[25] Early inflation results in increased afterload late in LV ejection with consequent impairment of LV systolic function.

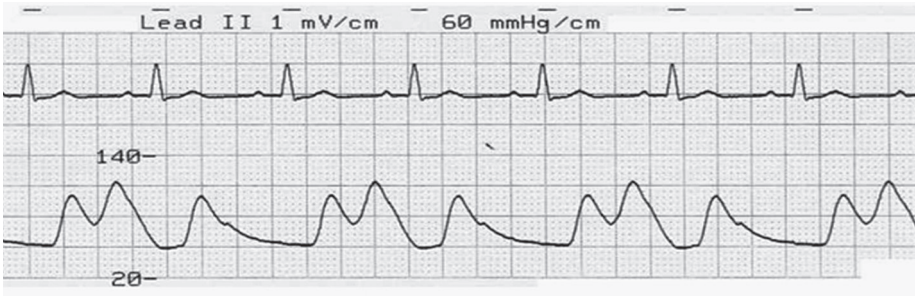
A common problem has been proper timing in patients with underlying arrhythmias. Particularly vexing has been atrial

A

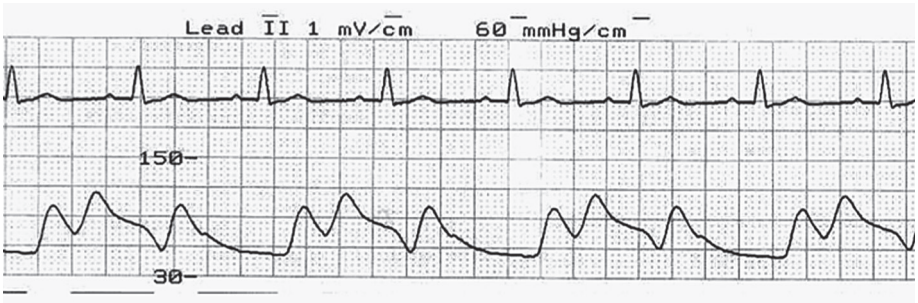


B

C



D



E

• **Fig. 7.7** Examples of timing of intraaortic balloon pump inflation and deflation with 1:2 balloon pumping, from top to bottom. Panel A demonstrates optimal timing, resulting in mild lowering of systolic pressure with diastolic augmentation. Examples are shown of early inflation before the dicrotic notch (B), late inflation (C), early deflation (D), and late deflation (E). (Figure courtesy Zoltan G. Turi, MD.)

fibrillation, with unpredictable beat-to-beat intervals. Rapid ventricular rates result in disproportionate decrease in the diastolic interval and limit the effectiveness of IABP because of the inherently short period of counterpulsation.[26] Operating at 1:2 rates may be required in this setting.

Adjunctive pharmacotherapy includes rhythm control, anticoagulation, and sedation. Antiarrhythmic agents to slow and regularize the heart rate can have important benefits for lengthening diastole and optimizing balloon timing, both of which in turn enhance IABP augmentation. The general consensus has been that anticoagulation should be administered if not contraindicated. Thrombus formation has been reported to be one of the most common complications, nearly 3% in one series of 911 patients undergoing coronary artery bypass grafting (CABG).[27]

Removing the balloon should be done with great care. Counterpulsation should not be turned off completely until the activated clotting time confirms that anticoagulation has been effectively discontinued and the patient is ready to have the balloon pulled, because thrombosis on the balloon surface occurs rapidly.[28] Most operators run the IABP at a low cycle rate, 1:3, until anticoagulation has worn off sufficiently and the balloon can be pulled. Nonfunctioning or stopped IABPs need to be removed promptly, preferably within 20 minutes. Because the balloon is delivered prefolded by the manufacturer (see Fig. 7.3), it passes readily through its delivery sheath during insertion. Once inflated, it will not refold when vacuum is applied, and the profile is too large for retrieval without bringing both the sheath and balloon out of the body together. The balloon gas line should be aspirated to reduce the balloon profile. It is essential to allow some bleeding after catheter removal and before compression to avoid stripping any clot off the balloon inside the common femoral artery. It is important to continue to monitor patients for adverse events because nearly 25% of complications have been reported to occur *after* IABP removal.[29]

Indications/Contraindications

Acute MI and Cardiogenic Shock

Historically cardiogenic shock (CGS) remained the most common indication for several decades[16]; however, recent studies have shown no clear mortality benefit from IABP in this setting.[30] Other common indications have included perioperative support for patients undergoing cardiac surgery, weaning from cardiopulmonary bypass, management of unstable angina, severe congestive heart failure, acute mitral regurgitation, and, with less evidence base, refractory ventricular arrhythmias or angina after myocardial infarction (MI), as well as a host of miscellaneous settings largely defined by case reports.

The classic understanding of CGS has been stunning or irreversible loss of a large amount of myocardium (≥40%) with resultant low output and compensatory elevated systemic vascular resistance to maintain central organ perfusion pressure. The most common current definition is hypotension (blood pressure <90 mm Hg systolic) for more than 30 minutes, with low cardiac index (<1.8 l/min per m^2 without support or <2.2 L/min per m^2 with support), and finally elevated filling pressure (pulmonary artery wedge pressure >15 mm Hg or LV end-diastolic pressure >18 mm Hg or right ventricular [RV] end-diastolic pressure >10–15 mm Hg).[31] Data from the SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK) trial have called several classic assumptions into question,[32] in part because some of the patients with CGS in the trial had relatively preserved ejection fractions, whereas some patients with an apparently much greater amount of dysfunctional or nonfunctional heart muscle were hemodynamically compensated.

Although heart failure in ST-segment elevation MI (STEMI) has declined, the incidence of CGS has risen[33]; the most recent estimates are that is it seen in approximately 5.5% to 6% of AMIs. Mortality remains high however, with a nearly 40% in-hospital death rate reported in the Benchmark registry.[18] As discussed later in this chapter, some newer interventions are being investigated to determine if there is potential benefit to alternative types of cardiac support for this still very high mortality. In addition, more modern parameters for assessing shock, including cardiac power output and pulmonary artery pulsatility index, are being incorporated. In the interim, the existing data on IABP have continued to show relative futility: the IABP SHOCK-II trial randomized IABP use in patients with CGS undergoing percutaneous coronary intervention (PCI)[34] and showed no benefit on 30-day mortality. A number of study design concerns exist (particularly between group cross-overs and selection of a relatively low-risk CGS population) as well as the possibility that IABP placement before rather than after PCI (most patients had IABP placement after revascularization) would have shown additional benefit.[35] A smaller study, IABP SHOCK, demonstrated no significant improvement in serial APACHE (Acute Physiology and Chronic Health Evaluation) II scores[36] with IABP use. Several meta-analyses have come to similar conclusions.[37,38] Use of IABP in CGS in American Heart Association (AHA) and American College of Cardiology guidelines now carries a class IIa recommendation with level B evidence.[30] More recently in 2017 the European Society of Cardiology downgraded their prior recommendation to class III for routine use of IABP in STEMI complicated by CGS.[39] In short, for treatment of CGS, IABP has largely been relegated to second-tier or even inappropriate therapy.

Myocardial Ischemia and Revascularization

IABP use in unstable angina dates from an era in which the available alternates were medical therapy and coronary bypass surgery, and IABP was used to stabilize patients before being taken to the operating room. In certain settings, such as severe left main disease or in unstable angina with attendant hemodynamic instability, this algorithm remains appropriate.[40] The most recent American College of Cardiology Foundation (ACCF)/AHA guidelines[41] list adjunctive use of hemodynamic support, including IABP, as a class IIb recommendation for hemodynamically unstable patients undergoing PCI. A randomized controlled trial (Balloon-Pump Assisted Coronary Intervention [BCIS]-1)[42] of a particularly high-risk group, published after the guidelines were written, studied patients with ejection fractions less than 30%; this study did demonstrate a 34% reduction in mortality in the group with IABP protection during PCI.

IABP has been used in approximately 10% to 15% of patients undergoing cardiac surgery.[43] About half of this use is for coronary bypass patients; two-thirds of the CGS patients in the Society of Thoracic Surgeons (STS) database had IABPs inserted.[44] A number of studies have demonstrated a favorable influence on outcomes including mortality,[45–47] but there is lack of consensus regarding indications for perioperative IABP.[48] The vast majority of IABP insertions occur preoperatively[43,44]; the effectiveness of this approach has been controversial.

IABP with pulsatile flow during cardiopulmonary bypass also appears to have favorable effects on end-organ perfusion[25,49–51] with protection of both coronary and cerebral blood flow.[52] IABP insertion can also be used to assess prognosis; the requirement for

catecholamine support and overall hemodynamics 1 hour after institution of perioperative balloon pump insertion is highly predictive of overall outcome.[53] In the STS database, operative mortality with CGS patients, the majority of whom received IABP, was high, ranging from 20% in isolated CABG to 33% for CABG and valve surgery and 58% for CABG and ventricular septal repair.[54] IABP use in conjunction with ECMO is covered later in the chapter.

Contraindications

The classic absolute contraindication to IABP use is aortic insufficiency. Because the acute hemodynamic effects are so deleterious, animal and clinical investigations were completed in the 1970s.[55] Increased volume displacement retrograde into the left ventricle during diastole greatly exacerbates wall stress, with increased potential for hemodynamic decompensation as well as LV pseudoaneurysm formation and left ventricle rupture in the post-MI setting. The amount of aortic insufficiency that constitutes an absolute contraindication has no objective basis, but most operators use a threshold of trivial to mild. Similarly, the presence of aortic dissection and aortic aneurysm are considered absolute contraindications because of the risk of extending dissection or causing aneurysmal rupture. Patent ductus arteriosus, like aortic insufficiency, has theoretical deleterious results from shunting blood flow from the aorta with IABP induction, in this case increasing left-to-right shunting into the pulmonary artery.

Relative contraindications include placement of an indwelling foreign body into a patient with active infection including sepsis (the existing evidence base does not suggest significant hemodynamic benefit for patients with septic shock), severe peripheral vascular disease likely to result in limb ischemia, bleeding diathesis (though in practice many patients with low fibrinogen levels or on aggressive anticoagulant or antiplatelet treatment receive IABPs), and contraindications to afterload reduction, such as dynamic LV outflow obstruction,[56] a condition that has on occasion been unmasked by institution of counterpulsation.[57]

Complications

As would be expected, duration of IABP use correlates with risk of complications overall[58,59] including sepsis.[60,61] The overall complication rates have declined to 15% in a large single-hospital review[62] and 6.5% in the Benchmark Registry, which incorporates the largest experience to date.[63] In general, diabetic patients and women have a higher complication rate.[64]

Vascular complications including limb ischemia are the most common serious adverse events.[65] Trauma to the aorta has been reported, with paraplegia caused by spinal necrosis owing to subadventitial hematoma,[66] cholesterol embolization to spinal and mesenteric arteries,[67] and aortic dissection,[68] as well as in patients with no obvious cause. A complication particular to IABP is thrombocytopenia, occurring presumably because of destruction of platelets that adhere to the IABP surface. Critical care patients with IABP and using heparin have a 7:1 odds ratio of a 50% drop in platelet count compared with patients without IABP but receiving similar doses of heparin,[69] minimizing the likelihood that heparin-induced thrombocytopenia is the etiologic factor. Finally, balloon rupture is made apparent by the appearance of blood in the gas lumen, with triggering of alarms. The usual site of rupture has been at a point when the aorta is at its nadir in diameter along the course of the IABP. Rupture of the balloon with a major gas leak, a rare event, has been reported to cause stroke secondary to gas embolization.[70] Fracturing of the IABP can occur with entrapment, including separation and migration of part of the device.[71]

Active Mechanical Circulatory Systems

Introduction

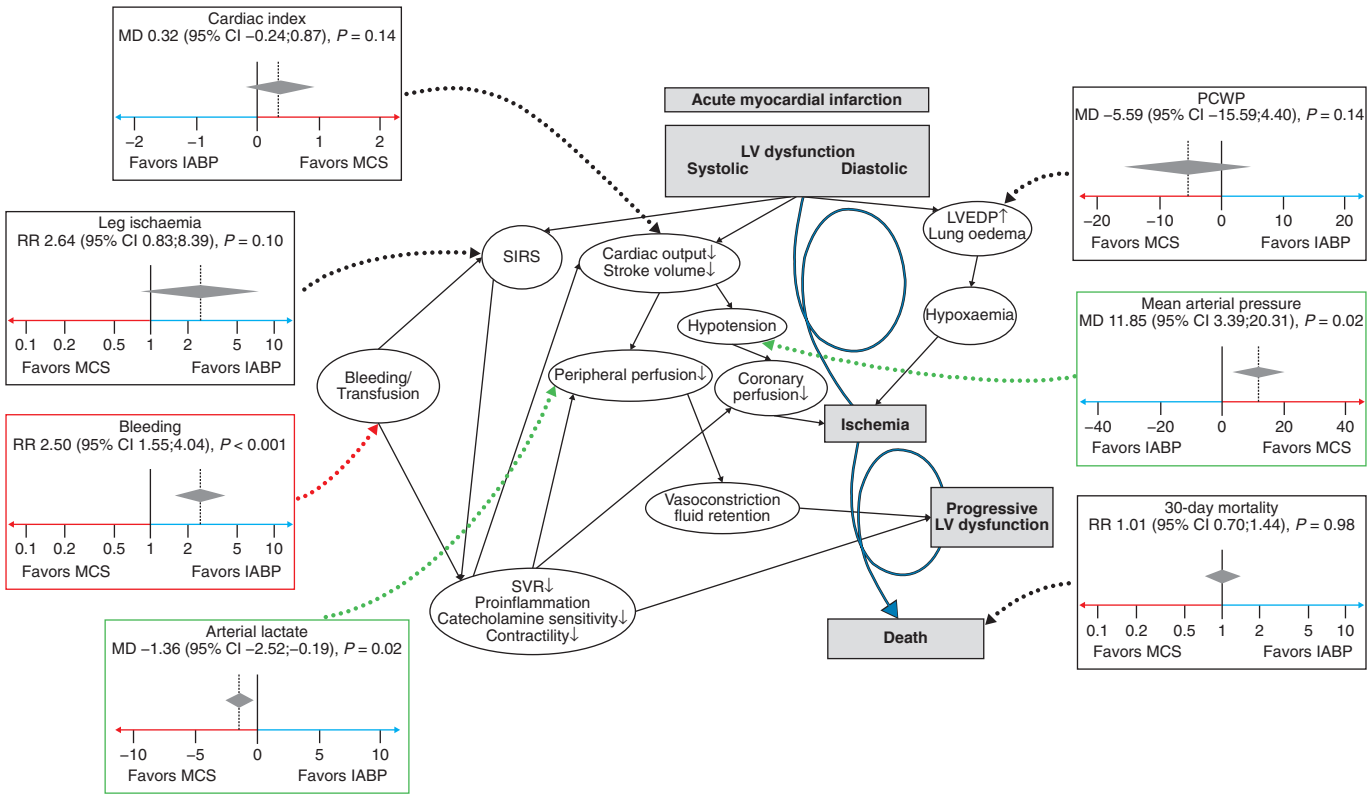
The use of surgically implanted LV assist devices (LVADs) as an approach to "bridge" patients to recovery or cardiac transplantation or as "destination therapy" has opened new opportunities for patients with advanced heart failure whose condition might otherwise have been rendered medically futile. Nearly 1500 LVADs are implanted annually in the United States alone.[72] These devices have evolved from large, bulky pulsatile systems to smaller, compact, fully implantable continuous-flow (CF) pumps that generate minimally pulsatile blood flow when functioning optimally. These CF-LVADs use rotodynamic pumps to transfer kinetic energy from a circulating impeller to the bloodstream, thereby generating forward flow. CF-LVADs can be divided into two categories: axial-flow and centrifugal-flow pumps. In both cases, blood is pulled into the impeller of the pump via an inlet cannula connected to the LV apex and delivered to the systemic circulation via an outflow cannula connected to either the ascending or descending aorta. In parallel to the evolution of surgically placed LVADs, percutaneously delivered mechanical circulatory support systems (MCS) have also grown from counterpulsation balloon systems to centrifugally driven circuits, or catheter-mounted axial-flow pumps.[72]

These devices are differentiated from IABP in that they actively support forward flow; in contrast IABP has been labeled as "passive" hemodynamic support.[73] As described in discussions of the individual MCS technologies, they have potential for subsequently improving outcomes in a variety of clinical settings, including CGS. Fig. 7.8 shows the physiologic effect as well as complications of these technologies in the CGS setting. In general the MCS devices result in superior hemodynamics, somewhat higher complication rates, and as yet no global improvement in overall survival, albeit the active devices have been subject to relatively small studies, typically underpowered for mortality, and with clinical algorithms that may not be optimal.[73]

Physiology

The overall goals of MCS are to (1) increase vital organ perfusion, (2) augment coronary perfusion, and (3) reduce ventricular volume and filling pressures, thereby reducing wall stress, stroke work, and myocardial oxygen consumption. Clinical scenarios in which these devices are commonly used include CGS, mechanical complications after AMI, high-risk coronary and noncoronary intervention, and high-risk electrophysiologic ablations. Percutaneous circulatory support devices can be categorized by the type of pump used to generate either pulsatile or continuous blood flow. Each device affects native ventricular function in a unique way and requires adequate preload for optimal use.[74]

Careful hemodynamic interrogation before, during, and after initiation of percutaneous MCS is essential for optimal device function because MCS systems are affected by changes in preload and afterload. Inadequate LV preload owing to volume depletion, poor RV function, hypotension, pulmonary obstruction, or valvular disease will reduce flow generation. Similarly, increased afterload owing to hypertension, elevated systemic vascular resistance, or valvular disease will reduce device flow.



• **Fig. 7.8** Summary of physiologic effects of cardiogenic shock and meta-analysis of hemodynamic effects of intraaortic balloon pump *(IABP)* devices compared with active mechanical circulatory support *(MCS)* devices. *CI,* Confidence interval; *LV,* left ventricular; *LVEDP,* left ventricular end-diastolic pressure; *MD,* mean differences; *RR,* relative risk; *SIRS,* systemic inflammatory response syndrome; *SVR*, systemic vascular resistance. (From Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J.* 2017;38:3523–3531. Used with permission.)

Three primary CF percutaneous MCS device platforms are currently used in clinical practice for LV hemodynamic support. These devices include (1) centrifugally driven left atrial–to–femoral artery bypass (TandemHeart), (2) centrifugally driven venoarterial ECMO (VA-ECMO), and (3) microaxial flow catheters (Impella and HeartMate Percutaneous Heart Pump [PHP]; Abbott Inc, St. Paul, MN). At present, the Impella devices are the only percutaneous MCS platform approved by the U.S. Food and Drug Administration (FDA) for high-risk PCI and CGS. The Impella RP device is approved for acute right heart failure.

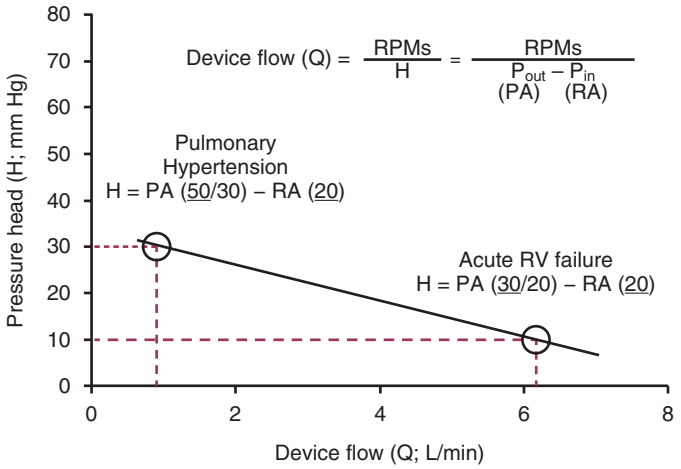
Flow through all CF (nonpulsatile) MCS devices is directly related to rotations per minute of the impeller and indirectly related to pressure at the inlet and outlet of the impeller. This pressure gradient (P_{in}-P_{out}) varies during systole and diastole. The relationship between pressure and flow is best described using an H-Q curve, where H is defined as the pressure head (P_{in}-P_{out}) and Q is defined as device flow. Each device has a specific H-Q curve signature (see Fig. 7.9). Axial-flow pumps tend to have a steeper H-Q slope, whereas centrifugal flow pumps have a flatter H-Q slope.

For the TandemHeart, Impella, and PHP devices, the pressure head (H) includes LV end-systolic pressure (LVESP) and aortic (Ao) pressure. For patients without decompensated heart failure or aortic valve disease (e.g., those undergoing high-risk PCI), peak aortic and LV systolic pressures (SPs) are matched and at peak systole (e.g., Ao SP-LVESP = 120 mm Hg − 120 mm Hg) the estimated systolic H is zero. Throughout diastole, typical aortic diastolic pressure ranges (DP) between 60 and 80 mm Hg (AoDP) and LVEDP is often below 20 mm Hg. Therefore the estimated H ranges between 40 and 60 mm Hg (AoDP − LVEDP) and 0 (AoSP − LVESP). Based on this principle, for a given rotations per minute, CF devices will provide higher flow at peak systole (H = 0) and lower flow in diastole (H = 40–60). In contrast, the patient with CGS may have a substantially lower H during diastole with high LVEDP and low AoDP. For this reason, for a given rotation per minute rate, CF devices provide higher flow at both peak systole and end-diastole compared with a patient without decompensated heart failure or shock.[72] This phenomenon is true for RV support devices like the Impella RP as well. The pressure head increases with pulmonary artery hypertension (when pulmonary vascular resistance increases), and consequently device flow decreases. With acute RV failure the pressure head decreases and at the same rotations per minute flow through the device increases. Fig. 7.9 shows an H-Q curve for RV failure.

Impella Devices

The Impella devices are a series of catheter-based, axial-flow, peripherally inserted heart pumps: the Impella 2.5, CP, 5.0, LD, and RP models. (The Impella LD model is designed for open, direct aortic surgical implantation.) They are useful in ventricular failure causing CGS, and as support used prophylactically before or during high-risk procedures, particularly complex PCI (but also

other procedures including high-risk ablation and some structural heart interventions). The left-sided Impella devices are placed retrograde across the aortic valve into the left ventricle and generate antegrade blood flow in the ascending aorta while simultaneously directly unloading the left ventricle.[75] In contrast, the RP model is positioned antegrade across the tricuspid and pulmonic valves, with the inlet in the right atrium and the outlet in the main pulmonary artery. The left-sided and right-sided devices have been used in tandem to support patients with biventricular failure, known as the BiPella approach.[76] As CF devices, none of the Impella pumps require being timed to the cardiac cycle. The 2.5, CP, and 5.0 devices provide 2.5, 3.5, and 5 L/min of flow, respectively, whereas the RP device can provide support in excess of 4 L. The devices require some preservation of contralateral ventricular function for maximal flows (left-sided devices require some RV function as described subsequently, and the RP requires some preservation of LV function; these are typical of VADs in general).

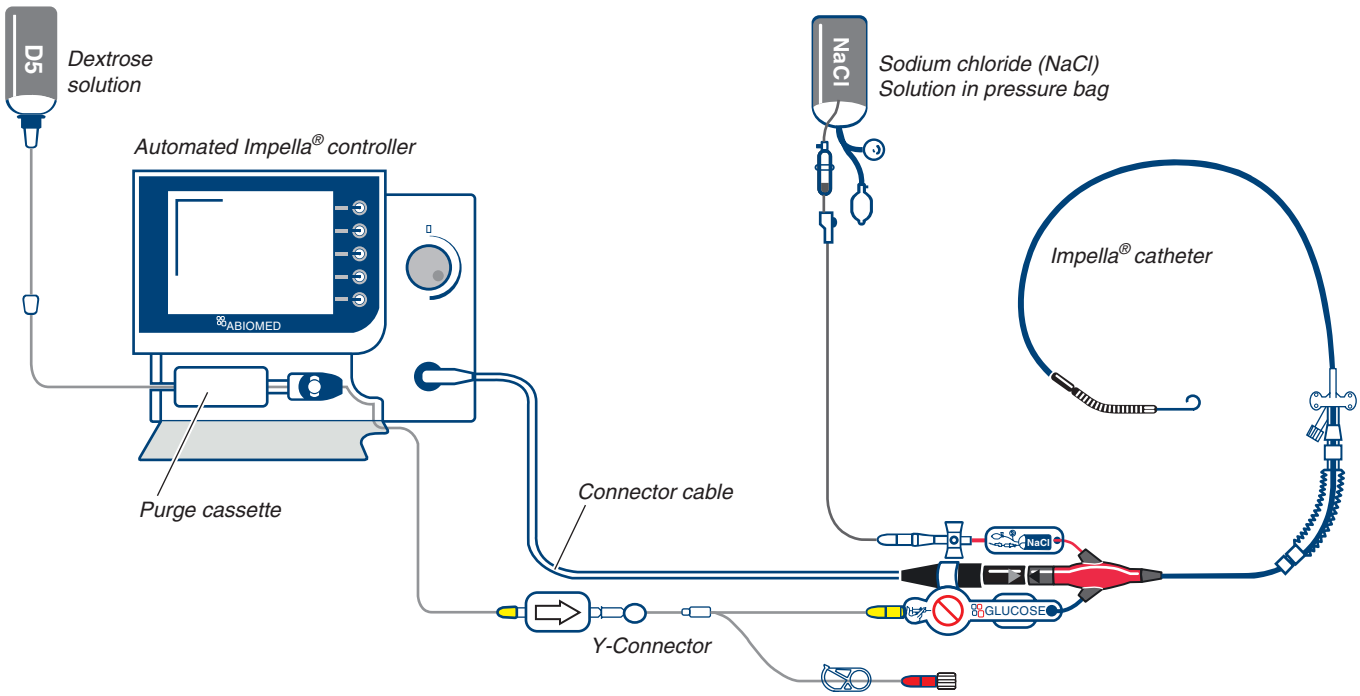


• **Fig. 7.9** Pressure *(H)* - flow *(Q)* curve for continuous flow device demonstrating H-Q curve for the Impella RP device. When pulmonary vascular resistance is elevated (pulmonary artery hypertension), device flow is limited. When acute right ventricular *(RV)* failure occurs, flow through device increases significantly because the pressure head *(H)* lessens. *PA,* Pulmonary artery; *RA,* right atrium; *RPMs,* rotations per minute. Underscore identifies pressure used for calculating the pressure head. (From Kapur NK, Esposito ML, Bader Y, et al. Mechanical circulatory support devices for acute right ventricular failure. *Circulation.* 2017;136:315–326.)

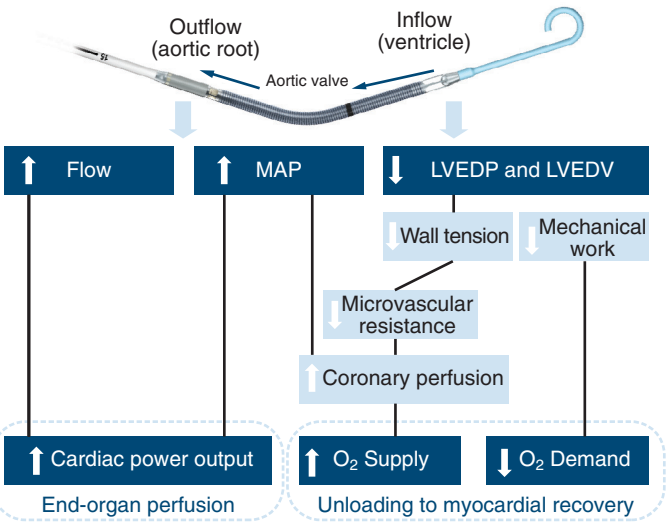
The Impella 2.5, CP, and RP devices are implanted using a percutaneous technique, most commonly via the femoral artery or vein (the only option for the RP model). It is imperative that these devices be placed with fluoroscopic guidance to ensure safety and aid in proper positioning. Each device has a pigtail that helps provide positioning stability. The 5.0 device, which is most commonly inserted surgically, can be placed via the femoral artery; however, current practice uses the axillary artery in most cases. The axillary approach allows for a stable and durable device position as well the possibility of patient ambulation. All devices are inserted over a guidewire using a monorail technique. Novel approaches, such as transcaval, have been used for patients with prohibitive peripheral vascular disease,[77] and the percutaneous approach to axillary artery implantation has also been described.[78] All Impella pumps require systemic anticoagulation, as well as a purge system that prevents blood from entering the motor. The Impella device is monitored and controlled by an automated console with the motor speed adjusted by P (performance) levels that correspond to rotations per minute (Fig. 7.10). This allows for the optimization of flows for any given patient as well as the ability to wean the patient from the device. The length of approved use for high-risk PCI is less than 6 hours and for treatment of CGS is less than 4 days.[79] In practice, dwell times have been longer when awaiting definitive therapy (e.g., bridge to durable VAD) or when there is evidence that myocardial recovery is continuing to improve and eventual weaning may be successful.

The devices include a controller that is powered by an alternating current plug and has an internal battery that can last up to 1 hour, which is helpful during transport. The setup of controller, infusion system, and catheter are shown in Fig. 7.11 and the effect on physiology in Fig. 7.12. Specific contraindications to the use of the LV Impellas include the presence of a mechanical aortic valve or LV thrombus. An aortic valve area less than 0.6 cm^2 makes passage of the cannula difficult, although Impellas have been used in patients with critical aortic stenosis who require PCI, with facilitation of Impella passage by placing a balloon simultaneously across the aortic valve. The latter, even without balloon aortic valvuloplasty, can facilitate device passage.[80] As is obvious, the device should not cross a mechanic valve. RV failure is a relative contraindication to percutaneous LVAD placement because unloading of the left side can

• **Fig. 7.10** Impella Controller monitor screen. (Image courtesy Abiomed, Inc.)



• **Fig. 7.11** The setup of the Impella system. *D5,* 5% Dextrose solution. (Image courtesy Abiomed, Inc.)



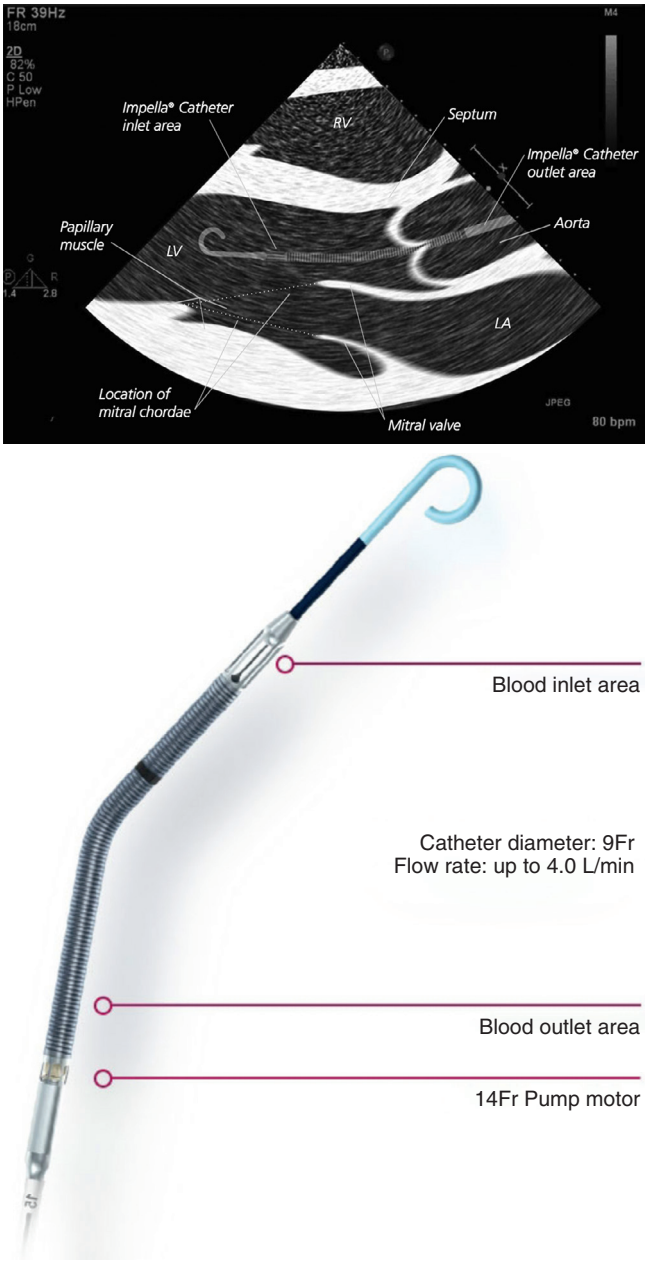
• **Fig. 7.12** The physiologic effects of the Impella device on cardiac output, mean arterial pressure *(MAP),* left ventricular end-diastolic pressure *(LVEDP)* and end-diastolic volume *(LVEDV),* wall tension, coronary perfusion, and myocardial oxygen *(O_2)* supply and demand. (Image courtesy of Abiomed, Inc.)

change septal and RV geometry, unmasking RV failure. In addition, a failing right ventricle is unable to deliver adequate LV preload, and the device may then be prone to suction events and associated hemolysis. Aortic regurgitation, aortic dissection, bleeding diathesis, and uncontrolled sepsis are typically contraindications. The Impella RP device is contraindicated in the presence of caval or right atrial thrombus; relative contraindications include the presence of an inferior venacaval filter or significant right-sided valvular heart disease as well as atrial and ventricular septal defects. Severe peripheral vascular disease may make placement of left-sided Impella devices difficult to impossible, in particular via the femoral artery, and may compromise remaining peripheral circulation, although as with IABP, an external femorofemoral shunt can address potential lower extremity ischemia distal to device insertion.[21]

Left-Sided Impellas

A standard placement signal for Impella 2.5 or CP devices can be seen in Fig. 7.10, with a pulsatile tracing that appears somewhat like an arterial line. Of note, this cannot be used as absolute blood pressure; true arterial monitoring from another line should be used for this purpose. Proper placement needs to be confirmed daily with x-ray imaging, and upon demand with transthoracic echocardiography if there is any change in placement signal, flows, or there is unexplained deterioration in the patient's condition. The most useful bedside confirmation of device location is via echocardiography; an idealized transthoracic echocardiography view is shown in Fig. 7.13. The end of the visualized catheter should be 3.5 cm past the aortic valve.[79] The catheter should be directed toward the apex and stay clear of the mitral apparatus and papillary muscles. After placement, the Impella device can be placed in auto mode where the flow is maximized by internal algorithm for 3 hours. Alternatively, the flow can be changed by increasing the power settings, P0 through P8, at the bedside. The bottom left of the controller screen shows the calculated flow in liters per minute (see Fig. 7.10); this is in addition to any native flow that is progressing through the heart. The higher the P level, the higher the flow and less stroke work attributable to the native heart.

The hemodynamics provided by the Impella devices are favorable for patients in CGS. The active forward flow and systemic aortic pressure contribution increase mean arterial pressure (MAP); the forward flow augments end-organ perfusion, which requires both pressure and flow. The objective measure of these parameters is their product (MAP × CO/451) and is referred to as the cardiac power output. This value has been identified as an important



• **Fig. 7.13** Simulator image showing TTE View of proper Impella placement *(top)* and for reference, the catheter is shown below. (Images courtesy Abiomed Inc.)

predictor of mortality in CGS.[81] Cardiac power output can be used to determine whether mechanical support is necessary, gauge the impact of a chosen support type and level after initiation, and whether support needs to be escalated or can be weaned. In addition to these two mechanisms, the left-sided Impella devices directly unload the left ventricle. The active removal of blood from the LV cavity reduces end-diastolic volume and pressure (LVEDV, LVEDP) and augments peak coronary flow. For patients in CGS, coronary flow increases through a dual mechanism. First, increased aortic pressure (the pressure head for coronary flow during diastole) increases the upstream pressure for myocardial perfusion, and second, through the Impella's unloading mechanism, with continuous removal of ventricular volume, LV wall tension falls. As LV wall tension (characterized by Laplace as Pressure × Diameter/Wall thickness) falls, so does the microvascular resistance within the myocardium. The end result of a rise in MAP and a drop in LVEDP is that the myocardial perfusion gradient improves along with coronary perfusion. This is relevant for patients in CGS when a low perfusion gradient can aggravate coronary ischemia and precipitate cardiovascular collapse. Impella support allows for maintenance of this gradient and augmentation of coronary perfusion. The coronary perfusion effects of Impella have also been assessed using the coronary flow velocity reserve technique with significant increased hyperemic flow velocity and coronary flow velocity reserve correlating with increasing levels of Impella support.[82] The myocardial perfusion effects of Impella devices can also be visualized on myocardial scintigraphy.[83] In addition, improvements in end-organ perfusion with an Impella device have been demonstrated through advanced imaging of the sublingual mucosal vasculature in the setting of STEMI with shock.[84]

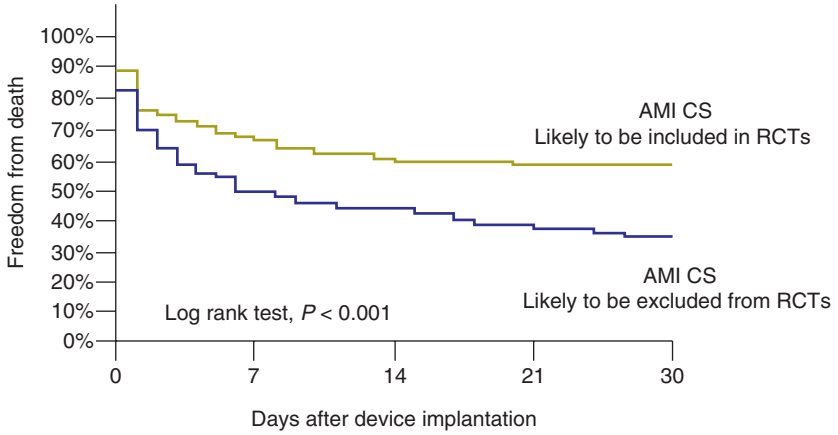
Another beneficial effect of ventricular unloading and the reduction of LVEDV and LVEDP is the potential for the reduction of infarct size, as demonstrated in the animal model.[85] Of particular note, the most significant reduction in infarct size resulted from unloading the left ventricle before revascularization. Extrapolating on this observation, again in an animal model,[86] two different management algorithms were compared. Both had 90 minutes of ischemia, but in one group animals had immediate reperfusion, whereas in the second LV unloading was performed first, thereby subjecting the heart to 60 minutes of additional ischemia followed by reperfusion. Despite the additional ischemic time, infarct size was significantly reduced in the LV-unloaded group. These animal laboratory results have led to the FDA approval of a clinical trial investigating the safety and feasibility of ventricular unloading in the setting of acute MI (AMI). The primary endpoint will be the reduction of infarct size at 30 days by magnetic resonance imaging.[87]

There are now numerous clinical society guidelines for Impella therapy (Table 7.2).[88] Currently the FDA has approved left-sided Impella devices for treatment of CGS occurring less than 48 hours after AMI or open heart surgery. Two registries are of note: the original USpella Registry[89] and the more recent Catheter based Ventricular Assist Device Registry (cVAD),[90] the latter an observational, multicenter, retrospective global registry designed to capture data reflecting "real-world" use of Impella devices. Data extracted from the latter[88] included 324 patients who underwent a PCI and were supported with a left-sided Impella in the setting of CGS and AMI. Before Impella support initiation, while receiving catecholamines and/or IABP support, these patients exhibited signs of tissue hypoperfusion and end-organ failure and required substantial pump flow. In keeping with extensive morbidity, the median duration of hospitalization was up to 23 days. To compare the outcomes in these patients to data from randomized CGS trials, the patients in this registry were divided into two groups: one that would have potentially been enrolled in prior studies (e.g., a group who may have qualified for the SHOCK trial) and a second "salvage" group of patients who would have been excluded from the randomized studies. The salvage population included those with anoxic brain injury before implanting of the device, out-of-hospital cardiac arrest, and those who were transferred from another hospital. The overall 30-day survival results (Kaplan-Meier curve estimates) for the two subgroups are shown in Fig. 7.14. As expected, the salvage group of patients had poorer outcomes than those who would likely have been enrolled in CGS trials. Although the analysis is based in part on historical controls, these results suggest improved outcomes for treated patients in CGS compared with the abysmal results noted in historical benchmarks.[88]

TABLE 7.2 Use of Impella in Guidelines for Management of Cardiogenic Shock, Acute Myocardial Infarction, and Coronary Revascularization

Clinical Society Guideline Populations (SCAI, ACCF, HFSA, STS, ISHLT, HRS)	Class	Latest Update	Impella FDA Approval
PCI in cardiogenic shock	I	2013	2016
Multiorgan failure, cardiogenic shock	I	2013	2016
PCI in low ejection fraction, complex CAD	IIb	2011[a]	2015
Bridge to recovery or decision, cardiogenic shock	IIa	2013	2016
STEMI and cardiogenic shock	IIb	2013	2016
STEMI and urgent CABG	IIa	2013	2016
Acutely decompensated heart failure	IIa	2012	TBD
Consensus document on hemodynamic support	N/A	2015	2015/16

[a]Does not include Protect II or FDA premarket approval studies due to timing of available data.
ACCF, American College of Cardiology Foundation; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *FDA,* U.S. Food and Drug Administration; *HFSA,* Heart Failure Society of America; *HRS,* Heart Rhythm Society; *ISHLT,* International Society for Heart & Lung Transplantation; *PCI,* percutaneous coronary intervention; *SCAI,* Society for Cardiovascular Angiography and Interventions; *STEMI,* ST-segment elevation myocardial infarction; *STS,* Society of Thoracic Surgeons.
From Clinical Dossier. Cardiogenic shock therapy with Impella. http://cardiogenicshock.com/assets/downloads/Clinical_Dossier.pdf.



• **Fig. 7.14** Outcomes between Impella Registry subgroups: patients likely to be eligible for randomized controlled trials *(RCTs)* versus patients likely to be excluded from RCTs ("salvage" patients). From the USPella Registry: the poor prognosis associated with patients who would have been excluded from trials of cardiac support for cardiogenic shock. *AMI,* Acute myocardial infarction; *CS,* cardiogenic shock. (From Cardiogenic Shock Clinical Dossier. https://www.protectedpci.com/cardiogenic-shock/#resources-protocols.)

There are only a few small randomized controlled trials evaluating the Impella device for patients with CGS. The bottom line on these small studies is that the Impella device resulted in superior hemodynamics without mortality benefits at short-term follow-up. The ISAR-SHOCK trial (Efficacy Study of LV Assist Device to Treat Patients with Cardiogenic Shock) is an example; it enrolled only 26 patients.[91] Secondary endpoints included lactic acidosis, hemolysis, and mortality after 30 days. After 30 minutes of support, CI increased more with the Impella 2.5 device (0.49 ± 0.46 L/min per m^2) than with IABP (0.11 ± 0.31 L/min per m^2; $P = 0.02$); 30-day mortality was unaffected, although the extent of lactic acidosis trended lower. In a more recent study,[92] the Impella CP model was compared to an IABP in 48 patients with shock after AMI; again 30-day mortality was identical. These trial data were combined with data from a study of the Impella 2.5 device versus IABP in 26 subjects with CGS.[93] The resultant meta-analysis[94] reported no difference in mortality or LV ejection fraction at 30 days. None of these studies were powered to detect differences in mortality. There are few studies, mostly nonrandomized trials, assessing the utility of Impella 5.0; all have significant limitations. In a retrospective, nonblinded, single-center 34-patient review that included patients who crossed over,[95] the Impella 5.0 group had 33% 30-day survival compared with 24% for patients who received the Impella 2.5 device. Several similar studies have shown more favorable outcomes for CGS when treated with the Impella 5.0 device.[96] In a multicenter, prospective, feasibility study without a control group, the Impella 5.0 device was used in 16 patients with postcardiotomy CGS with 94% survival at 30 days.[97]

Similar to the findings in the animal laboratory already discussed,[86] in 154 consecutive real-world patients from the USpella Registry with CGS undergoing PCI, those who received the Impella 2.5 device before PCI had reduced mortality compared with those

receiving the device after PCI (40.7% vs. 65.1%; $P = 0.003$).[89] Almost 90% of these patients had not responded to inotrope therapy and/or IABP, and 38% of them would have been considered too ill to be included in the IABP-SHOCK II trial.[34] A small recently reported study of even more critically ill patients (40% had cardiac arrest before Impella placement and 9% had active cardiopulmonary resuscitation at the time of implantation) demonstrated 48.1% 30-day survival when the Impella device was placed before PCI and only 12.5% when it was placed afterward.[98] These findings might be expected based on the physiology already described; in the ischemic myocardium setting, the Impella device not only augments CO and increases MAP, but it also minimizes stoke work of the native heart, minimizes LV end-diastolic pressure, reduces oxygen consumption of the myocardium, and brings the supply/demand mismatch into balance. This outcome is supported in animal models of coronary ischemia where placement of Impella devices in swine limited infarct size—a phenomenon termed mechanical preconditioning.[99] Following up on the study just described, Basir et al. recently reported a preliminary experience with systematic multi-center early institution of Impella CP support in AMI CGS prior to revascularization.[100] The outcomes included a dramatic improvement in survival compared to historical data, as well as ability to wean the device. In turn, these early results have fostered the National Cardiogenic Shock Initiative; the algorithm for management is included as Fig. 7.15. Despite considerable enthusiasm generated by pilot data, it is worth noting that routine unselected use of these devices in CGS is not yet supported by recent analysis of the admittedly limited available evidence base.[73] Regardless, in the future there will likely be more focus on "shock to unload time" rather than "door to balloon time" in patients already in CGS.[82]

High-Risk Percutaneous Coronary Intervention

A total of 10 studies have examined the use of Impella devices for myocardial protection during high-risk PCI, such as last remaining vessel and unprotected left main disease.[101] However, only one study, the PROTECT II trial, was a randomized controlled comparison to IABP. It enrolled 448 patients and demonstrated no difference in major adverse events but a superior hemodynamic profile for the Impella 2.5 device compared with IABP.[102] Smaller nonrandomized studies[103] have looked at prophylactic use of the Impella device in acute coronary syndromes excluding patients with STEMI and described low mortality rates with the ability to perform high-risk procedures while maintaining patient hemodynamic stability. Similarly, a recent examination of the USPella database[104] revealed a significant number of such patients (127) had left main PCI with prophylactic Impella use, low mortality, and relatively low complication rates. Thus despite a relative paucity of high-level evidence, and with the guidelines for elective coronary revascularization relatively out of date, the practice of routine use of the Impella device in high-risk PCI has become fairly widespread.

Impella RP

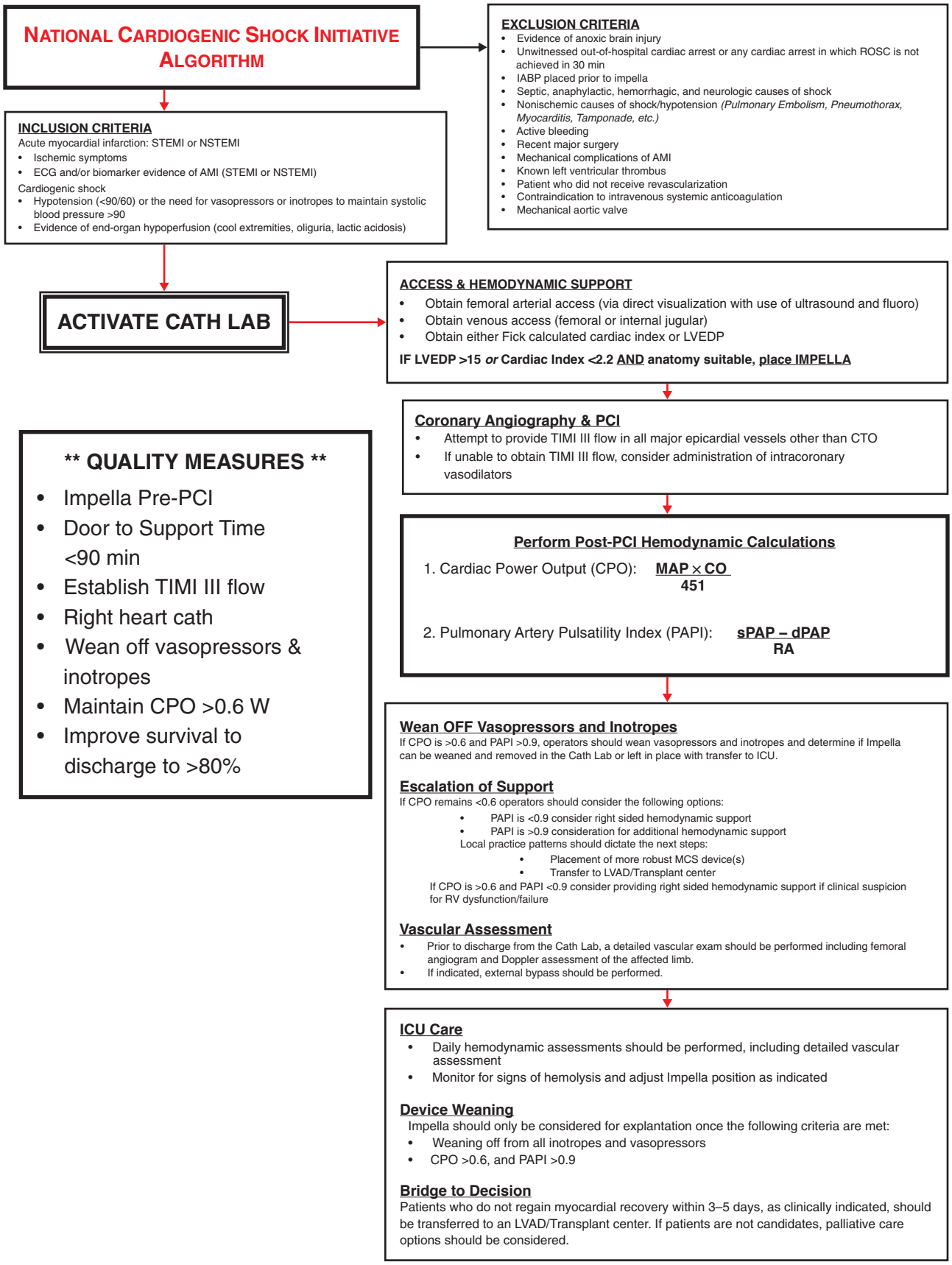
Data for the use of the Impella RP device are considerably more limited and consist primarily of findings in the Recover Right trial[105] and subsequent continued access and postapproval studies. In these, the use of the RP device in RV shock was evaluated in two groups: after durable LVAD implant or after AMI or cardiac surgery. The mean duration of support for all patients ($n = 60$) was 90 hours with RP flows in excess of 3 L/min. Similar to the left-sided Impella devices, hemodynamics were favorably impacted with reduction of central venous pressure and improvement of left-sided CO (Fig. 7.16). The overall survival at 30 days or to next therapy was 73%. In a review of the global usage of the Impella RP device, CGS after AMI is the leading indication for support. One-third of these patients were supported with a BiPella configuration. Lala et al. applied the inclusion criteria from the Recover Right trial to the hemodynamic data from the SHOCK trial and registry.[106] They found that RV failure was quite common, often underrecognized and undertreated. Finally, data on the use of BiPella support in a small group of CGS patients was recently reported.[107] Although the results were favorable, the overall experience is limited. This remains a challenging group of patients deserving of further study. An excellent review of the use of the Impella and other ventricular support devices can be found in a recent review by Kapur and colleagues.[108]

TandemHeart

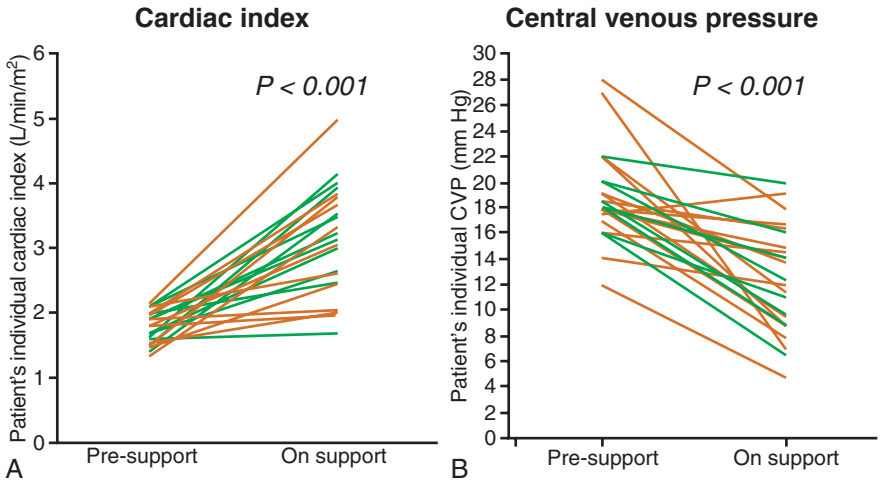
The TandemHeart device (TandemLife, Pittsburgh, PA) is a left atrial to femoro-iliac bypass, powered by an external centrifugal pump that provides up to 5 L/min of forward flow (Fig. 7.17). It requires transseptal puncture and institution of cardiac bypass with relatively large arterial cannulas (21F in the left atrium, 15F–19F in the iliac artery). Left atrial–to–femoral artery cannulation reduces LV preload and thereby limits the propensity for LV overload associated with right atrial–to–femoral artery cannulation such as seen with VA-ECMO (described later). It unloads the ventricle by decreasing left atrial volume and thus lowers LVEDP; however, it returns blood into the arterial tree and thus can increase afterload, which limits its benefits for LV workload.[72] The TandemHeart configuration does not require an oxygenator in the circuit because oxygenated blood is displaced from the left atrium into the arterial circulation. The left atrial–to–femoral artery configuration is particularly well suited for chronic left heart failure and mitral valve pathology (i.e., stenosis, prosthetic valve thrombosis, or regurgitation), where left atrial volume is large.[109–116] Like the Impella device, it cannot be shut off temporarily and requires more aggressive monitoring than balloon counterpulsation.

Small randomized trials have been performed comparing the TandemHeart with IABP in patients with CGS, demonstrating superior hemodynamics[117,118] but higher complication rates with the TandemHeart.[118] There is a paucity of multicenter clinical trial data for the TandemHeart, with primarily single-center series reports.[113,119,120] Like the Impella, the TandemHeart device has been used to support patients undergoing high-risk PCI, albeit with significantly less evidence base.[121,122] The TandemHeart device receives a class IIb recommendation in the guidelines for use of LVADs in CGS in the 2017 European Society[39] and IIa in the 2013 AHA/American College of Cardiology guidelines.[30] The TandemHeart RVAD device has been used similar to the Impella RP device in patients with right heart failure.[108]

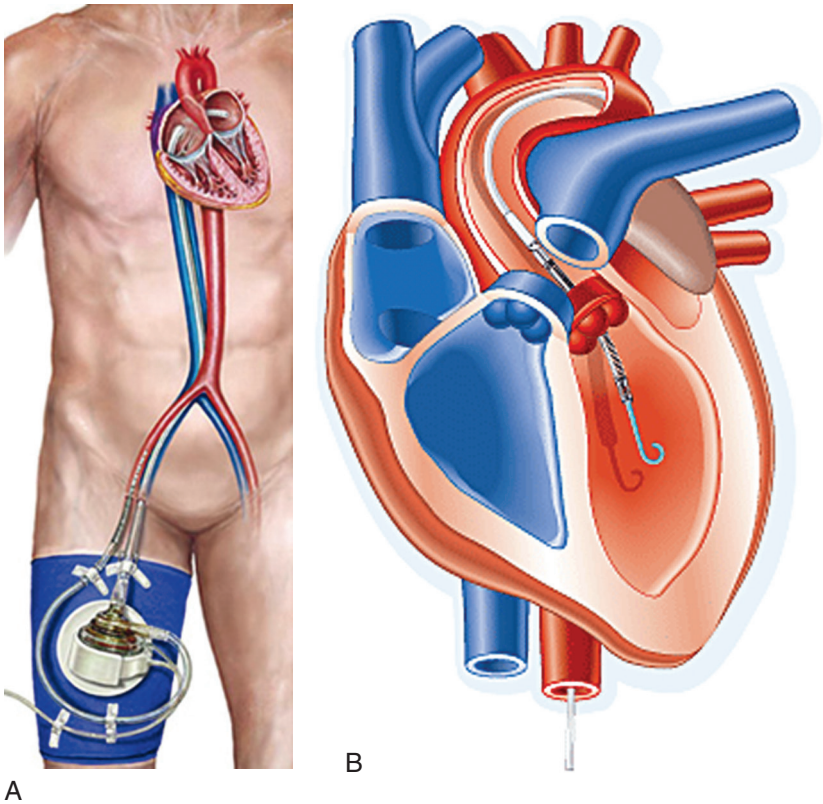
As with Impella devices, potential contraindications for the TandemHeart device include aortic insufficiency and peripheral vascular disease. Because there is no cannula placed across the aortic valve, it is not per se contraindicated in aortic stenosis, although dramatic decreases in preload could potentially have significant adverse hemodynamic effects. Monitoring for excessive left atrial volume depletion is generally important during TandemHeart use. Unlike the Impella device, it can potentially be used



• **Fig. 7.15** National Cardiogenic Shock Initiative algorithm. *AMI,* Acute myocardial infarction; *CO,* cardiac output; *CTO,* chronic total occlusion; *dPAP*, diastolic pulmonary artery pressure; *ECG,* electrocardiogram; *IABP,* intraaortic balloon pump; *ICU,* intensive care unit; *LVAD,* left ventricular assist device; *LVEDP,* left ventricular end-diastolic pressure; *MAP,* mean arterial pressure; *MCS,* mechanical circulatory support; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCI,* percutaneous coronary intervention; *RA,* right atrial; *ROSC,* return of spontaneous circulation; *RV,* right ventricular; *sPAP,* systolic pulmonary artery pressure; *STEMI,* ST-segment elevation myocardial infarction; *TIMI III,* thrombolysis in Myocardial Ischemia trial III. (Adapted from https://citoday.com/2018/02/the-national-cardiogenic-shock-initiative.)



• **Fig. 7.16** Results of the RECOVER RIGHT study demonstrating improved cardiac index (A) and decreased central venous pressure (B) in patients in right ventricular shock. (From Anderson MB, Goldstein J, Milano C, et al. Benefits of a novel percutaneous ventricular assist device for right heart failure: the prospective RECOVER RIGHT study of the Impella RP device. *J Heart Lung Transplant.* 2015;34:1549–1560. Used with permission.)



• **Fig. 7.17** The TandemHeart device (A) draws oxygenated blood from a left atrial catheter placed across the interatrial septum and provides arterial return via a cannula placed into the femoral artery. The Impella catheter (B) draws blood from the left ventricle via a pigtail catheter placed retrograde across the aortic valve and pumps blood into the aorta. Both devices actively provide cardiac output independent of left ventricular ejection.

in patients with LV thrombus because no cannula is placed into the left ventricle. Although post-MI ventricular septal rupture is uncommon, caution should be applied in using TandemHeart or Impella in that setting, since they could theoretically trigger severe right-to-left shunting because of low LV pressure as a result of substantial volume extraction from the left heart circulation.

Complications

The Impella device requires 14F access and is therefore associated with potential limb ischemia or other vascular injury, hemolysis (isolated cases of severe hemolysis have been reported, a complication associated with axial flow devices), renal failure, and thrombocytopenia; valve injury has not been noted in analysis of randomized trial data.[102] The TandemHeart's complication profile adds those associated with transseptal puncture and the need to maintain a fully anticoagulated large-bore bypass circuit (with optimal de-airing) in addition to the vascular issues associated with large arterial and venous cannulae.[118]

Extracorporeal Membrane Oxygenation

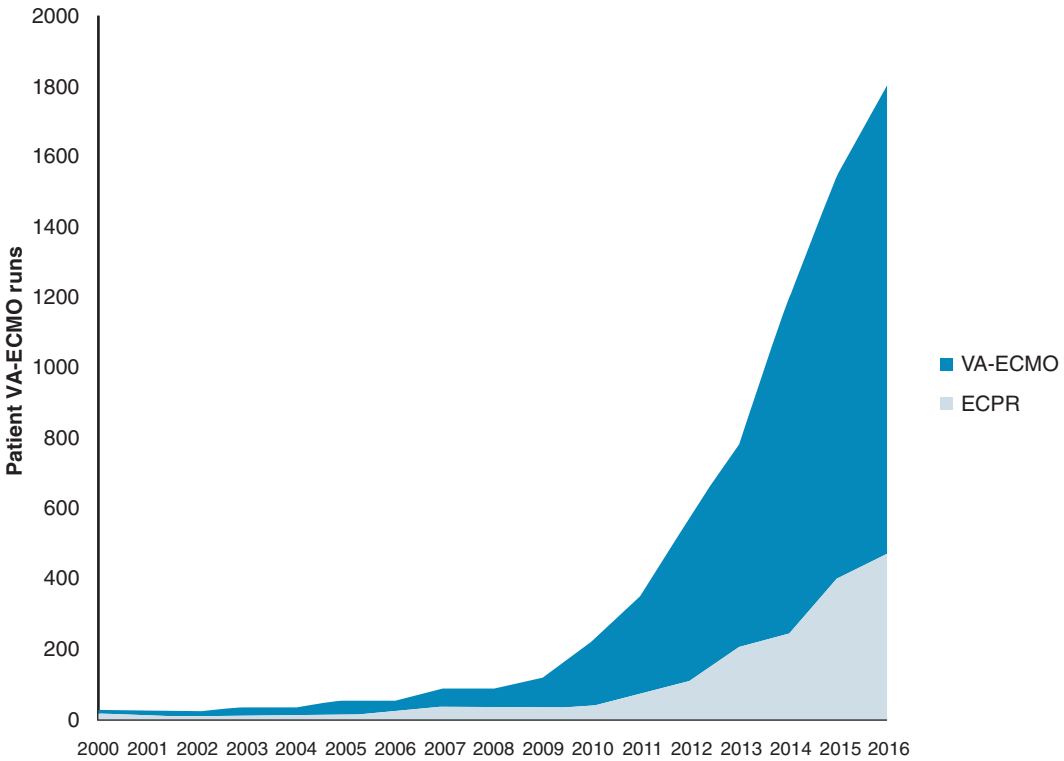
History

ECMO began with the advent of the "heart-lung machine" in the 1950s followed by the development of membrane oxygenators in the 1960s. Pioneering work by Hill and Bartlett in the 1970s introduced the use of ECMO as a method to support patients with respiratory failure followed by the establishment of the Extracorporeal Life Support Organization in the late 1980s to advance engineering, logistics, and clinical protocols associated with the use of ECMO and to develop a global registry to evaluate clinical outcomes.[123–125] With more than 50 years of experience, ECMO is now an integral part of any advanced critical care program. Its use has grown exponentially in the past decade. Several reasons for the expanding use of ECMO include (1) global familiarity with large bore femoral venous and arterial access; (2) no mandate for fluoroscopic guidance for cannula deployment, thereby allowing for bedside or out-of-hospital cannulation; (3) ability to provide rapid increases in systemic blood pressure and oxygenation; and (4) versatile use for cardiac arrest, CGS, biventricular failure, septic shock, and primary pulmonary failure. Furthermore, ECMO use outside the operating room for primarily medical indications has grown similarly.

ECMO implantation is being performed more commonly by nonsurgical personnel, including invasive cardiologists, pulmonologists, and critical care intensivists. A recent analysis from the Extracorporeal Life Support Organization reported more than 320 centers and more than 8000 ECMO implants in 2016 in the United States alone[126] (Fig. 7.18). Another analysis confirmed a 433% increase in ECMO utilization in the adult population between 2006 and 2011 in the United States.[127] In this section, we discuss the technical features of various percutaneously delivered ECMO configurations, the hemodynamic effects of VA-ECMO, and clinical outcomes associated with VA-ECMO.

ECMO Configurations (Table 7.3)

The basic components of any ECMO circuit include a rotary blood pump, an oxygenator, a heat exchanger, inflow and outflow



• **Fig. 7.18** Adult cardiac venoarterial ECMO *(VA-ECMO)* and extracorporeal cardiopulmonary resuscitation *(ECPR)* runs in the United States. (Recreated from ELSO Registry of Adult ECMO for Cardiogenic Shock and ExtraCorporeal CPR, 2000–2017 International Extracorporeal Life Support Organization Report 2016. www.elso.org.)

TABLE 7.3 Extracorporeal Membrane Oxygenation Configurations

Inflow	Outflow	Configuration and Indications
Femoral, subclavian, or internal jugular vein	Femoral, subclavian, or internal jugular vein	Peripheral cannulation VV-ECMO
Dual lumen (inflow and outflow)		
Right atrium, IVC, SVC	Right atrium, IVC, SVC	Central cannulation VV-ECMO
Femoral artery	Right atrium	Peripheral cannulation VA-ECMO
Right atrium, SVC or IVC	Femoral/subclavian artery	Central cannulation VA-ECMO
Right internal jugular	Subclavian artery	Ambulatory VA-ECMO
Right atrium	PA or left atrium	Right ventricular support
Left atrium	Aorta or femoral artery	Left ventricular support
Left and right atrium	Femoral/subclavian artery	Peripheral cannulation biatrial ECMO

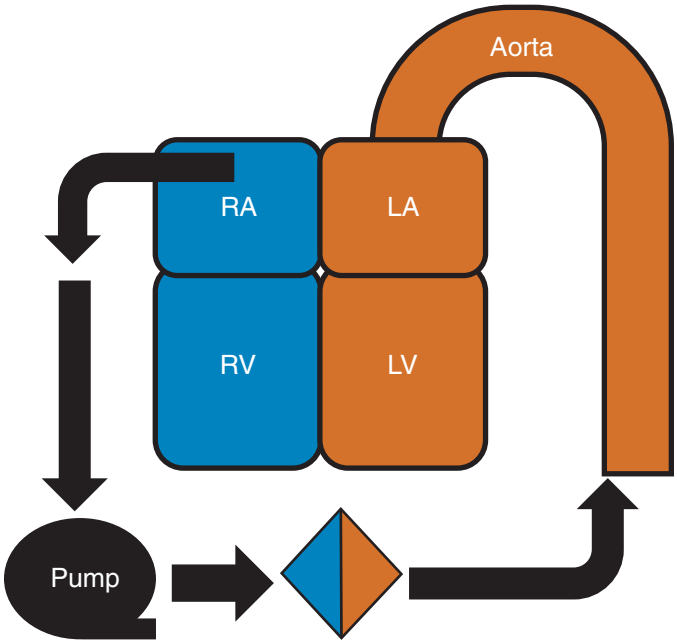
ECMO, Extracorporeal membrane oxygenation; *IVC,* inferior vena cava; *PA,* pulmonary artery; *SVC,* superior vena cava; *VV,* veno-veno; *VA,* venoarterial.

cannulas, connecting tubing, systemic anticoagulation, and specialized personnel to manage the ECMO circuit.[128,129] The most common blood pump used is a rotodynamic, centrifugal pump that transfers kinetic energy from a circulating impeller to the bloodstream, thereby generating forward flow. Depending on the clinical scenario, ECMO can be applied as a venovenous (VV) or venoarterial (VA) circuit. A major indication for VV-ECMO is primary pulmonary failure without cardiovascular collapse. VV-ECMO drains deoxygenated venous blood from the body and returns oxygenated blood into the venous circulation. Inflow and outflow cannulas can be positioned in the right atrium, inferior or superior vena cava, or other central veins such as the subclavian, internal jugular, or femoral veins. Two separate cannulas or a single, dual-lumen venous cannula can be used to support VV-ECMO. In rare instances, if arterial blood pressure is sufficiently high, systemic oxygenation can be augmented without use of a pump or oxygenator by cannulating and connecting the femoral artery and vena cava or right atrium, also known as reverse arteriovenous cannulation.[130,131]

Primary objectives for VA-ECMO are to increase systemic blood pressure and oxygenation during cardiovascular or cardiorespiratory collapse. VA-ECMO (Fig. 7.19) withdraws deoxygenated venous blood and pumps oxygenated blood to the arterial circulation. Inflow cannulas are often positioned in the right atrium or across the superior and inferior vena cava using a large multistaged venous cannula. Outflow cannulas can be positioned in the femoral or subclavian arteries. Of note, a vascular graft surgically attached to the subclavian or femoral arteries can also be used in lieu of outflow cannulas to return oxygenated blood back to the arterial system. Because no venous reservoir is used, VA-ECMO cannot be described as cardiopulmonary bypass.

Several unique ECMO configurations can also be used. For profound biventricular failure, inflow cannulas can be positioned in both the left atrium (via transseptal puncture) and right atrium to reduce both right and LV preload (biatrial ECMO).[132–134] Another approach for biventricular failure is to place a second venous inflow cannula into the pulmonary artery in addition to the standard VA-ECMO configuration to reduce left atrial preload (PA-ECMO).[135] Venovenoarterial (VVA)-ECMO refers to two venous inflow cannulas spliced together to enhance venous drainage into the centrifugal pump, thereby leading to a greater reduction in cardiac and pulmonary preload. Venoarterial-veno (VAV)-ECMO refers to a single venous inflow cannula that drains deoxygenated blood into the pump and oxygenator, which then returns oxygenated blood via an arterial cannula and back into the venous system using a venous cannula. VVA-ECMO and VAV-ECMO are more commonly used when a patient has severe cardiopulmonary failure.[128,129] "Ambulatory" VA-ECMO can also be achieved by using a right internal jugular inflow venous cannula and an outflow cannula or graft in the subclavian artery.[136]

Central or surgical cannulation with ECMO can be performed to replicate the hemodynamic effects of a VAD. Direct right atrial–to–pulmonary artery cannulation or pulmonary artery–to–left



• **Fig. 7.19** Configuration of venoarterial extracorporeal membrane oxygenation. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

atrial (PA-LA)-ECMO can be used to provide RV support, whereas direct left atrial–to–aortic cannulation (LA-Ao) can provide LV support.

Hemodynamics and Left Ventricular Venting Strategies (Table 7.4)

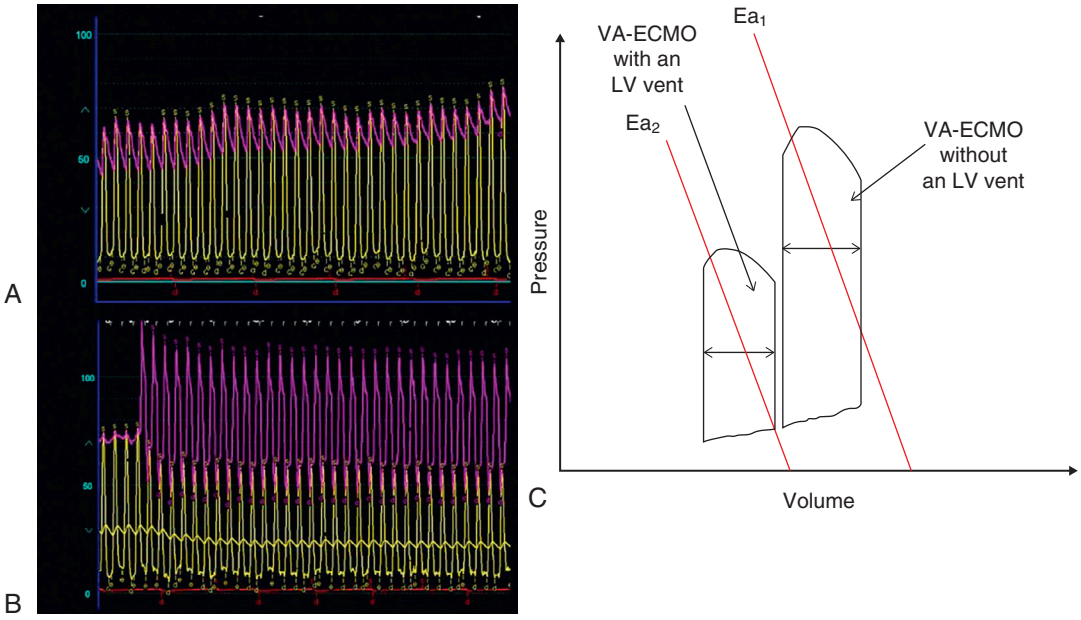
VA-ECMO displaces blood volume from a large venous reservoir into the arterial circulation. Depending on the capacity of the venous reservoir and degree of venous congestion, VA-ECMO may reduce RV filling pressures. By pressurizing the arterial system, systemic blood pressure increases rapidly. If native LV function is preserved, LV systolic pressure will increase with a minor increase in LV diastolic pressure.[128,129,137,138] However, if native LV function is compromised, LV systolic and diastolic pressures will increase as the native left ventricle is unable to pump effectively against the increased afterload imposed by the centrifugal flow pump and pressurized arterial tree. This increase in LV afterload increases LV wall stress and myocardial oxygen consumption, and may lead to worsening pulmonary congestion, acute lung injury, and in rare instances, pulmonary hemorrhage.[139]

To mitigate the potential for LV loading during VA-ECMO support, close hemodynamic monitoring with a pulmonary artery catheter is required. If elevated LV filling pressures are identified, operators often combine VA-ECMO with LV venting strategies. Inotropes are commonly used to enhance LV contractility to achieve LV decompression. However, inotropes may be of limited value if a patient has minimal contractile reserve or is prone to atrial or ventricular tachyarrhythmias. IABP counterpulsation (Fig. 7.20) can also be used as an adjunct to VA-ECMO in patients with CGS as a successful venting strategy.[140–142] Theoretically, by augmenting central aortic diastolic pressure, the addition of an IABP to VA-ECMO may improve coronary flow in critically ill patients with ischemic heart failure. An alternative to IABP-mediated venting, insertion of an Impella axial-flow catheter, can also reduce LV pressure and volume in the setting of increased afterload owing to VA-ECMO.[143–147] The Impella 2.5 LP, CP, and Impella 5.0 devices have all been used as venting strategies. Percutaneous implantation of an Impella 2.5 or CP device can be performed rapidly without the need for surgical vascular access. Importantly, when using an Impella device or any transvalvular axial flow pump as an LV vent, the flow setting on the Impella should be reduced during VA-ECMO support to avoid LV suction and hemolysis. A recent analysis among six patients with VA-ECMO plus Impella LV support reported reduced pulmonary capillary wedge pressure, pulmonary vascular resistance, and increased RV stroke volume.[148] Alternative invasive approaches to LV venting with VA-ECMO include advancing a second venous cannula into the left atrium or pulmonary artery to indirectly reduce LV preload (as described

TABLE 7.4 Left Heart Decompression Strategies With VA-ECMO

Percutaneous	Intraaortic balloon pump Impella axial flow catheter Transseptal LV cannulation Transseptal LA cannulation Pulmonary artery cannulation Atrial septostomy
Surgical	Direct LV apical cannulation Direct LA cannulation
Noninvasive	Inotropic support Reducing VA-ECMO flow

ECMO, Extracorporeal membrane oxygenation, *LA,* left artery; *LV,* left ventricle; *VA,* venoarterial.



• **Fig. 7.20** Increased left ventricular afterload owing to venoarterial extracorporeal membrane oxygenation *(VA-ECMO)* (A–C). Simultaneous left ventricular *(yellow)* and central aortic *(purple)* hemodynamic tracings after initiation of VA-ECMO (A) and after venting the left ventricle by combining VA-ECMO and an intraortic balloon pump (B). (From Aghili N, Kang S, Kapur NK. The fundamentals of extracorporeal membrane oxygenation. *Minerva Cardioangiol* 2015;63:75–85.)

earlier), balloon atrial septostomy, or blade and balloon atrial septostomy.[149–153]

The use of a concomitant LV decompression strategy can improve clinical outcomes for patients with CGS requiring VA-ECMO. One series[154] compared outcomes among 42 patients receiving VA-ECMO alone to 21 patients receiving VA-ECMO plus Impella LV (ECPella) support. Compared with VA-ECMO alone, the ECPella group had significant lower in-hospital mortality and a higher success rate bridging to recovery, durable mechanical support, or orthotopic heart transplantation.

Inadequate preload as the result of volume depletion or venous obstruction will reduce VA-ECMO flow. Similarly, increased afterload from hypertension, elevated systemic vascular resistance, or arterial obstruction can also reduce VA-ECMO flow. For these reasons, careful hemodynamic interrogation before, during, and after initiation of VA-ECMO is required for optimal device function.

Pulmonary Indications and Clinical Outcomes

VV-ECMO is commonly used to support patients with acute respiratory distress syndrome, refractory hypoxemia, or hypercapnic respiratory failure.[155–163] Patients with refractory hypoxia as the result of acute respiratory distress syndrome continue to have a high mortality, in the 70% to 90% range based on different reports. Whether this strategy improves outcomes compared to conventional treatment remains poorly understood.[155–161] A potentially catastrophic presentation of respiratory collapse often occurs secondary to acute pulmonary embolism (PE). VV-ECMO will improve systemic oxygenation and should be considered in acute PE with refractory hypoxemia and without cardiovascular collapse. For patients with right heart failure refractory to inotropes in the setting of a PE, right atrial–to–pulmonary artery cannulation can be performed to provide RV support with or without an oxygenator. If a patient has profound CGS in the setting of a PE, then VA-ECMO with consideration of a concomitant LV vent strategy may be more effective. Because all ECMO circuits require systemic anticoagulation, the combination of antithrombotic therapy with hemodynamic and respiratory support can effectively stabilize patients with acute PE. Several reports identified that ECMO for acute PE is associated with up to 70% survival to discharge when combined with other strategies, including anticoagulation, surgical embolectomy, or thrombolysis.[162,163] ECMO should be used with caution in the setting of thrombolytic use owing to the large-bore cannulation and risk of bleeding.

Cardiac Indications and Clinical Outcomes

Ventricular Arrhythmias and Cardiac Arrest

Use of VA-ECMO during cardiopulmonary resuscitation is known as extracorporeal cardiopulmonary resuscitation (ECPR). Two observational, single-center studies report that ECPR may improve survival for *in-hospital* cardiac arrest.[164,165] Factors associated with improved survival after ECPR for in-hospital cardiac arrest include a shockable initial rhythm, a shorter duration of cardiopulmonary resuscitation, lower lactate levels before ECPR, and lower Sequential Organ Failure Assessment scores within 24 hours of admission to an intensive care unit.[166]

ECPR for out-of-hospital cardiac arrest is currently under study with mixed results from recent reports indicating a trend toward improved survival but no definitive evidence of improved outcomes.[167,168] Other single-center series have reported 30% survival rates to hospital discharge combining ECPR with traditional resuscitation efforts in experienced centers where extracorporeal life support can be rapidly implemented.[169–172] A prospective study was done of patients with refractory in-hospital and out-of-hospital cardiac arrest. Return of spontaneous circulation was achieved successfully in 96% of patients. Median duration of ECMO support was 2 days, with 54% of patients successfully weaned from ECMO. Survival to hospital discharge with full neurologic recovery occurred in 54% of patients.[172] Future studies are required to understand the potential clinical utility of EPCR for in-hospital and out-of-hospital cardiac arrest.

Use of VA-ECMO has also been reported in patients with refractory ventricular arrhythmias[173–178] and acute heart failure owing to myocarditis.[179–182] A recent preclinical study reported that VA-ECMO provided superior systemic hemodynamic support compared with the Impella 2.5 and TandemHeart devices in a swine model of ventricular fibrillation.[183] In addition to being used as a bailout strategy, VA-ECMO is now more commonly being used to support high-risk electrophysiologic ablation procedures. An advantage of this approach for electrophysiologists is the lack of cannula penetration into the heart, thereby allowing for free movement of ablation catheters and minimal interference with electric fields for detection and treatment.[184,185]

Advanced Heart Failure and Cardiogenic Shock

The role of peripherally cannulated, VA-ECMO in advanced, chronic heart failure remains poorly understood. Owing in part to the loading effect on the LV, patients with isolated LV failure are more commonly supported with a dedicated LV support device (i.e., Impella, TandemHeart, IABP). At present, no specific algorithms exist to identify which patients will develop LV pressure overload as the result of VA-ECMO. However, experience with VA-ECMO in left heart failure is growing rapidly. Common applications for VA-ECMO in CGS with LV-dominant failure include (1) failure to wean from cardiopulmonary bypass,[186] (2) AMI,[187–189] and (3) mechanical complications after AMI.[190]

VA-ECMO is also more commonly being used to temporarily support patients with refractory CGS or multiorgan failure being evaluated for LVAD implantation or orthotopic heart transplantation. Small case series suggest that hepatic and renal function may improve with use of VA-ECMO in patients with CGS awaiting LVAD implantation.[191–193] In some reports, VA-ECMO can be converted to VV-ECMO after LVAD implantation in case of respiratory failure.[194] Other retrospective studies have reported a 73% survival-to-hospital discharge rate in patients supported with VA-ECMO as a bridge to heart transplantation strategy.[195–197] One of the major challenges with VA-ECMO in the pre-VAD population is limited ability to assess RV function during support. This can be problematic if a patient supported by VA-ECMO is being considered for destination therapy LVAD implantation (DT-LVAD) because the development of RV failure after destination therapy LVAD implantation would represent a major clinical challenge for this population. Future studies are required to confirm the potential utility of VA-ECMO in advanced left heart failure and as a support mechanism before LVAD or orthotopic heart transplantation.

Primary graft failure (PGF) after orthotopic heart transplantation is one of the strongest risk factors for mortality after heart transplant. The incidence of PGF has increased over the past few years, likely the result of increasing use of marginal donors in high-risk patients. The incidence has been described as between

3% and 26% with mortality as high as 50%. The use of VA-ECMO in severe PGF after heart transplantation has been reported.[198–200] One study of PGF with ECMO support demonstrated that 72% of patients were able to be weaned from support with 44% of them eventually discharged.[201]

Right Heart Failure

VA-ECMO can be considered for patients with RV failure caused by decompensated pulmonary hypertension,[202] RV MI,[203] pulmonary embolism,[162,163] after LVAD implantation,[204,205] or after orthotopic heart transplantation.[206,207] As already described, dedicated acute MCS devices for RV support include the Impella RP or TandemHeart RVAD.[105,108,208–210] No data exist comparing the use of VA-ECMO to a dedicated RV support device. More recently, the Protek Duo (TandemLife) dual-lumen cannula for right atrial–to–pulmonary artery bypass has been introduced into practice.[211]

Complications

Major complications associated with VA-ECMO include (1) vascular injury, (2) limb ischemia, (3) bleeding, (4) infection, (5) deep venous thrombosis, (6) stroke, and (7) insufficient upper body oxygenation (North-South syndrome). Other potential complications include hemolysis, thrombocytopenia, acquired von Willebrand syndrome, disseminated intravascular coagulopathy, and air embolism. Bleeding events are exacerbated by the mandate for systemic anticoagulation during ECMO support. However, anticoagulation is required to limit thrombosis and limb ischemia. Among these complications, proper cannulation technique and critical care management can reduce the likelihood of limb ischemia and North-South syndrome. Limb ischemia is best prevented by inserting an antegrade perfusion sheath into the arterial vessel distal to the insertion site of the arterial cannula.[21,212–216] North-South syndrome occurs in the setting of severe lung injury, which causes deoxygenated blood to enter the left ventricle where it is pumped into the systemic circulation.[128,129,217] If VA-ECMO is initiated in this setting via femoral cannulation, retrograde flow from the femoral arterial cannula may provide oxygenated blood up to the aortic arch. However, deoxygenated blood pumped from the native left ventricle will compete with ECMO flow in the aortic arch and the great vessels may distribute deoxygenated blood to the brain and upper extremities. Monitoring arterial saturations from the right radial or axillary artery will help identify North-South syndrome, which can often be resolved by changing the cannula configuration to either VAV or VVA-ECMO. In rare instances, adding a negative inotrope can be used to reduce native LV ejection, thereby allowing for less competition for retrograde VA-ECMO flow in the aortic arch.

Key Points

- IABP improves hemodynamic parameters but has no mortality benefit in cardiogenic shock.
- Microaxial flow percutaneous ventricular assist devices provide superior increase in cardiac output compared with IABP. They increase mean arterial pressure, coronary perfusion, increase cardiac output, decrease myocardial stroke work, and decompress the ventricle setting the stage for myocardial recovery.
- Patients in severe hemometabolic shock require the highest flow and oxygen delivery to reverse shock. VA-ECMO offers the highest flow rate and less deployment time in comparison with the Impella 5.0 device.
- Peripheral VA-ECMO does not reduce left ventricular end-diastolic pressure, which is important for both left ventricular functional recovery and recovery of lungs. Venting of the left ventricle with another procedure or device is often required.
- ECPR is extremely resource intensive, but can improve mortality in out-of-hospital and in-hospital arrest if specific inclusion criteria are followed.

Acknowledgment

The authors acknowledge the adaptation of portions of this chapter from previous versions by Zoltan G. Turi, MD, and his kind editing of the current chapter.

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Review Questions

1. A 75-year-old man with known coronary artery disease status post–coronary artery bypass grafting has ischemic cardiomyopathy and a baseline left ventricular ejection fraction of 20%. He comes to the catheterization laboratory with acute onset of chest pain and ST-segment elevation myocardial infarction (STEMI). He had chest pain for 5 hours at home before calling emergency medical services. Two stents were placed to a culprit lesion in a bypass graft to the left anterior descending (LAD) artery. He had nonobstructive lesions not amenable to stenting. In the cardiac care unit afterward he develops a cool and clammy appearance, low blood pressure (90s/50s), and lactate level of 3.5 mEq/L (normal 0.5–2.2 mEq/L). He has a right heart catheter placed that shows a central venous pressure (CVP) of 15 mm Hg, pulmonary artery pressure (PAP) 40/20 mm Hg, wedge 18 mm Hg, and cardiac index of 1.8 L/min per m^2. He is returned to the catheterization laboratory and an intraaortic balloon pump IABP is placed. His cardiac index in the intensive care unit increases to 2.2, urine output increases to 100 mL/h, the lactate level normalizes, and he no longer appears to be in shock. The next morning his cardiac index improves to 2.3, his lactate level is normal, the creatinine level on morning laboratory tests is normal, but urine output drops from 100 mL/h to 5 mL/h at 5 a.m. after receiving a sponge bath and changing his bed sheets. What is the most likely diagnosis?

a. IABP balloon rupture
b. Timing error of IABP
c. Malpositioning of IABP
d. Return of cardiogenic shock

Answer: c. The patient's laboratory values indicate that his shock indices have improved from the prior day with higher cardiac index, normalization of lactate level, and on morning laboratory tests even his creatinine is improving. An acute decrease in urine output in a patient with IABP should prompt investigation. A chest x-ray (CXR) should be ordered to verify that the tip of the IABP is just distal to the subclavian artery. The CXR in this patient would have revealed a change in position coinciding with the IABP now positioned across the renal arteries and impairing their perfusion, essentially causing a prerenal state in a patient with improving hemodynamic profile. The IABP should be readjusted. Rupture of balloon pump (choice a) would result in blood inside the sheath and loss of inflation pressures. Timing error (choice b) could cause decrease in cardiac index. Return of cardiogenic shock (choice d) is incorrect because the cardiac index is improving. Acute kidney injury is a possibility and may not have been evident on morning laboratory tests; renal function should continue to be monitored going forward.

2. A 52-year-old male presents with anterior STEMI and has ventricular tachycardia (VT), arrests twice on the catheterization laboratory table during revascularization with percutaneous coronary intervention and two drug-eluting stents placed in the LAD. After return of spontaneous circulation the patient is requiring drips of epinephrine 30 μg/min, norepinephrine 50 μg/min, and vasopressin 0.04 units/min. Doses of drug continue to quickly escalate. Pink frothy secretions are noted from the endotracheal tube, and the point-of-care lactate level is 18 mEq/L (normal 0.5–2.2 mEq/L). Which of the following is the next appropriate step?

a. Trial of a second inotrope to see if this improves shock.
b. Perform echocardiography and place a pulmonary artery catheter to further classify the type of cardiogenic shock.
c. Place a left-sided Impella CP device and right-sided Impella RP device to provide biventricular support.
d. Book the patient in the operating room for a placement of an Impella 5.0 device.
e. Proceed directly to venoarterial extracorporeal membrane oxygenation (VA-ECMO).

Answer: e. This patient has advanced hemometabolic shock and has limited time before sustaining irreversible end-organ damage or having an arrest. The most important thing at this time is to restore perfusion, correct metabolic derangements, restore normal acid-base balance, and spare the stunned myocardium the toxic milieu of high-dose vasopressors and inotropes. Pink frothy exudate shows that there is high left atrial pressure and LV failure. The best and simplest way to restore perfusion quickly is VA-ECMO (choice e), which offers the highest flows of all acute mechanical circulatory assist devices. Placement and classification of shock, left ventricular/right ventricular (LV/RV) function in this patient can be done after perfusion is restored and during weaning. He is already on the catheterization laboratory table with fluoroscopy available, so deployment should be rapid. This advanced degree of shock is too profound to be medically managed (choice a). Performing echocardiography and pulmonary catheter placement, although desirable for future management (choice b), may delay treatment and should not be the next step, which is the question asked. However, a right heart catheter should be placed once ECMO is deployed. It should be noted that right heart catheterizations are more difficult while the patient is supported by ECMO, but it will be facilitated by the availability of fluoroscopy while the patient is still on the catheterization table. The Impella CP device may not provide sufficiently high lows to reverse this state of shock and does not address hypoxemia (choice c). Impella 5 device placement (choice d) takes too long to deploy and will not immediately address hypoxemia either.

3. A 35-year-old previously healthy woman presents to the emergency room with shortness of breath for 3 weeks after an upper respiratory viral illness a month ago. CXR shows hilar fullness and bilateral pulmonary edema. Echocardiography shows global hypokinesis with left ventricular ejection fraction of 10%, dilated left ventricle and left atrium, and only mild RV dysfunction. Dobutamine and milrinone are started empirically. Laboratory testing results show a lactate level of 5 mEq/L (normal 0.5–2.2 mEq/L) and elevated creatinine level of 3.1 mg/dL (normal 0.57–1.3 mg/dL). Her arterial blood gas testing shows partial pressure of arterial oxygen (PaO_2) 80 mm Hg on 4 L via nasal cannula. A right heart catheterization reveals central venous pressure (CVP) 22 mm Hg, pulmonary artery pressure (PAP) 48/29, with wedge pressure of 28 mm Hg, systemic vascular resistance (SVR) 1280 dynes/s per cm^{-5} and cardiac output 3.0 (L/min), and cardiac index of 1.7 L/min per m^2. Coronary angiography reveals no coronary artery disease. Which of the following is the next therapeutic intervention?

a. Start third inotrope epinephrine and consult nephrology for acute kidney injury.
b. Start sildenafil to reduce pulmonary hypertension.
c. Place left-sided Impella CP device and start furosemide bolus with infusion.
d. Place right- and left-sided Impella microaxial percutaneous ventricular assist devices (VADs; BiPella).
e. Proceed directly to VA ECMO because she has end-organ failure

Answer: c. The patient has a clinical picture of viral myocarditis with resultant nonischemic cardiomyopathy. She has end-organ impairment and pulmonary congestion. Right heart catheterization and echocardiographic findings classify this as left heart–dominant shock with relatively preserved oxygenation (although certainly not normal). The patient needs support of the cardiac index and is not responding to medical management. The best chance of recovery is workup and treatment of the underlying myocarditis in conjunction with support of the cardiac index to limit end-organ impairment and addressing the pulmonary congestion with diuretics. Choice a would expose the patient to potential additional toxicity of epinephrine without substantially improving her overall picture and choice b would not help greatly given relatively unimpressive PAP and pulmonary vascular resistance. This patient does not appear to need a BiPella strategy (choice d) at this time given mild RV dysfunction by echocardiography and preserved pulmonary artery pulse pressure. VA-ECMO (choice e) subjects the patient to the risks of ECMO, would still require an LV venting strategy to encourage LV recovery, and it could potentially increase left atrial pressures and worsen pulmonary edema.

4. A 45-year-old male weighing 70 kg collapses at the 22nd mile while running a marathon. He receives immediate bystander cardiopulmonary resuscitation (CPR) and has ventricular tachycardia (VT) rhythms that are shocked twice and the rhythm then converts to pulseless electrical activity en route to a hospital that is 5 minutes away. The hospital has a cardiac catheterization laboratory with advanced heart failure therapies, including ECMO capabilities in both the catheterization laboratory and the emergency department. CPR continues in the emergency department with a total CPR time of 20 minutes after cardiac arrest. Point-of-care laboratory test results reveal normal sodium, elevated creatinine 2.0 mg/dL (normal 0.57–1.3 mg/dL), and elevated lactate 13 mEq/dL levels and PaO_2 35 mm Hg while intubated with fraction of inspired oxygen (FIO_2) of 100%. Which of the following is the next best therapy?

a. Proceed to the catheterization laboratory while maintaining CPR for planned left heart catheterization.
b. Continue CPR and if the patient has return of spontaneous circulation, then proceed immediately to the catheterization laboratory for therapeutic left heart catheterization.
c. Proceed to the catheterization laboratory while maintaining CPR for planned BiPella placement.
d. Try to reach a family member by phone to discuss therapies for acute mechanical circulatory support before proceeding.
e. Initiate ECMO in the emergency department and then proceed directly to the catheterization laboratory for planned left heart catheterization and potential percutaneous coronary intervention.

Answer: e. Door-to-balloon time has been a standard quality process metric. However, this has been shifting with respect to patients in cardiogenic shock. Now the focus is shifting to door-to-unloading (of ventricle), or door-to-mechanical support times. Quick action is indicated. The 2015 American Heart Association guidelines for resuscitation state that ECMO can be deployed when readily available and the suspected etiology can be treated with a short course of mechanical support. Although the etiology of this patient's collapse is unknown, it is rational to believe that it is potentially reversible. Studies have shown that ECMO increases neurologically intact survival compared with conventional CPR, even in out-of-hospital arrest when it is of cardiac origin. Instituting full mechanical support with ECMO will allow for preservation of end-organs, reverse shock, and allow time to safely diagnose and treat the underlying condition. In addition, the patient is hypoxemic and even if CPR is effective at promoting blood flow, it is lacking sufficient oxygen content (PaO_2 = 35) to preserve end-organ function. Choice a would be reasonable if no ECMO program were available. Choice b does not address the underlying cause of arrest, and if resources are available to support the patient they should be instituted. Choice c is inappropriate: BiPella placement is time intensive and not easily deployed while also maintaining high-quality CPR. In addition, BiPella therapy does not adequately address the hypoxemic component of the shock. Choice d is inappropriate owing to the acuity of the situation. Time should not be wasted trying to discuss therapies or obtain consent as organ systems begin to fail. After stabilization and rescue of the patient, a thorough briefing with the family and medical decision maker can take place.

8

Echocardiography

PRISCILLA PETERS AND SAJJAD A. SABIR

CHAPTER OUTLINE

Approach to Echocardiography
- Cardiac Anatomy
- Basic Echocardiographic Principles

Echocardiographic Modalities
- Transesophageal Echocardiography
- Contrast Enhancement
- Goal-Directed Echocardiography
- Three-Dimensional Echocardiography

Indications for Echocardiography
- Assessment of Left Ventricular Function
- Ischemia/Infarction Including Complications
- Cardiomyopathies
- Assessment of RV Function
- Determining Valvular Function and Dysfunction
- Infective Endocarditis
- Pericardial Disease
- Aortic Disease

Hemodynamic Assessment

Stroke and Other Systemic Emboli

Summary

Echocardiography has evolved into a crucial noninvasive imaging modality in the critically ill patient. Its portability, safety, and widespread availability allow for the rapid diagnosis of life-threatening cardiac problems and rapid exclusion of cardiac disease in critically ill patients who present in an undifferentiated fashion. This chapter uses a systematic approach to the use of echocardiography in the critically ill, from the assessment of left ventricular (LV) and right ventricular (RV) function to valve disease, as well as pericardial disease, aortic disease, stroke, and rapid hemodynamic assessment.

Approach to Echocardiography

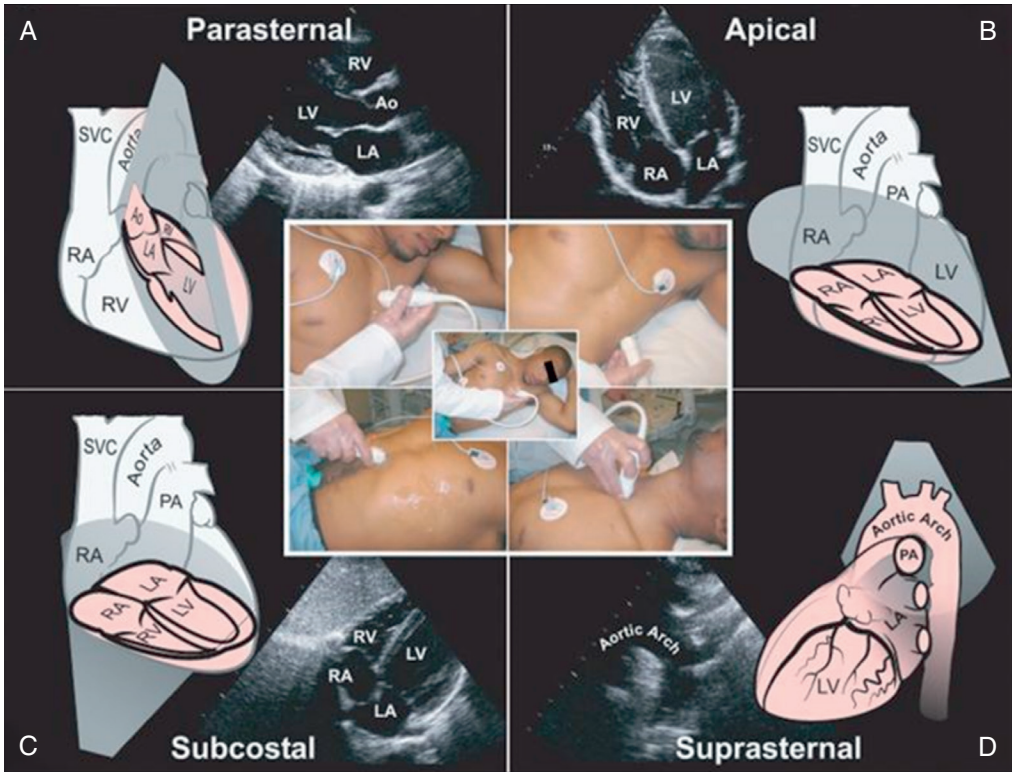
Cardiac Anatomy

Transthoracic echocardiography provides an excellent noninvasive means of assessing cardiac anatomy. The standard examination consists of parasternal views, taken from approximately 2 cm leftward from the sternum and the fourth to fifth rib interspace; apical views, taken from the LV apex; subcostal views, taken from the xiphoid process; and suprasternal views, taken from the sternal notch. Multiple images from different projections are needed to provide a complete view of the heart, manipulating the probe to provide long- and short-axis images of each structure interrogated.[1–3] The position of the echocardiographic transducer and the subsequent views produced are summarized in Fig. 8.1 (Videos 8.1 to 8.8).

Basic Echocardiographic Principles

Echocardiography uses ultrasound (i.e., sound above the audible range) to evaluate the heart and proximal great vessels and typically combines two modalities: tissue imaging (two-dimensional [2D]) and blood flow detection with velocity determination (Doppler). Cardiac tissue imaging is based on the transmission of ultrasound into the chest and its reflection by intrathoracic structures, which is determined by their acoustic properties. Imaging modalities in general use are 2D (transthoracic and transesophageal), Doppler, and, with increasing frequency, three-dimensional (3D) imaging. M-mode imaging, no longer applied as an isolated technique, can still provide useful information for timing of events, such as valve opening and closing.

Two-dimensional images are obtained from multiple sequential scan lines generated electronically (phased array) and processed to create a tomographic imaging plane with an expanded field of view. The time required to obtain all necessary scan lines reduces the frame rate to the range of 30 to 80 frames per second. Current ultrasound systems use both fundamental and harmonic imaging. Harmonic imaging transmits sound at a particular frequency (the *fundamental frequency*) but creates the image from sound reflected at twice the fundamental frequency, called the *second harmonic*, which improves image quality because the stronger harmonic signal undergoes considerably less distortion. This is particularly useful for endocardial border definition.



• **Fig. 8.1** Line graphic demonstrating the four basic probe positions for transthoracic echocardiography. A, Parasternal long-axis imaging plane. B, Apical four-chamber view. C, Subcostal view. D, Suprasternal notch view. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *SVC,* superior vena cava. (With permission of Solomon S. *Essential Echocardiography: A Practical Handbook* (with DVD). New York: Springer Science+Business Media (Humana Press); 2007.)

Doppler echocardiography uses ultrasound to determine blood flow velocity and direction within the heart. Two principal types of *spectral* Doppler techniques are used, termed *continuous wave* (CW) and *pulsed wave* (PW). CW uses two separate transducer crystals, one continuously transmitting and one continuously receiving the ultrasound signal. The high sampling rate of CW allows it to measure high velocities, but the source of any specific velocity measurement along the interrogated path cannot be differentiated *(range ambiguity).* On the other hand, PW uses one crystal, which alternates between sending and receiving an ultrasound pulse. The principal advantage of PW is that signals arise only from the area of interrogation, called the *sample volume (range resolution)*; however, because the same crystal is used for sending and receiving the signal, a new pulse of ultrasound cannot be transmitted until the previous returning signal has been detected. This "pulsed" process results in a sampling rate too low to quantitate high velocities. PW and CW are thus complementary, with PW localizing the source of a signal and CW allowing for the unambiguous measurement of high velocities.[4] *Color flow imaging* is a form of PW in which information is coded with colors and superimposed on a 2D ultrasound image. The colors black and white identify anatomic structures and color identifies blood flow velocities. Color Doppler has great utility in the evaluation of valvular regurgitant lesions and intracardiac shunts. An example of color Doppler identification of an atrial septal defect (ASD) is shown in Fig. 8.2 (Videos 8.9 and 8.10). Pulsed Doppler can also evaluate the velocity of moving myocardium, producing a signal of low velocity but high amplitude, called tissue Doppler imaging (TDI). Systolic and diastolic velocities within the myocardium and at the corners of mitral annulus can be recorded. Mitral annular velocities as measured by TDI are commonly used to evaluate diastolic function.[5]

Echocardiographic Modalities

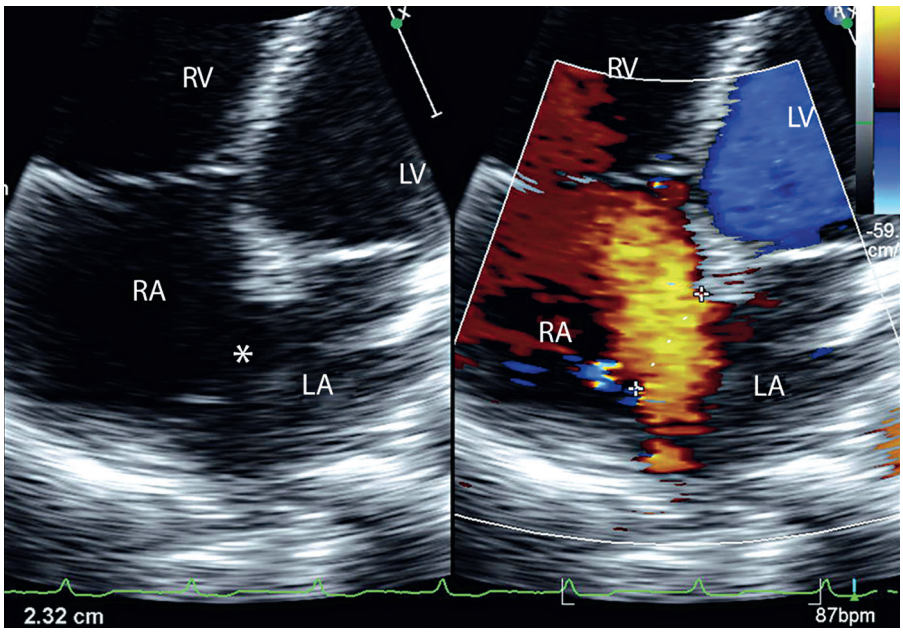
Transesophageal Echocardiography

Transthoracic echocardiographic (TTE) image quality may be suboptimal in patients who are obese, ventilated, or immobilized, and transesophageal echocardiography (TEE) can be of great use in this context.[6,7] TEE involves insertion into the esophagus of an endoscope-like probe with an ultrasound transducer on its tip. Image resolution is improved with TEE because the ultrasound beam is unimpeded by bone and air, and because proximity to the heart enables use of high-frequency (7 MHz) probes. TEE can easily be performed at the bedside. Active esophageal disease is the major contraindication. The TEE can be done with a nasogastric tube in place, but the nasogastric tube should be removed if there are any difficulties with passing the TEE probe or with acquiring the images. As some form of sedation is required, vital signs need to be monitored during the procedure. A comprehensive transesophageal examination typically takes about 20 minutes for imaging.

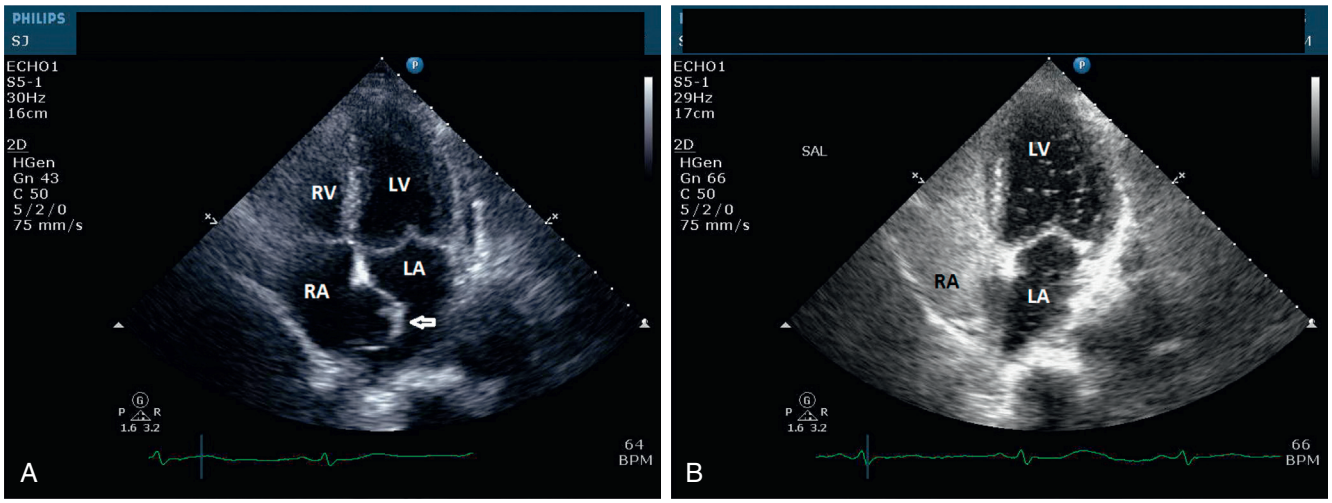
Contrast Enhancement

Saline Solution Contrast

Echocardiographic contrast agents are substances that enhance the reflected ultrasound signal. Simple agitated saline solution contrast can be used to detect intracardiac shunts, commonly at the atrial

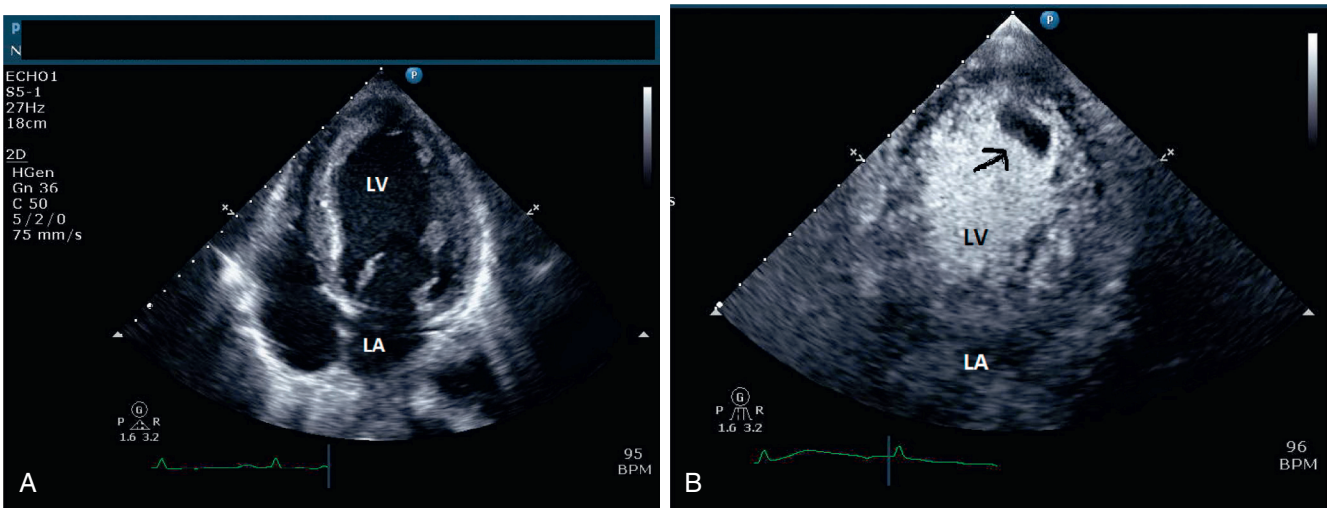


• **Fig. 8.2** Color flow of secundum atrial septal defect. A, Apical image of dilated right-sided structures. The asterisk indicates ASD. B, Color flow *(orange)* from left atrium through defect. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.



• **Fig. 8.3** Apical four-chamber view demonstrating atrial septal aneurysm *(arrow)* bulging into the left atrium (A) and (B) saline solution opacifying the right heart and bubbles crossing over into the left heart. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

level. In this technique, a prefilled 10-mL syringe of normal saline solution is connected to a second 10-mL syringe via a three-way stopcock. Brisk exchange of the saline solution between the syringes creates microbubbles, which are then rapidly injected as an intravenous bolus, resulting in opacification of the right chambers of the heart. Saline solution contrast bubbles are too large to pass through the pulmonary capillaries but may appear in the left atrium and left ventricle as a result of passage across an intracardiac (ASD or patent foramen ovale [PFO]) or intrapulmonary communication; occasionally, a cough or Valsalva maneuver may transiently increase right-sided heart pressures and facilitate right-to-left crossover of bubbles.[8] Although controversial, PFO may be implicated in embolic strokes, and these patients represent the most common group of patients who benefit from saline solution injection. Patients with persistent hypoxia without obvious cause may also benefit from saline contrast injection with echocardiographic imaging. Pulmonary arteriovenous malformations will demonstrate appearance of saline contrast in the left atrium; however, these bubbles are typically smaller than those that transit across an intracardiac shunt and usually appear late after injection (after >7–10 beats) and *persist* in the left heart after the right side of the heart empties of contrast saline, representing the typical transit time of the contrast saline through the pulmonary bed and the arteriovenous malformation into the pulmonary veins. An example of saline contrast echocardiography in a patient with an atrial septal aneurysm (ASA) and right-to-left interatrial shunt is shown in Fig. 8.3 (Videos 8.11 through 8.15).



• **Fig. 8.4** Apical four-chamber view with and without contrast enhancement, demonstrating dilated left ventricle *(LV)* without contrast (A) and (B) dilated LV with contrast demonstrating apical thrombus *(arrow). LA,* Left atrium.

Contrast for LV Opacification

Commercially available contrast agents are specifically formulated to pass through the pulmonary capillary bed, and they can be used to opacify intracardiac chambers to enhance endocardial border definition. When activated, contrast agents yield perfluorocarbon microbubbles encapsulated in either a lipid or albumin shell, which exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood.[9] The most important clinical use of contrast agents in critical care is for left ventricular opacification (LVO), to be used when standard TTE images of all LV wall segments are suboptimal.[10] These agents can provide substantial additional diagnostic information and are especially useful in identifying LV thrombus (Fig. 8.4). In patients in whom contrast for LVO is used, spectral Doppler signals can also be enhanced, enabling the detection of faint tricuspid regurgitant signals to enable measurement of pulmonary artery (PA) pressure, or for enhancing signals across the aortic valve (Videos 8.16 and 8.17).[11,12]

Goal-Directed Echocardiography

Laptop and handheld ultrasound devices are small, highly portable devices that can easily go to the bedside without requiring an external power source. Although these devices have limited analysis capabilities, they can provide reasonable 2D and color Doppler images, have been shown to correlate reasonably well with full echocardiographic platforms, and can detect clinically relevant findings.[13] "Goal-directed" 2D imaging (focused ultrasound exam [FOCUS]) is typically limited to the assessment of biventricular size and function, the presence or absence of pericardial effusion, and the evaluation of volume status—that is, a *study done to provide assessment relevant to the immediate clinical situation.* A focused 2D study done by a trained individual with a handheld device has great potential for rapid triage of select patients in the emergency room or the intensive care area.[14–17] It is important to emphasize that unclear or ambiguous findings on a focused examination should be followed by a complete study on a full echocardiographic platform to obtain an accurate and comprehensive diagnosis.

Three-Dimensional Echocardiography

Matrix-array transducers have allowed acquisition and display of real-time 3D imaging. Three-dimensional echocardiography has been shown to be more accurate in the assessment of LV volumes and ejection fraction (EF) because it avoids geometric assumptions about cardiac chambers.[18,19] In addition, it offers more accurate "surgical" views of cardiac valves, provides better assessment of regional wall motion abnormalities,[20] and can quantify LV dyssynchrony in patients with heart failure to guide cardiac resynchronization therapy.[21] In addition, 3D imaging affords reliable volumetric quantification of shunts, cardiac output, and valve regurgitation.[22] Importantly, 3D imaging can provide guidance for the rapidly expanding interventional procedures that are currently available for structural heart disease.[22]

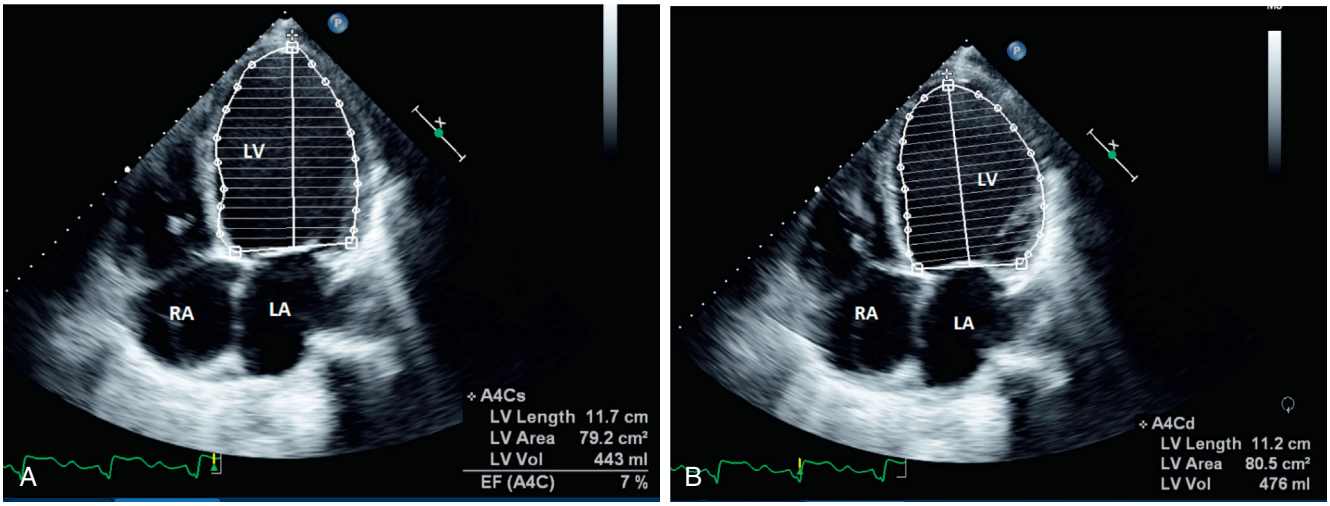
Indications for Echocardiography

Although a broad range of critically ill patients are candidates for TTE to assess cardiac pathology and function, specific indications are summarized in Box 8.1. In general, any critical care patient with unexplained hypotension, pulmonary congestion, hemodynamic instability, known cardiac disease, a significant unexplained cardiac murmur, thoracic trauma, or suspected endocarditis are candidates for echocardiography. Common indications for TEE in critical care include suspected infective endocarditis (IE), aortic dissection, cardiac source of embolus, and as a supplement to inadequate TTE images (Box 8.2).

Assessment of LV Function

Systolic Function

Although there are a variety of methods to assess LV systolic function by echocardiography (Doppler calculation of stroke volume, the first derivative of pressure measured over time using mitral regurgitation [MR] signal, tissue Doppler systolic velocity, and systolic strain and strain rate), the most commonly used and clinically relevant is the calculation or estimation of LV ejection fraction (EF).[18,23,24] As defined in current guidelines, calculation of left



• **Fig. 8.5** Left ventricular volumes and ejection fraction calculated using Simpson's method of discs from an apical four-chamber view. A, Systole. B, Diastole. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium.

• BOX 8.1 Indications for Transthoracic Echocardiography in Critical Care

Hemodynamics
Left ventricular function
- Regional wall motion abnormalities
- Global dysfunction
- Transient dysfunction (sepsis, ischemic/catecholamine stunning)

Right ventricular function
Hypotension
Pericardial effusion/tamponade
Assess volume status
Outflow tract obstruction
Valvular stenosis/insufficiency

Hypoxia
Right ventricular function
Right ventricular pressure
Intracardiac/extracardiac shunting
Pulmonary embolus

Infections
Bacterial endocarditis

Trauma
Blunt thoracic trauma
Penetrating thoracic trauma

General
Assess proximal ascending aorta—dissection, hematoma
Source of murmur
Source of embolus
Procedural guidance (especially pericardiocentesis)

• BOX 8.2 Indications for Transesophageal Echocardiography in Critical Care

Inadequate or nondiagnostic transthoracic echocardiographic images
Evaluate suspected aortic dissection or trauma
Evaluate prosthetic valves, especially mitral
Investigate persistent hypoxemia
Detect presence of valvular vegetations
Identify complications of infective endocarditis:
- Abscesses
- Leaflet perforation
- Pseudoaneurysm formation
- Fistulas

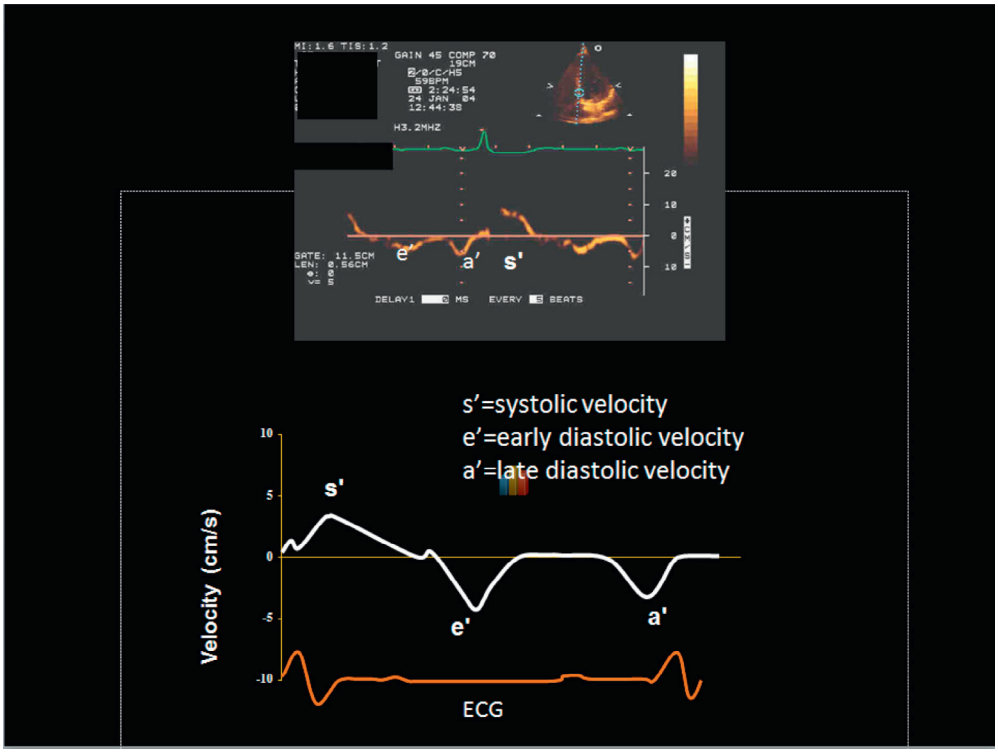
Identify cardiac source of systemic embolus:
- Thrombus in left atrium and left atrial appendage
- Patent foramen ovale/atrial septal aneurysm
- Atheromatous debris of the aorta

Identify pulmonary embolus in transit
Characterize intracardiac shunts:
- Atrial septal defect (ASD)
- Ventricular septal defect (VSD)
- Anomalous pulmonary venous connections

Guide invasive procedures:
- Shunt closure
- Percutaneous balloon valvuloplasty
- TAVR, MitraClip
- LAA Closure Devices

LAA, Left atrial appendage; *TAVR,* transcatheter aortic valve replacement.

ventricular ejection fraction (LVEF) by Simpson's method of discs (Fig. 8.5) is recommended.[18] EF (end-diastolic volume – end-systolic volume/end-diastolic volume) is dependent not only on intrinsic contractility but also on LV preload and afterload. Therefore both factors should be considered when assessing LV systolic function. Normal values are shown in Table 8.1. In the presence of regional dysfunction, EF from multiple views should be integrated to accurately assess LV systolic function. To improve the accuracy of EF calculation by echocardiography, it is essential to avoid foreshortened apical views and to use intravenous contrast material when needed to enhance endocardial border definition. Aside from measurements of systolic function, 2D echocardiography is of great use in reliably assessing LV dimensions, wall thickness, volumes, and mass.[18] In experienced hands, 3D echocardiography–derived LVEF measurements are more accurate and reproducible.[18,19] Reliable assessments of LV dimensions and EF, particularly when combined with knowledge of filling pressures, can be used to guide and assess the response to therapeutic measures of volume infusion or



• **Fig. 8.6** Example of tissue Doppler recording of the lateral mitral annulus from the apex. *a′,* Late diastolic velocity; *e′,* early diastolic velocity; *ECG,* electrocardiogram; *s′,* systolic velocity.

TABLE 8.1 Grading Left Ventricular Systolic Function by Left Ventricular Ejection Fraction

Systolic Function	Ejection Fraction (%)
Normal—men	52–72
Normal—women	54–74
Mildly depressed—men	41–51
Mildly depressed—women	41–53
Moderately depressed—men	30–40
Moderately depressed—women	30–40
Severely depressed	<30

intravenous administration of inotropic/vasodilator or vasopressor drugs.

TDI-derived myocardial velocities (Fig. 8.6) have been used to assess global LV systolic properties.[25,26] This approach is dependent on tissue Doppler technology to record mitral annulus and myocardial signals, which can be acquired from any area of the heart. However, because of their dependence on Doppler principles, they are of limited value when proper alignment cannot be achieved between the ultrasound beam and the plane of cardiac motion. TDI measurements of systolic annular velocity have been shown to reflect systolic dysfunction, even in the presence of normal LVEF (such as in hypertrophic cardiomyopathy [HCM] or infiltrative cardiomyopathy [ICM]).[25,26] Using speckle tracking imaging, a 2D echocardiographic technique that measures myocardial motion over time, myocardial deformation (strain) and rate of deformation (strain rate) can also be used to assess LV systolic function.[27,28] As in TDI, strain and strain rate can detect significant myocardial systolic abnormalities, even in the presence of preserved LVEF.[29,30] As with TDI, this is of particular importance in patients with diastolic heart failure, hypertensive heart disease, HCM, and infiltrative disease, when normal EF can coexist with significant and clinically important abnormalities of systolic function.

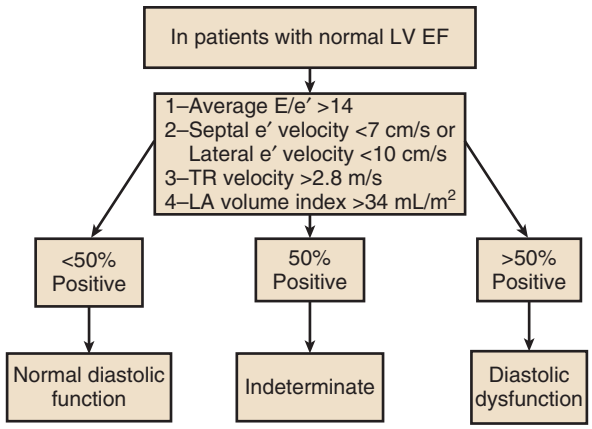
Diastolic Dysfunction

LV diastolic function refers to the filling phase of the cardiac cycle. Filling is dictated by LV relaxation (measured as the rate of decay of LV systolic pressure during the isovolumic relaxation period) as well as atrial systole and atrial and ventricular compliance. LV relaxation is an adenosine triphosphate–expending process. This active process is responsible only for early diastolic filling, whereas compliance is important throughout filling and particularly during atrial systole. The LV compliance is calculated using measurements of LV volume and pressure during the diastolic filling period. However, prediction of LV filling pressures integrates the effects of the preceding hemodynamic variables as well as other factors such as RV filling, pericardial constraint, and left atrial (LA) function on LV diastolic function. Increased LV filling pressure is often used as a clinical surrogate for diastolic dysfunction. LV filling pressure can be measured as a mean pulmonary capillary wedge pressure, mean LA pressure, mean LV diastolic pressure, or LV end-diastolic pressure. A direct measurement of LV filling pressure requires an invasive intervention, which has significant risk and costs. Echocardiography offers a noninvasive evaluation of diastolic function and estimation of LV filling pressures.

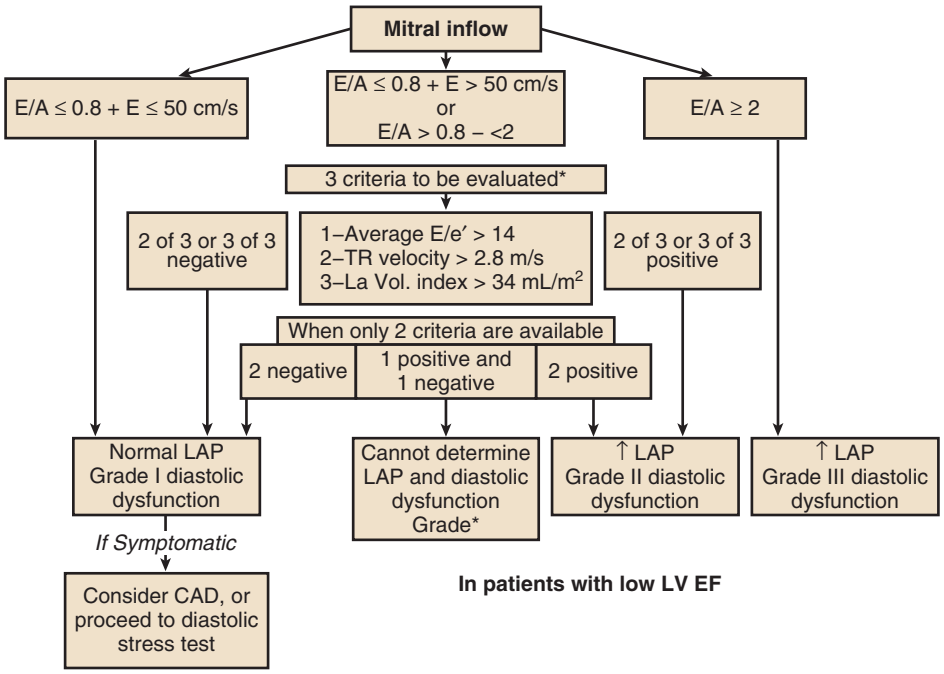
LV diastolic dysfunction in the intensive care unit (ICU) may be present as a result of cardiac as well as systemic disorders that

can affect cardiac function: coronary and hypertensive heart disease, diabetes mellitus, amyloidosis, and HCM. A careful assessment of LV diastolic function by echocardiography can contribute essential information for the management of these patients,[31–33] whereas the serial estimation of filling pressures can serve as an important guide for titration of diuretic therapy.

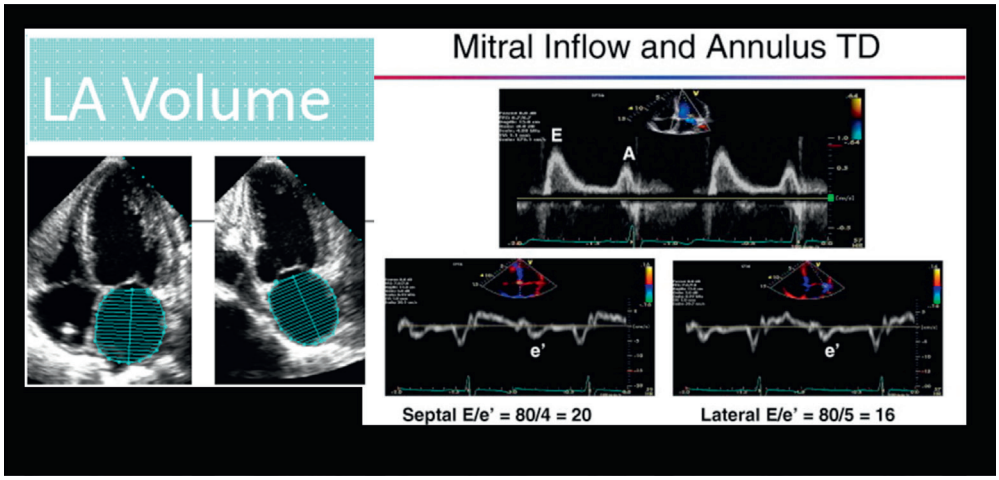
The recommended clinical approach for the assessment of LV diastolic function begins with the 2D examination to determine LV dimensions and volumes and to define the presence and extent of LV hypertrophy (Figs. 8.7 and 8.8). Patients with a depressed EF or LV hypertrophy have impaired LV relaxation. Therefore, even in the absence of any corroborating Doppler information, one can still conclude that LV relaxation is impaired in these patients. Furthermore, this information can be combined with the mitral inflow pattern to predict filling pressures. It is also important to measure LA volume using apical four- and two-chamber views because LA volume is related to the extent of diastolic dysfunction when an increase in LA volume parallels deterioration of LV diastolic function.[34] Mitral inflow is obtained using pulse Doppler, with a 1- to 2-mm sample volume placed at the level of mitral valve tips.[35,36] Early diastolic flow and velocity (the E wave) occur in response to a positive pressure gradient between the LA and the LV, resulting from a rapidly decreasing LV pressure owing to LV relaxation and early diastolic suction. In late diastole, LA contraction leads to another positive-pressure gradient and late diastolic flow, or the A velocity. With normal LV relaxation, early diastolic flow predominates and the E/A ratio is greater than 1. However, when LV relaxation is impaired, LV diastolic pressure is elevated and a reduced E velocity is observed. This leads to a higher LA preload and contraction velocity. Therefore the E/A ratio decreases in the presence of impaired LV relaxation. Because LA pressure usually increases to maintain forward stroke volume, the early diastolic transmitral pressure gradient increases, leading to a higher E velocity and E/A ratio. Because of the simulation to normal mitral inflow, this pattern is referred to as a pseudonormal mitral inflow pattern. In more advanced disease with markedly elevated LA pressure, the E velocity increases even



• **Fig. 8.7** Algorithm for estimation of diastolic function with normal ejection fraction. (From Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29:277–314.)



• **Fig. 8.8** Algorithm for estimation of diastolic function with depressed ejection fraction. *CAD,* Coronary artery disease; *E,* early mitral diastolic flow; *E/A,* the ratio of peak velocity flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); *e′,* early diastolic velocity; *LAP,* left atrial pressure; *LA vol.,* left atrial volume; *LV EF,* left ventricular ejection fraction; *TR,* tricuspid regurgitation. (From Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29:277–314.)



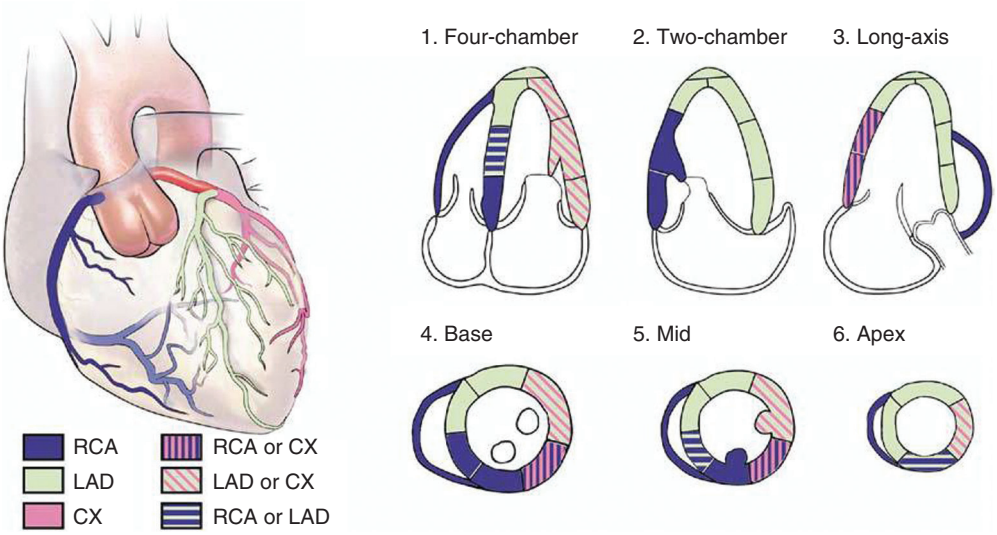
• **Fig. 8.9** Integration of Doppler-derived data for assessment of left ventricular diastolic function. *Left,* Measurement of left atrial volumes. *Right, top,* Mitral inflow E- and A-wave velocities; *right bottom,* septal and lateral tissue Doppler *(TD)* velocities *(e′). LA,* Left atrial. (Left from Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.e14. Right from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009;22:107–133.)

further, resulting in a "restrictive" inflow pattern, in which the E/A ratio is 2 or greater. It is possible to unmask the presence of impaired LV relaxation in these cases by performing a Valsalva maneuver. The decrease in venous return during the strain phase of Valsalva results in a decrease in LA pressure and E/A ratio.[37,38] Tissue Doppler–derived early diastolic mitral annular velocity (e′) can be recorded by pulsed Doppler at mitral annulus. When combined with E, the E/e′ ratio is obtained, which has been shown to be a reasonable correlate of LV filling pressure,[39] although multiple diastolic echo-Doppler variables need to be synthesized to result in an accurate assessment of LV diastolic function.[40–42]

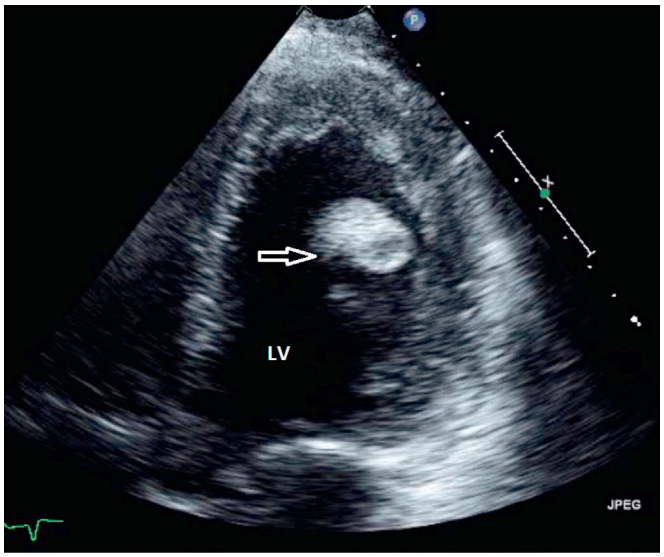
Pulmonary venous flow can also be analyzed to predict LV filling pressures. Pulmonary venous flow signals are readily recorded in the majority of patients seen in the outpatient laboratory but can be challenging in the critical care setting. Antegrade forward flow from the pulmonary vein into the left atrium occurs during systole (S) and early and mid-diastole (D). After atrial contraction, retrograde flow (atrial reversal) from the left atrium into the pulmonary vein occurs. At the earlier stages of diastolic dysfunction where LV end-diastolic pressure is increased, the peak velocity and duration of atrial reversal become more prominent.[41] Subsequently, with the rise in mean LA pressure, antegrade systolic flow decreases, whereas the D velocity increases with a shortening of its deceleration time. Assessment of PA systolic and diastolic pressures (see later text) can provide helpful corroborating evidence of the status of LV filling pressures. In the absence of pulmonary parenchymal and vascular disease, and in the presence of significant cardiac valvular disease or cardiomyopathy, one can reasonably infer that PA pressures are increased due to an elevated LA pressure. Fig. 8.9 shows an example of the assessment of diastolic function integrating multiple echo-Doppler variables.

Ischemia/Infarction Including Complications

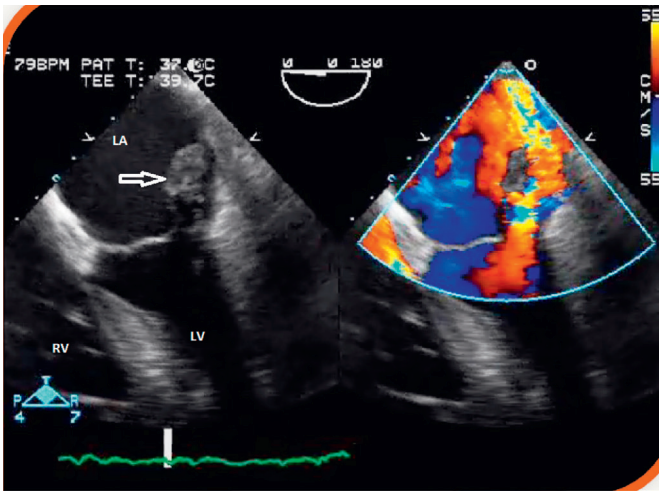
Echocardiography is essential for the assessment of LV regional function in the critical care setting when the diagnosis of ischemia/infarction is entertained. Adequate images, particularly when combined with harmonics and intravenous contrast, can provide reliable information regarding the presence and extent of segmental wall motion abnormalities.[43] Furthermore, serial assessment of regional function is possible after the administration of any therapeutic intervention. In addition to technically good images, interpretation by an experienced echocardiographer is essential for achieving high accuracy. Regional function is determined by examining endocardial motion as well as local thickening. Abnormal LV regional function is usually determined when the dysfunction is observed in more than one plane, with particular LV segments corresponding to specific coronary artery distributions. An echocardiographic regional map for the identification of wall motion abnormalities and their correlation to coronary anatomy is shown in Fig. 8.10. In general, thinned (<5 mm in diameter) bright segments with abnormal or absent motion are indicative of scars (Videos 8.18 through 8.20). When there is a thinned segment that moves in a direction opposite to adjacent, normal walls ("bulging"), aneurysm is often the cause. Regional wall motion abnormalities can occur in the absence of epicardial coronary artery disease; thus final conclusions regarding the cause of wall motion abnormalities should be made only after integration of all clinical findings. In the setting of acute myocardial infarction, a number of studies have substantiated the prognostic power of echocardiography, particularly determination of LVEF, LV diastolic function, RV function, and significant valve dysfunction.[43] Regional function is most reflective of long-term outcome when imaging is performed after recovery of myocardial stunning (usually a week to 10 days after presentation). However, in the acute setting, echocardiography may be obtained to help establish the diagnosis of an acute ischemic syndrome, determine the extent of myocardium at risk, identify apical thrombus (Fig. 8.11), and detect the presence of mechanical complications such as a ruptured papillary muscle (Fig. 8.12), contained cardiac ruptures called pseudoaneurysms (Fig. 8.13), MR, pericardial effusion, and RV infarction, all of which may require urgent intervention (Videos 8.21 through 8.31).[44]



• **Fig. 8.10** Graphic for relating coronary artery distribution to echocardiographic wall segments. *CX,* Circumflex; *LAD,* left anterior descending; *RCA,* right coronary artery. (From Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiograpy's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440–1463.)



• **Fig. 8.11** "Zoomed" apical four-chamber view of the left ventricle demonstrating thrombus *(arrow)*. *LV,* Left ventricle.

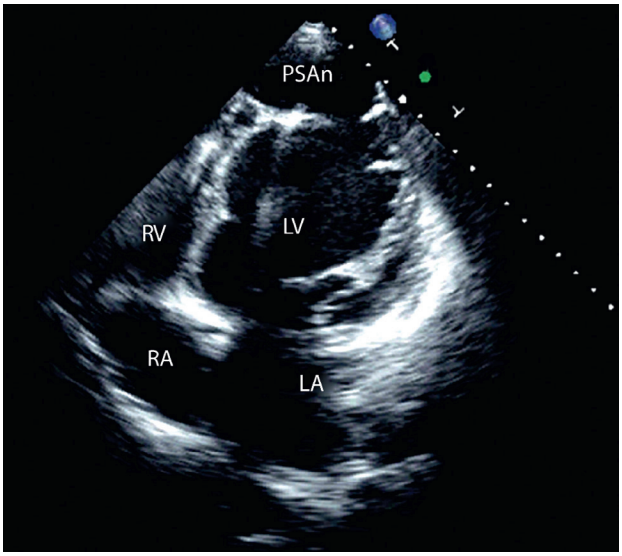


• **Fig. 8.12** Transesophageal echocardiography image of ruptured papillary muscle *(arrow)* after infarct, without *(left)* and with *(right)* color Doppler, demonstrating severe mitral regurgitation. *LV,* Left ventricle; RV, right ventricle.

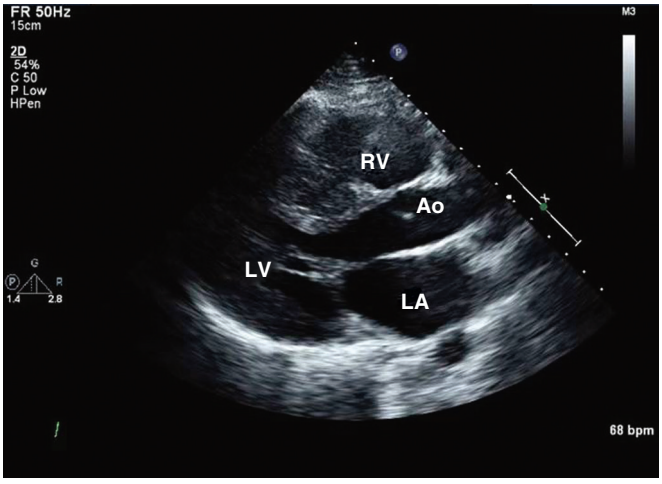
Cardiomyopathies

Hypertrophic Cardiomyopathy

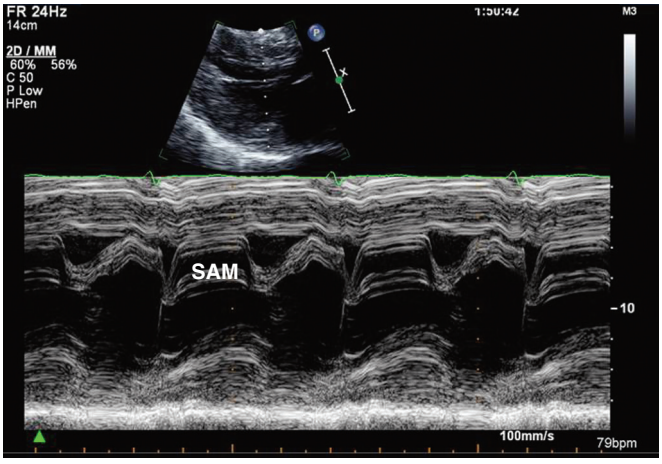
HCM is an inherited disorder characterized by marked, commonly asymmetric hypertrophy without an identifiable cause.[45] At the pathologic level, there is myocyte disarray, wherein healthy myocytes are replaced by fibrosis. Thick walls are the hallmark of the echocardiographic findings (Fig. 8.14). Hyperdynamic LV systolic function is typical early in the disease and can progress to depressed systolic function, occasionally with aneurysm formation at the apex. There are various morphologic types of HCM, including asymmetric septal hypertrophy with systolic anterior motion of the mitral valve (Figs. 8.15 and 8.16, Video 8.32), concentric (uniform) hypertrophy, apical hypertrophy, and hypertrophy located in myocardial segments other than the septum. Apical hypertrophy, originally described in Japan in 1976, can be associated with giant negative T waves on the electrocardiogram (ECG). Although the overall mortality of apical HCM is low (0.1% annually), a continuum of apical abnormalities may exist wherein apical ischemia leads to apical outpouching or aneurysmal remodeling. There is a high incidence of ventricular dysrhythmias and atrial fibrillation and stroke in this cohort.[45] Echocardiography is uniquely positioned to differentiate the various morphologic types of HCM, to determine LV systolic function, to assess left ventricular outflow tract (LVOT)



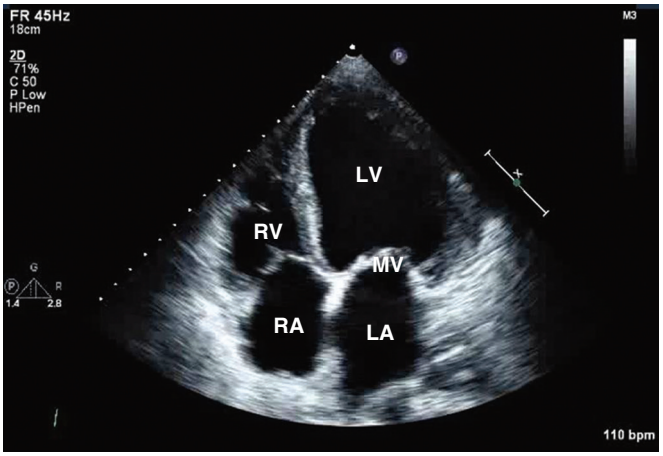
• **Fig. 8.13** Pseudoaneurysm *(PSAn)* of the left ventricular apex. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.



• **Fig. 8.14** Long-axis view of patient with hypertrophic cardiomyopathy. Note marked septal thickness. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.



• **Fig. 8.15** M-mode of classic systolic anterior motion *(SAM)* in hypertrophic cardiomyopathy.



• **Fig. 8.16** Apical four-chamber view of dilated cardiomyopathy. *LA,* Left atrium; *LV,* left ventricle; *MV,* mitral valve; *RA,* right atrium; *RV,* right ventricle.

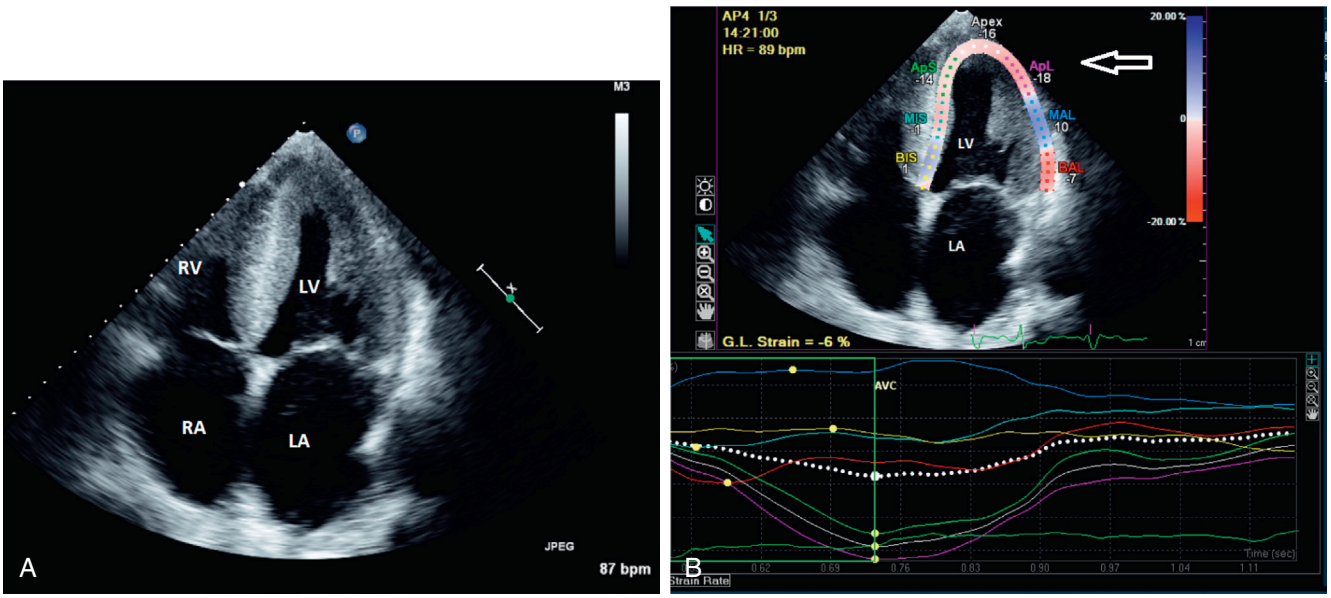
or intracavitary obstruction, to identify associated MR, and to determine LV filling pressures and PA pressure.[46] Reduced LV compliance eventuates elevation of left atrial and pulmonary venous pressures, and abnormal myocardium, with or without obstruction, results in rhythm disturbances. Clinically, HCM patients can present to critical care with hypotension, congestive heart failure, arrhythmias, stroke, and cardiac arrest; echocardiography is crucial in differentiating the underlying disease state and the functional and morphologic associations with these presentations.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is global LV dilatation and systolic dysfunction often associated with RV dysfunction. Although viral myocarditis can cause this same picture, in general, DCM refers to familial inherited cardiomyopathy but can also be caused by a variety of conditions, including alcohol abuse, chemotherapeutic agents, and endocrine disorders. As genetic methods for diagnosing inherited DCM become more refined, an increasing proportion of idiopathic nonischemic cardiomyopathy is found to be inherited.[47] Echocardiography demonstrates a dilated LV and depressed EF, usually with associated RV dysfunction and biatrial enlargement (see Fig. 8.16); for final diagnosis, exclusion of a sufficient degree of coronary artery disease to explain the degree of LV dysfunction is necessary.[48] Secondary MR and tricuspid regurgitation (TR) can be seen by color Doppler. LV filling and PA pressure assessments are important in clinical management (Videos 8.33 through 8.36).

Infiltrative/Restrictive Cardiomyopathy

ICMs are characterized by the deposition of abnormal substances within the myocardium that cause the ventricular walls to become progressively rigid, thereby impeding ventricular filling.[49] This impedance to normal LV filling is termed "restrictive filling"; hence the other name, "restrictive cardiomyopathy." However, because any cardiomyopathic process can have restrictive filling (ischemic, dilated, hypertrophic), the preferred term is ICM. Some ICMs can cause LV and RV thickening, such as the archetypal ICM cardiac amyloidosis, although others can cause ventricular thinning, such as sarcoidosis. From the echocardiographic point of view, thickened ventricular walls, occasionally "smudgy" in appearance, in association with restrictive LV filling and at times depressed LVEF, are seen in amyloidosis, as well as "sparing" of the apical



• **Fig. 8.17** Apical four-chamber view (A) of cardiac amyloidosis. Note bright thick walls. B. Strain imaging demonstrating typical apical sparing *(arrow). LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

segments by strain imaging (Fig. 8.17).[50,51] The low voltage on the ECG as typically seen in patients with amyloid can help make the distinction between HCM and hypertensive disease. For sarcoidosis, many LV patterns can be seen, but focal LV aneurysms are typical; heart block on the ECG is also often seen.

Takotsubo Syndrome

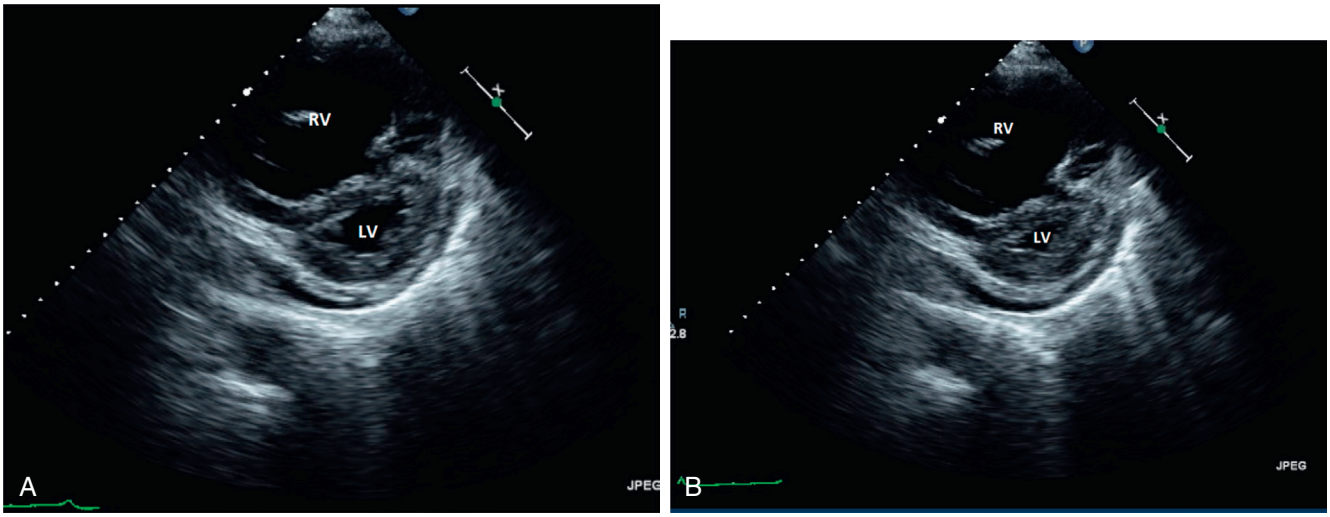
The Takotsubo (*Japanese octopus pot*) syndrome, originally described in Japan in 1990, is characterized by regional LV wall motion abnormalities, commonly completely reversible, that occur in the absence of significant coronary artery disease.[52] In the early experience, it was most commonly found in women older than 50 years of age, occurred after an emotional or physical stressor, and presented with ST-segment elevation and an apical "ballooning" LV contraction abnormality. It is now recognized to be more clinically varied, has been identified in men and younger individuals and, importantly, diverse LV contraction patterns beyond the classic apical ballooning pattern (75%–80%) are now recognized, including midventricular ballooning (10%–20%) and basal segment ballooning ("inverted ballooning"; uncommon and occurring in only 1%–2%).[52,53] It can present during diagnostic procedures or during hospitalization for acute illness, and recent evidence suggests an association with sepsis.[54,55] Although no single feature distinguishes Takotsubo from other conditions with a similar acute presentation, characteristic symptoms include chest pain, ischemic ECG changes with a troponin elevation, and an LV wall motion abnormality in a segment being supplied by a normal coronary artery. *Reversibility* of LV wall motion abnormalities is expected within 3 months. Hemodynamic instability requiring intervention with vasopressor agents or intraaortic balloon pumping occurs in up to 15% of patients, and in-hospital mortality is as high as 5%. The recurrence rate may be as high as 20%. Elevated catecholamine levels may be involved in Takotsubo pathophysiology. Current evidence does not suggest survival benefit with the use of β-blockers in the hospital, although 1-year survival showed marginal improvement with the use of angiotensin-converting enzyme inhibitors.[54,55] A registry has been established (the International Takotsubo Registry) to improve diagnosis, treatment, and outcomes (Videos 8.37 and 8.38).[56]

Assessment of RV Function

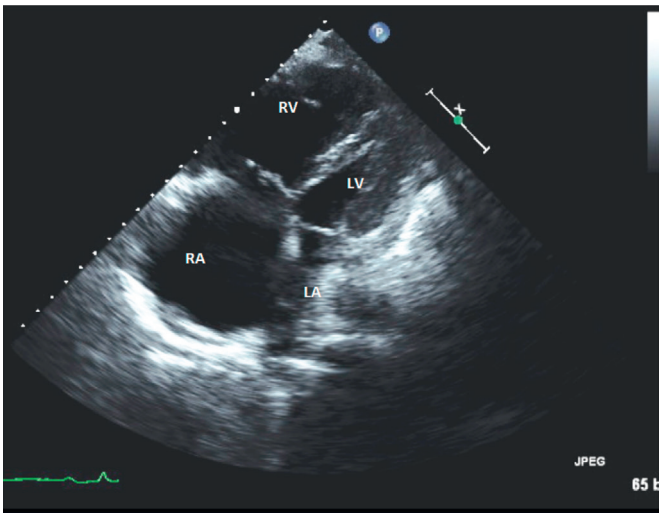
Echocardiographic assessment of the right ventricle is challenging because of its complex shape. However, it is possible to integrate information from multiple views to reach reasonably accurate conclusions on RV size and function. Visually, assessment of RV size is usually done by comparing RV and LV transverse dimensions in the parasternal short-axis (Fig. 8.18) and apical views (Fig. 8.19). In general, the RV dimensions are one-third of the LV dimensions. Severe RV enlargement is operant when the RV is bigger than the left and the RV forms the cardiac apex. It is possible to measure RV end-diastolic and end-systolic dimensions and area in the apical four-chamber view; however, caution should be exercised to avoid tangential and foreshortened views. Normal RV dimension at the tricuspid annular level in the apical four-chamber view is less than 4.1 cm.[57] RV wall thickness is normally less than 0.5 cm and is most reliably measured by 2D echocardiography in subcostal views at the level of the tricuspid valve chordae tendinae.[57]

RV systolic function is estimated qualitatively in clinical practice as normal or mildly, moderately, or severely depressed function. It is also possible to obtain a quantitative measurement of RV systolic function by measuring RV fractional area change (FAC = end-diastolic area − end-systolic area/end-diastolic area) in the apical four-chamber view. This is a simple method with reasonable reproducibility and accuracy, and normal value is greater than 35%. The tricuspid annulus motion can provide useful information in patients with suboptimal visualization of RV free wall; normal tricuspid annular plane systolic excursion (TAPSE) is greater than 1.6 cm.[57,58] Additional information may be obtained by the tissue Doppler–derived tricuspid annulus systolic velocity.[59,60]

Conditions of RV volume overload (e.g., ASD, severe TR or pulmonary regurgitation) result in diastolic flattening of the



• **Fig. 8.18** Short-axis view of "D-shaped" left ventricle in systole (A) and diastole (B) with marked right ventricular enlargement. *LV,* Left ventricle; *RV,* right ventricle.



• **Fig. 8.19** Apical four-chamber view of marked right ventricular dilatation. *LA,* left atrium; *LV,* Left ventricle; *RA,* right atrium; *RV,* right ventricle.

interventricular septum, but RV pressure overload (primary pulmonary hypertension, acute or chronic thromboembolic disease, cor pulmonale) results in systolic and diastolic flattening of the interventricular septum ("D-shaped ventricle" in systole and diastole; see Fig. 8.18).[61] Acute RV dilatation can reduce LV filling through an increase in intrapericardial pressure, which in turn reduces LV transmural filling pressure.[62,64] An acute decline in RV function is usually accompanied by RV dilatation and a decrease in RV systolic function in the presence of normal wall thickness. In the setting of an acute coronary syndrome, this may happen as a result of RV ischemia or infarction. The presence of normal/reduced PA pressures along with regional dysfunction can help identify these patients. Patients with chronic RV pressure overload (for example, idiopathic pulmonary hypertension) often exhibit a dilated right ventricle with reduced contractility and increased wall thickness (see Fig. 8.19) in the presence of increased PA pressures and vascular resistance. A simple echocardiographic prediction rule using LA size measurement, the lateral E/e′ ratio, and the pulsed wave Doppler of the right ventricular outflow tract has been proposed by Opotowsky et al. to predict the likelihood that a given patient has pulmonary hypertension attributable to either pulmonary vascular disease or to left heart disease.[63] In this population, all subjects with a positive score had pulmonary vascular disease; all subjects with negative scores had elevated wedge pressure.

Although it is true that as many as 70% of patients with proved pulmonary embolus (PE) have no significant echocardiographic abnormalities, recent data suggest that several parameters of RV function are associated with mortality in patients presenting with acute PE.[65] These parameters include (1) the ratio of RV to LV end-diastolic diameter (≥0.9); (2) RV systolic pressure derived from the tricuspid regurgitant jet velocity (≥50 mm Hg); (3) TAPSE (<15 mm); and (4) inferior vena cava (IVC) collapsibility.[64] Another study suggested that the (1) McConnell sign (hypokinesis of the RV free wall with normal contraction of the RV apex); the (2) "60/60" sign, which is the coexistence of a shortened pulmonary ejection acceleration time (AcT) (<60 msec) with mid-systolic velocity deceleration ("notch") and a tricuspid regurgitation peak gradient <60 mm Hg; and (3) right heart thrombus were all strongly suggestive of pulmonary embolus.[65] Work by Dahhan et al. found an association of free wall global RV strain and RV Tei index with mortality.[66,67] They did not find such a relationship between other measures, including TAPSE, RV size, and the RV/LV ratio; in fact, TAPSE, subjective RV dilation, and subjective RV dysfunction were not statistically different between survivors and nonsurvivors.[67] *All* studies agree, however, that there is a paucity of data from large clinical trials defining which echocardiographic parameters are actually useful in risk assessment in acute PE, and whether such parameters are of utility in identifying patients who might benefit from an intervention (Videos 8.39 through 8.43).

Determining Valvular Function and Dysfunction

Echocardiography provides important anatomic and physiologic information on cardiac valves. Features of valve morphology and motion, such as a flail leaflet, can be reliably assessed using 2D imaging. Importantly, secondary changes such as chamber

TABLE 8.2 Echocardiographic Assessment of Aortic Regurgitation Severity

Finding	Mild	Moderate	Severe
Central jets: color jet width/LVOT diameter	<25%	25%–64%	≥65%
Vena contracta	<0.3 cm	0.3–0.6 cm	>0.6 cm
Pressure half-time	>500 ms	200–500 ms	<200 ms
LV end-diastolic dimension	Normal	5–6 cm	>6 cm
Regurgitant volume	<30 mL	30–59 mL	≥60 mL
Regurgitant fraction	<30%	30%–49%	≥50%
Regurgitant orifice area	<0.1 cm^2	0.1–0.29 cm^2	≥0.3 cm^2

LV, Left ventricle; *LVOT,* left ventricular outflow tract.

TABLE 8.3 Echocardiographic Assessment of Mitral Regurgitation Severity

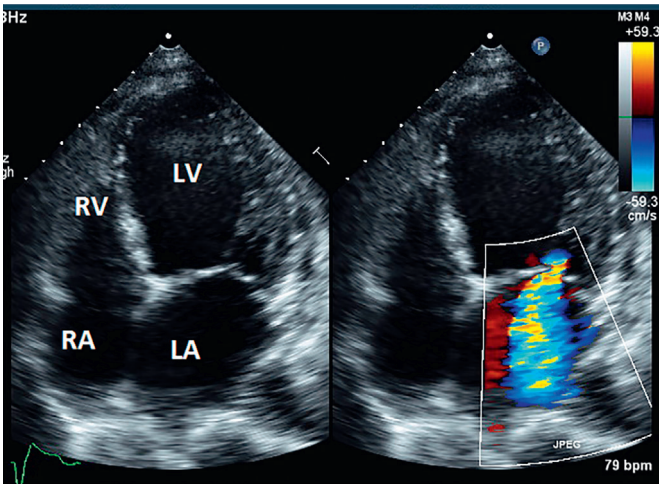
Finding	Mild	Moderate	Severe
Central jets: jet area by color Doppler/LA area	<20%	20%–49%	>50%
Vena contracta	<0.3 cm	0.3–0.69 cm	≥0.7 cm
Pulmonary veins	Predominant systolic	Blunted systolic	Systolic reversal
LA size	Normal	Normal or dilated	Dilated
LV size	Normal	Normal or dilated	Dilated
Regurgitant volume	<30 mL	30%–59% mL	≥60 mL
Regurgitant fraction	<30%	30%–49%	≥50%
Regurgitant orifice area	<0.2 cm^2	0.2–0.39 cm^2	≥0.4 cm^2

LA, Left atrium; *LV,* left ventricle.

TABLE 8.4 Echocardiographic Assessment of Tricuspid Regurgitation Severity

Finding	Mild	Moderate	Severe
Central jets: jet area by color Doppler	<5 cm^2	5–10 cm^2	>10 cm^2
Vena contracta	Not defined	Not defined, but <0.7 cm	>0.7 cm
PISA radius	≤0.5 cm	0.6–0.9 cm	>0.9 cm
RA size	Normal	Normal or dilated	Dilated
RV size	Normal	Normal or dilated	Dilated
Jet density	Soft	Dense	Dense
Jet contour	Parabolic	Variable	Triangular with early peak
Hepatic veins	Predominant systolic	Blunted systolic	Systolic reversal

PISA, Proximal isovelocity surface area; *RA,* right atrium; *RV,* right ventricle.

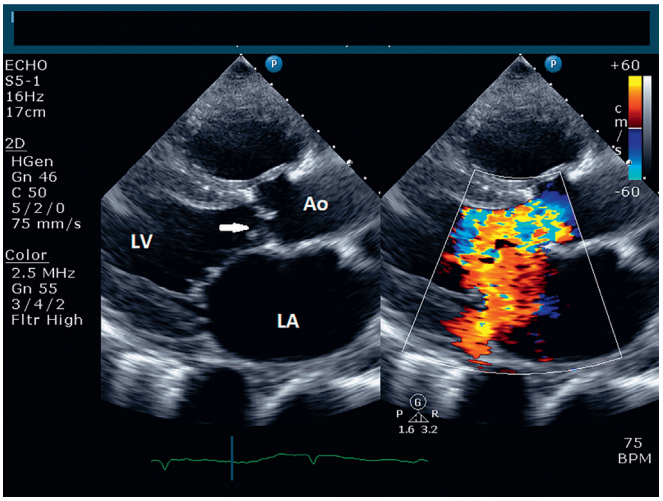


• **Fig. 8.20** Apical four-chamber view demonstrating severe mitral regurgitation *(right panel). LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

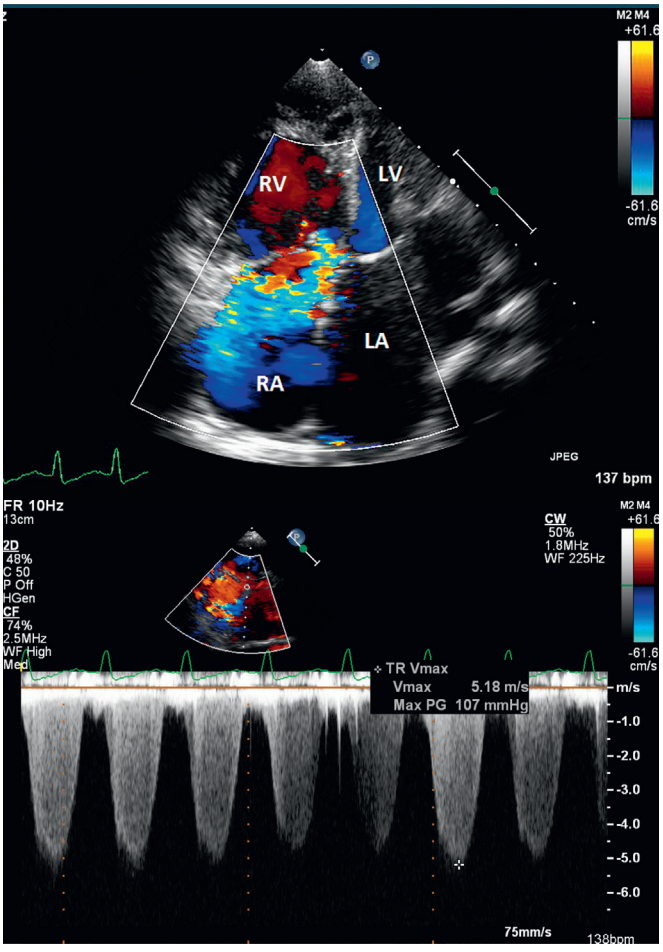
enlargement and LV/RV function can be followed serially, thus enabling timely decisions with respect to surgery or percutaneous interventions. Using 2D images and Doppler, it is possible to assess the severity of valvular stenosis or regurgitation and to calculate PA pressures.

Evaluation of Mitral, Tricuspid, and Aortic Regurgitation

Similar principles apply to the assessment of mitral (MR), tricuspid (TR), and aortic (AR) regurgitation. Pulsed, CW, and color Doppler are useful, when combined, in identifying and accurately grading AR (Table 8.2), MR (Table 8.3), and TR (Table 8.4).[68] Echocardiographic assessment of regurgitant valves includes the 2D and comprehensive Doppler imaging in multiple views to identify the direction and size of regurgitant jets. Color Doppler has reasonable accuracy in assessing the severity of MR, TR, or AR when jets are central, although the severity of eccentric jets can be underestimated. In addition, several technical and physiologic factors can affect the size of the jet, irrespective of regurgitant volume, including color gain, pulse repetition frequency, filter settings, and atrial (or aortic)/ventricular pressures. Therefore it is important to record blood pressures at the time of echocardiography. For MR and TR, the ratio of the jet area to the LA or RA area has been used in clinical and research studies to assess these lesions; it is important that the Nyquist limit for color Doppler be greater than 55 cm/sec for accurate assessment. For AR, the width of the jet at its origin is related to that of the LVOT to arrive at the ratio that expresses the severity of AR. It is also possible to measure the cross-sectional area of the regurgitant jet by planimetry and relate that to the corresponding area of the LVOT in the short-axis views. Fig. 8.20 shows an image of severe MR, Fig. 8.21 demonstrates significant AR, and Fig. 8.22 shows severe TR.



• **Fig. 8.21** Long-axis view demonstrating severe aortic regurgitation *(arrow). Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.



• **Fig. 8.22** Severe tricuspid regurgitation *(TR)* by color Doppler *(upper panel).* Continuous wave Doppler demonstrating very high gradient consistent with severely elevated pulmonary pressures *(lower panel). RA,* Right atrium; *RV,* right ventricle; *LA,* left atrium; *LV,* left ventricle.

The "vena contracta" of the regurgitant jet, defined as the narrowest area of the jet that occurs at the orifice,[69] can be readily imaged and measured. As the regurgitant volume increases, vena contracta width increases (Fig. 8.23). The flow convergence method (proximal isovelocity surface area, or PISA, method) is a quantitative approach that can measure the regurgitant volume and the effective regurgitant orifice (ERO) area. Color flow mapping enables the visualization of the concentric hemispheres of flow as they approach the ERO. The ERO area is calculated as:

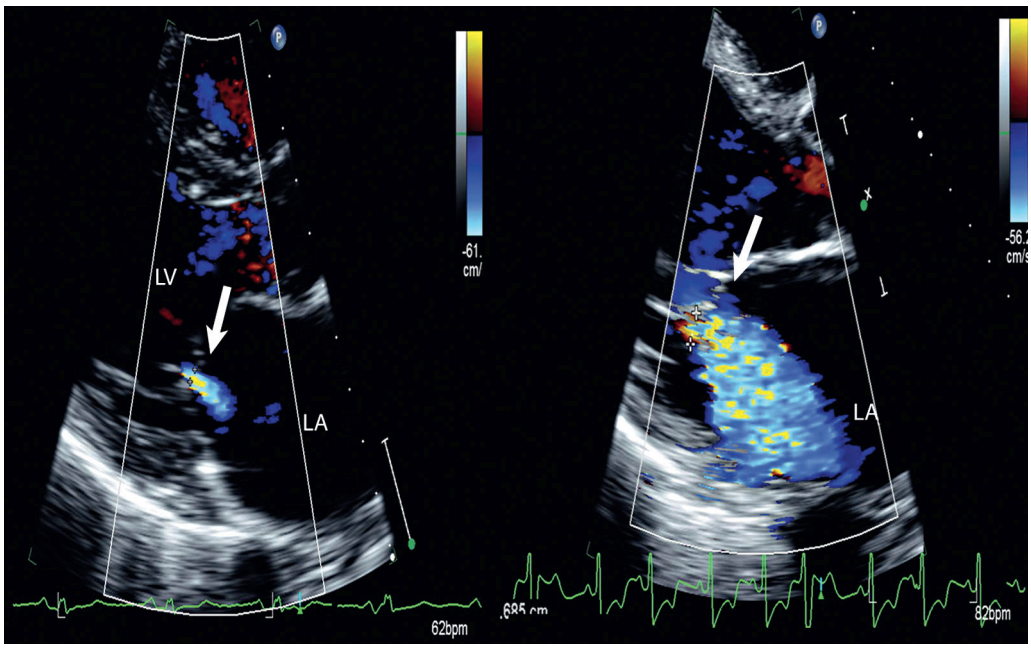
$$6.28 \times r^2 \times V_a / V_{peak},$$

where V_a is the aliasing velocity, r is the maximal radius of the PISA, and V_{peak} is the peak velocity of the regurgitant signal by CW Doppler[70] (Fig. 8.24). This method is most reliable when jets are centrally located and the regurgitant orifice is adequately visualized. The CW signal can provide useful information, as the density of these signals relative to antegrade flow increases with increasing severity of regurgitation. For patients with MR or TR who have severe lesions and a rapid rise in LA or RA pressure resulting in a large regurgitant V wave, low-velocity, early systolic peaking Doppler regurgitant signals are seen. For AR, the deceleration time (DT) (pressure half-time = 0.29 × DT) of the AR spectral Doppler signal is related to the rate at which aortic and LV pressures equilibrate in diastole, such that patients with hemodynamically significant lesions exhibit a rapid rise in LV diastolic pressure, leading to steep deceleration of the AR velocity signal. In general, severe AR correlates with pressure half-time less than 250 msec, and mild AR with pressure half-time greater than 500 msec.[68] The pressure half-time is most reliable in cases with acute AR and may be prolonged in patients with chronic severe AR owing to a concomitant increase in LV compliance. For MR and TR, peak early diastolic filling velocity by PW (peak E velocity) is increased in the setting of significant regurgitation because of the increased transvalvular flow generated by the regurgitant volume; in severe MR, a peak E velocity greater than 1.2 m/sec is usually present. In addition, pulmonary and hepatic venous flow will show systolic reversal of flow in severe MR or TR, respectively, corresponding to the large regurgitant V wave in atrial pressure. In hemodynamically significant AR, diastolic flow reversal is noted in the descending aorta. Normally, no (or minimal) flow reversal is seen in the descending aorta in early diastole. In patients with severe AR, holodiastolic flow reversal is observed.[68]

In arriving at final conclusions, it is important to integrate all the findings obtained by 2D and Doppler imaging.[68] For example, patients with chronic severe regurgitant lesions usually have dilatation of cardiac chambers (for MR, LA and LV; for TR, RA and RV; for AR, LV) along with a large regurgitant volume. If the quality of the transthoracic images precludes the assessment of valvular disease, or the severity of MR or AR, it is reasonable to proceed to TEE. All of the preceding methods can be applied for the quantification of regurgitant lesions imaged by TEE. However, with respect to MR assessment by TEE, given the proximity of the TEE probe to the left atrium, the MR jet area can be larger than that acquired by transthoracic imaging. In addition, TEE can provide unique information that is essential for successful mitral valve repair. Particularly, 3D TEE provides excellent anatomic information on specific mitral anatomy and function[22] (Fig. 8.25).

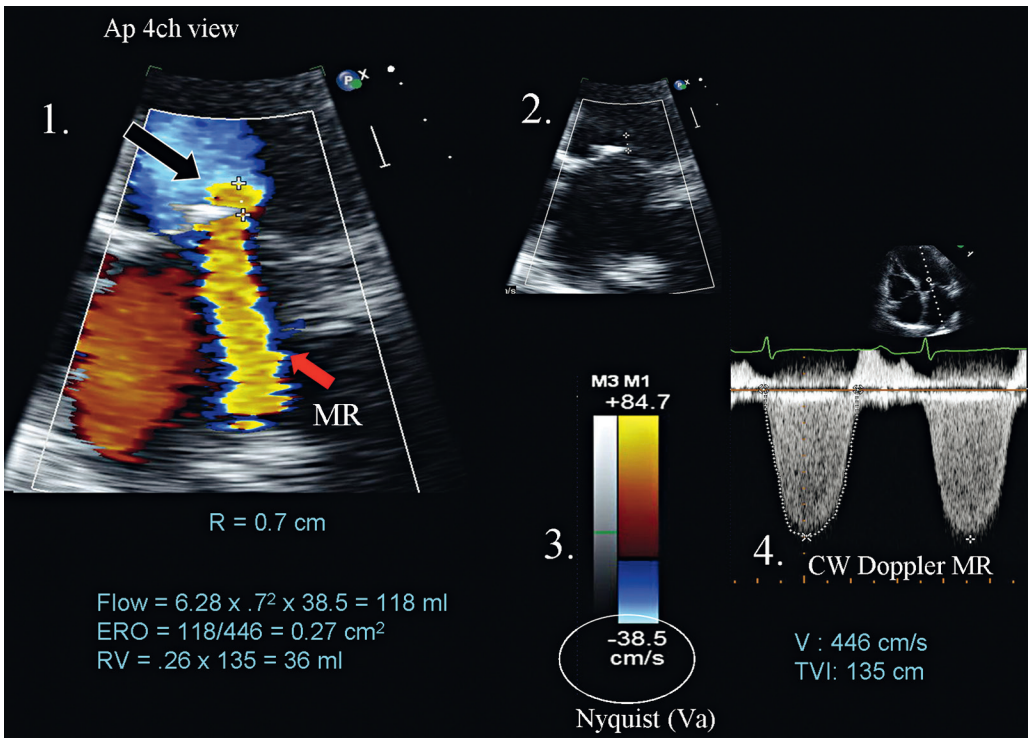
Evaluation of Aortic Stenosis

Patients with aortic stenosis (AS) have abnormally thickened or calcified valve leaflets along with reduced leaflet excursion, as seen by 2D echocardiography (Fig. 8.26, Video 8.44).[71] In patients older than 70 years of age, the most common cause is degeneration of a trileaflet valve; in patients younger than 70 years, the most common cause is a bicuspid aortic valve. In addition to morphologic changes of the aortic valve, 2D imaging is needed to determine LV size, wall

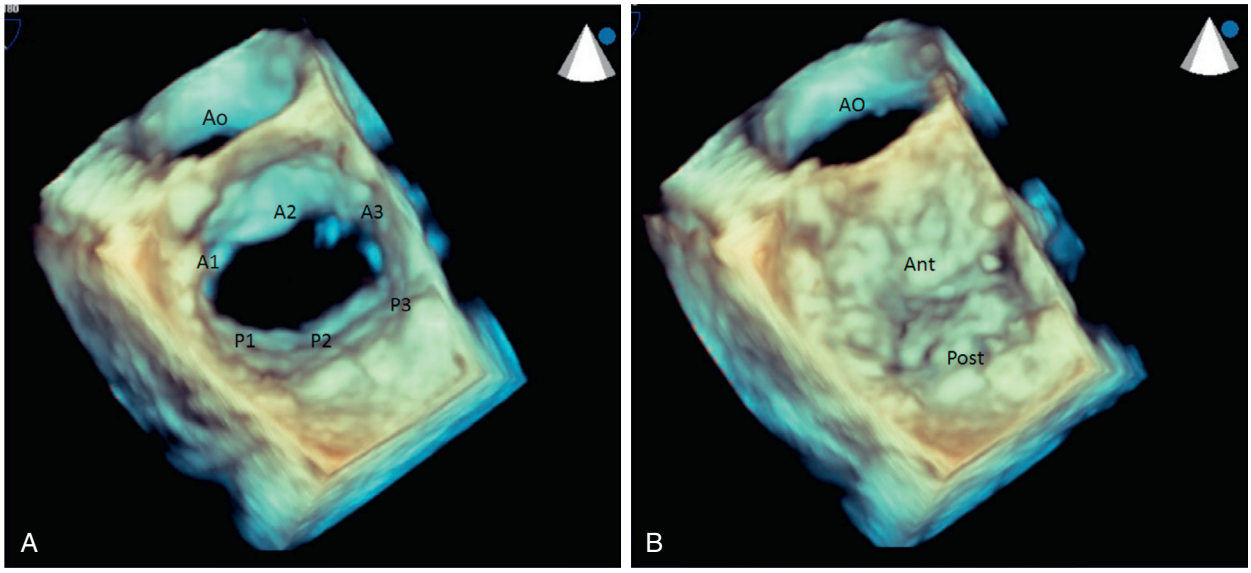


A B

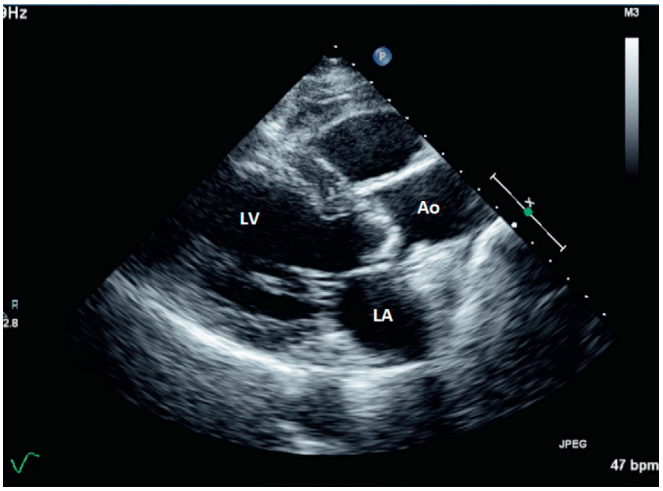
• **Fig. 8.23** Vena contracta measurements *(arrows)* of mild (A) and severe (B) mitral regurgitation. *LA,* Left atrium; *LV,* left ventricle.



• **Fig. 8.24** Apical four-chamber view of moderate mitral regurgitation *(MR)* as calculated by the proximal isovelocity surface area method. *1*, Isolation and measurement of proximal color radius *(black arrow).* MR jet *(red arrow). 2*, Confirmation of caliper placement without color. *3*, Nyquist *(Va)* velocity. *4*, Continuous wave *(CW)* Doppler of MR velocity and time velocity integral. *ERO,* Effective regurgitant orifice; *RV,* right ventricle.



• **Fig. 8.25** Three-dimensional "surgeon's view" of the mitral valve. *Ao,* Aorta; P1, P2, P3, A1, A2, and A3 identify the individual scallops of the anterior *(Ant)* and posterior *(Post)* leaflets.



• **Fig. 8.26** Parasternal long axis image of calcific aortic stenosis. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

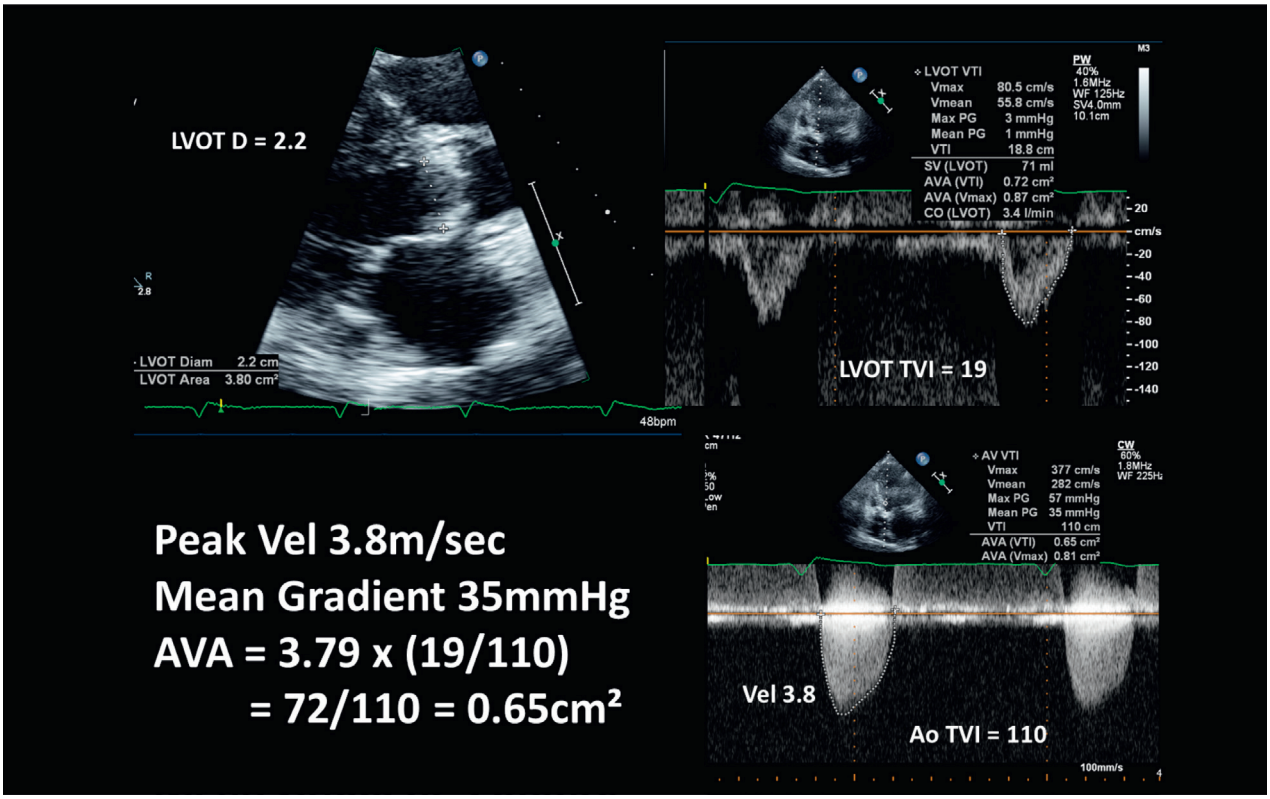
thickness, and EF. Such data are essential to assess the impact of AS on LV function, which is needed as part of the routine evaluation of patients with this disease. AS severity is assessed most reliably by the mean transvalvular systolic pressure gradient across the aortic valve and by the valve area, both of which are measured by Doppler echocardiography. Using the modified Bernoulli equation ($\Delta P = 4v^2$), the peak and mean gradients across the aortic valve can be calculated from the velocity (v) CW Doppler signal. An excellent correlation was observed between invasive and Doppler measurements of mean gradient when both measurements were obtained simultaneously.[72] However, several technical requirements are needed, including parallel alignment of the ultrasound beam with aortic flow and the use of multiple imaging windows (apical, right parasternal, subcostal, and suprasternal). Patients with a mild degree of AS may develop increased velocity and gradient when the transvalvular flow rate is increased, whether because of AR or the development of a hyperdynamic state; however, in this case the valve area will reflect the mild severity. Likewise, patients with severe AS may have lower than expected gradients with significantly depressed EF, severe MR, severe RV dysfunction, severe TR, or intravascular volume depletion; again, in such cases, AV area is very useful to put the gradients in context of the stroke volume.[75]

Aortic valve area is calculated using the continuity equation. The underlying principle is that the amount of blood flow through the LVOT and aortic valve will be the same because they are in continuity.[71] Aortic valve area (in centimeters squared) is given by systolic flow through LVOT/time velocity integral (TVI) of AS signal by CW (LVOT diameter^2 × 0.785 × LVOT TVI/aortic TVI) (Fig. 8.27). The main source of error in this calculation is in the measurement of the LVOT diameter. However, when there is doubt, and in the absence of other significant valvular lesions, it is possible to use systolic flow through the RV outflow tract or diastolic mitral inflow in the numerator. Alternatively, LV stroke volume measured by 2D echocardiography (difference between end-diastolic and end-systolic volumes) may be used, provided adequate 2D images are present.

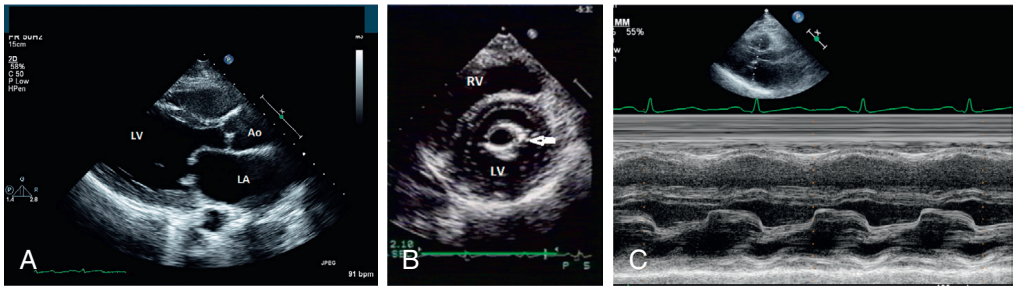
Some patients with severely depressed EF have only mildly or modestly elevated transvalvular gradients across the aortic valve, yet significant AS when the valve area is calculated (typically <1 cm^2). It is reasonable to proceed to low-dose (up to 20 μg/kg per minute) dobutamine echocardiography in these patients to assess not only LV contractile reserve but also the effect of increased transvalvular flow on the calculated aortic valve area.[73] Patients with a dobutamine-induced increase in aortic valve area (>1 cm^2) are unlikely to have real AS, but their reduced valve area is largely the result of reduced flow rate. On the other hand, when there is an increase in gradient but still a severely reduced aortic valve area, valvular surgery should be considered because LV function and clinical status are likely to improve after valve replacement.[74,75]

Evaluation of Mitral Stenosis

In patients with rheumatic mitral stenosis, 2D imaging shows the presence of valvular thickening and calcification along with abnormal leaflet mobility, such that there is doming of the anterior mitral leaflet along with reduced mobility of the posterior leaflet. Doming



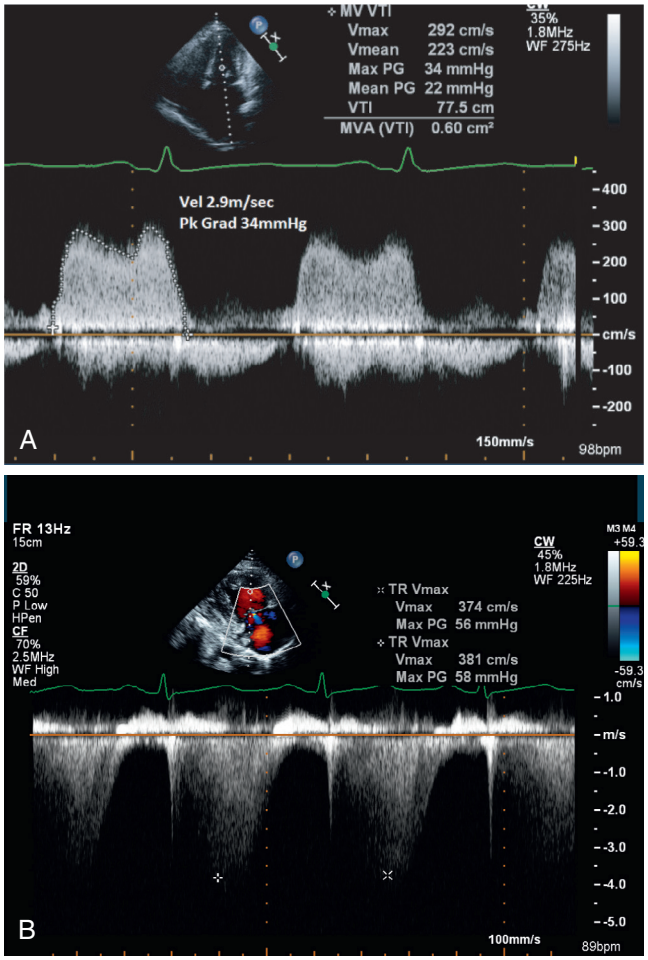
• **Fig. 8.27** Assessment of aortic stenosis using the continuity equation. *Ao,* Aorta; *AVA,* aortic valve area; *LVOT,* left ventricular outflow tract diameter; *TVI,* time velocity integral; *Vel,* velocity.



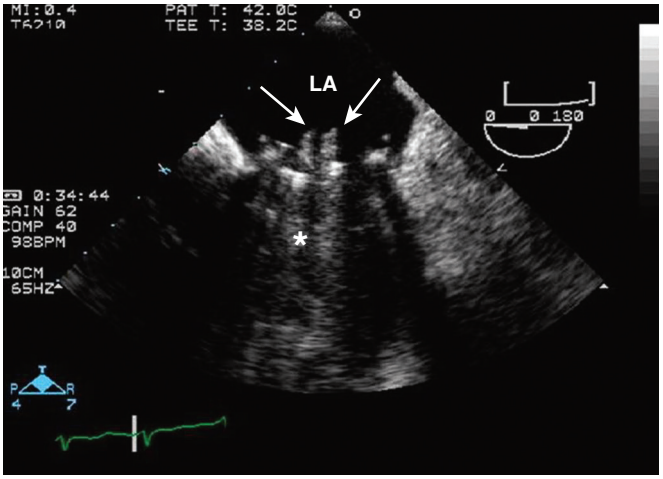
• **Fig. 8.28** Long-axis view *(left)* of mitral stenosis demonstrating typical "hockey-stick" appearance of mitral valve. Short-axis view *(center)* demonstrating mitral orifice *(arrow)* in the ideal placement for tracing valve area. Typical M-mode *(right)* of mitral stenosis. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

of leaflets occurs as a result of commissural fusion and produces the typical "hockey-stick" appearance of the valve when viewed in the parasternal long-axis and apical views (Fig. 8.28). Variable degrees of calcification, thickening, and subvalvular disease may be present. Direct planimetry of the mitral valve area is feasible in cases in which the mitral valve orifice is well visualized in the parasternal short-axis view. However, this measurement can be inaccurate when there is extensive calcification of valve leaflets, and when the short-axis plane is not positioned correctly at the level of valve tips. Spectral Doppler can provide reliable peak and mean transmitral pressure gradients and mitral valve area in most patients with mitral stenosis, as well as determining the hemodynamic impact on the right side of the heart with the development of pulmonary hypertension (Fig. 8.29). Doppler-derived gradients have been shown to have excellent reproducibility and accuracy when compared to the simultaneously obtained LA-LV pressure gradient by cardiac catheterization. However, the transmitral pressure gradient is dependent on many variables other than the valve area. Therefore the mean gradient can be increased with high transvalvular flow (whether because of a hyperdynamic flow state or MR), or short RR interval, even though mitral stenosis is only of a mild degree.

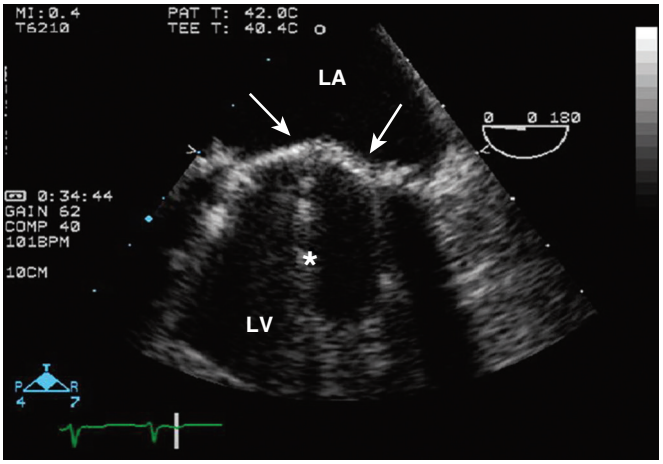
Mitral valve area is most easily calculated by Doppler, using the pressure half-time method. This method was originally conceived in the cardiac catheterization laboratory.[76] The severity of the stenosis is judged based on the time needed for the transmitral pressure gradient to decrease by 50% from its initial value in early diastole. This time increases with the severity of the stenosis, and mitral



• **Fig. 8.29** A, Continuous wave Doppler across stenotic mitral valve, demonstrating peak/mean gradients of 34/22 and a valve area of 0.6 cm^2. B, Continuous wave Doppler of tricuspid regurgitation in same patient demonstrating gradient of 56 mm Hg, c/w elevation of pulmonary pressures.



• **Fig. 8.30** Transesophageal echocardiography of open mechanical mitral valve *(arrows)*, demonstrating prosthetic artifact *(asterisk). LA,* Left atrium.



• **Fig. 8.31** Transesophageal echocardiography of mechanical mitral valve when closed *(arrows)* demonstrating artifact *(asterisk). LA,* Left atrium; *LV,* left ventricle.

valve area (in centimeters squared) can be derived as 220/pressure half-time (in milliseconds). Although simple and highly reproducible, its accuracy is limited in patients with abnormal LA or LV compliance and in those with significant AR.[77] The continuity equation is an additional method that is applicable in cases without significant AR and MR. In this method, the mitral valve area is calculated by systolic flow through the LVOT/TVI of the mitral stenosis jet by CW.

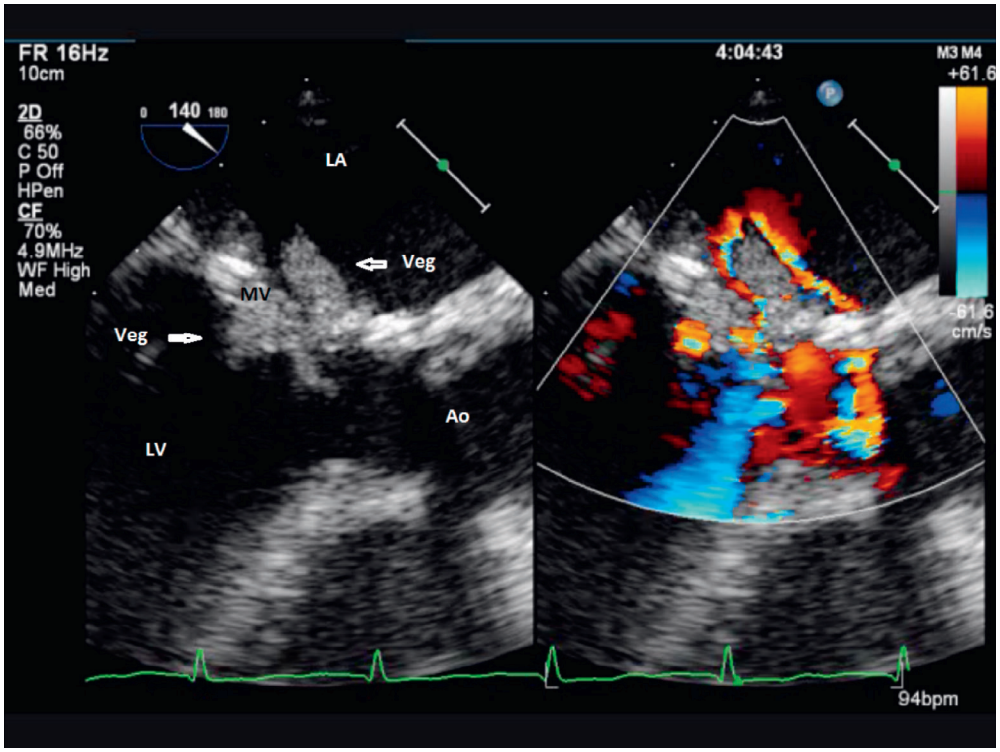
Evaluation of Prosthetic Valves

Echocardiography is the test of choice to assess prosthetic valve function.[78–80] From transthoracic windows, it is possible to identify the type of prosthetic valve, whether tissue or mechanical, the latter producing significant prosthetic echo artifact (Figs. 8.30 and 8.31). In some cases, large vegetations (Fig. 8.32) or thrombi may be visualized. However, in many situations of suspected prosthetic valve disease, TEE is needed because TTE images, especially with mechanical valves, can be obscured by echo artifact. Reliable recording of transvalvular gradients is possible by Doppler in almost all cases, provided the ultrasound beam is parallel to the direction of flow. Prosthetic valve gradients should be interpreted with the knowledge of the valve type, size, and position, as values vary depending on these variables (Table 8.5). Furthermore, consideration should be given to stroke volume/ventricular function/heart rate when conclusions are drawn about prosthetic valve function. It is very useful to compare Doppler-derived gradients to previous results (taking into consideration both flow and heart rates) in detecting

TABLE 8.5 Normal Doppler Values in Patients With Prosthetic Valves

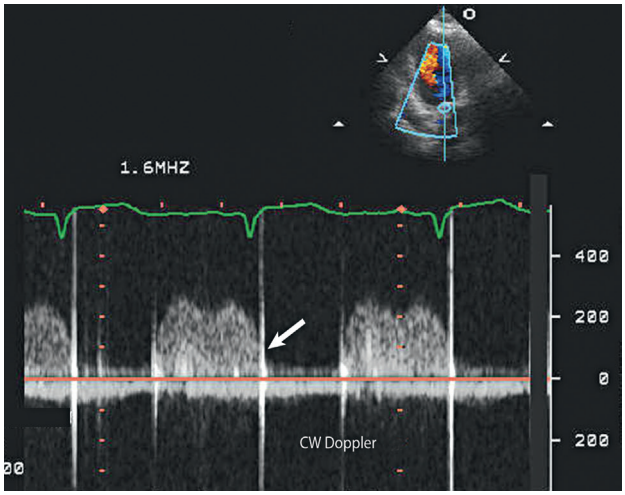
Valve Type	Peak Velocity	Mean Gradient	Doppler Velocity Index
Aortic	≤3 m/s[a]	≤25 mm Hg[a]	≥0.30
Mitral	<1.9 m/s[b]	≤5 mm Hg[b]	
Tricuspid	<1.5 m/s[b]	≤3 mm Hg[b]	
Pulmonary	≤3 m/s[a]	≤25 mm Hg[a]	≥0.30

[a]Assuming normal stroke volume/ventricular function.
[b]Assuming normal heart rate (50–70 beats/min).



• **Fig. 8.32** Transesophageal echocardiography image of a bioprosthetic mitral valve with multiple large vegetations (*arrows* in left panel). *Right,* significant incompetence by color Doppler through and around the valve apparatus. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *MV,* mitral valve; *Veg,* vegetations.

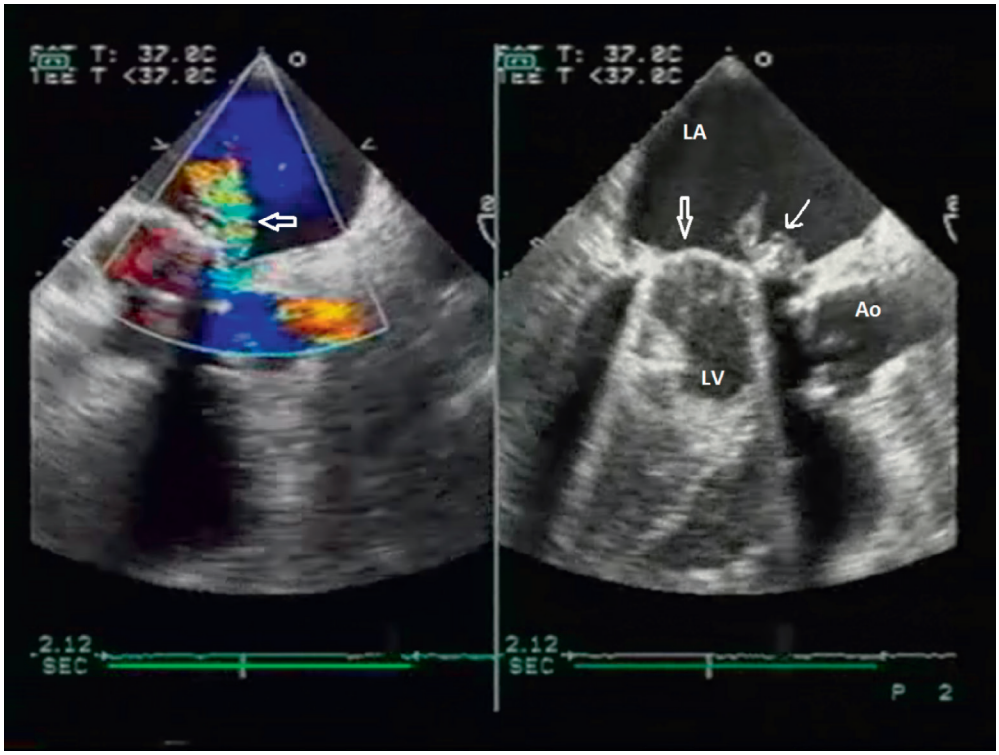
possible changes in prosthetic valve function over time. For prosthetic aortic valves, the Doppler velocity index is calculated as peak velocity in LVOT/peak velocity across the valve by CW Doppler. Patients with normal function have a ratio that is 0.25 or greater. This ratio is particularly helpful in patients with increased transvalvular flow rate leading to increased mean gradient, as they will also have an increased flow velocity in the LVOT and therefore a normal Doppler velocity index.[81] Prosthetic mitral valves are best assessed by mean gradient, taking into account heart rate, as the faster the heart rate, the higher the gradient. In general, a mean prosthetic mitral gradient at a heart rate of 60 to 70 beats/min should be less than 5 mm Hg in a normally functioning mitral prosthesis (Fig. 8.33). When there is doubt about structural or functional abnormalities of prosthetic valves, TEE should be considered. Complications of prosthetic valve endocarditis such as abscess are readily assessed by TEE (Fig. 8.34). A pannus or thrombus may result in reduced or absent leaflet motion and prosthetic valve stenosis. Depending on the thrombus burden and the clinical status of a given patient, TTE and TEE may be used to guide and follow the response to intravenous thrombolytic therapy. Although the severity and cause of prosthetic valve regurgitation may not be easily determined by TTE because of acoustic shadowing, TEE is extremely useful in evaluating the degree of regurgitation and in identifying the site of origin and direction of perivalvular leaks. Unlike prosthetic mitral valves, adequate visualization and Doppler interrogation of mechanical prosthetic aortic valves can be challenging by TEE. Therefore if doubt remains, one should consider biplane fluoroscopy to assess the mobility of aortic valve discs. Normal Doppler values for prosthetic valves in the aortic, mitral, tricuspid, and pulmonary positions are shown in Table 8.5.



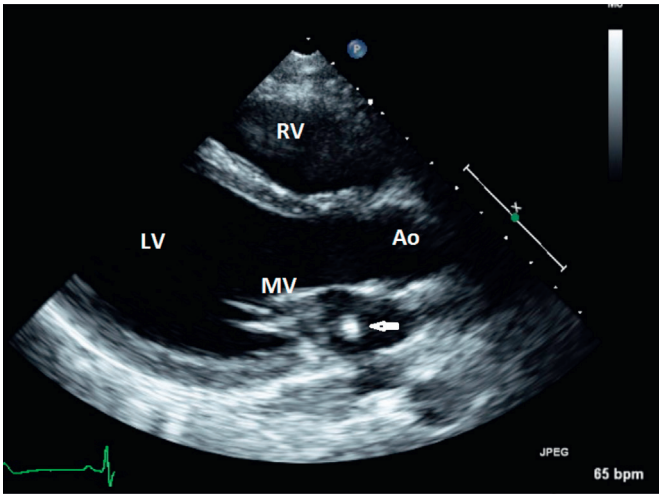
• **Fig. 8.33** Continuous wave Doppler image of an obstructed mechanical mitral valve prosthesis. Peak velocity 2.5 m/sec; time velocity integral, 80 cm; mean gradient, 18 mm Hg; heart rate, 93 beats/min. The *arrow* indicates mitral closing click.

Infective Endocarditis

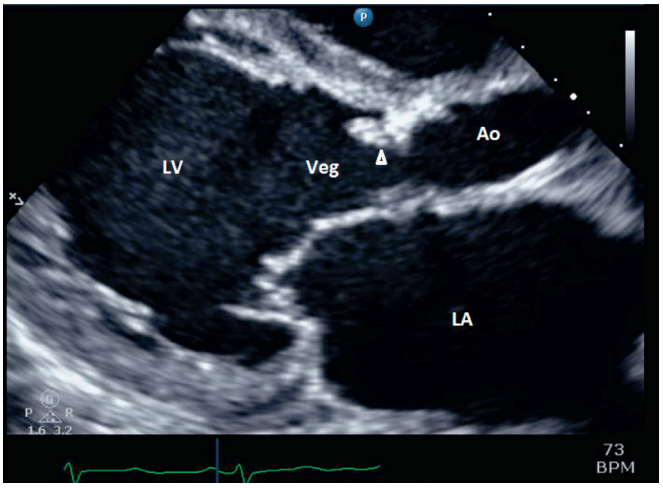
Echocardiography is particularly well suited to the evaluation of IE and is the technique of choice for the diagnosis and subsequent monitoring and management of patients with IE. Echocardiography should be used to (1) visualize the location, size, and morphology and motion of vegetations (Figs. 8.35 through 8.37); (2) define the structural integrity of the infected valve and identify any coincidental valve disease; (3) define ventricular size and function;



• **Fig. 8.34** Mechanical mitral prosthesis (*solid arrow* on right) with large prolapsing vegetation *(arrows)*. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.



• **Fig. 8.35** Long-axis view of large prolapsing mitral valve vegetation *(arrow). Ao,* Aorta; *LV,* left ventricle; *MV,* mitral valve; *RV,* right ventricle.



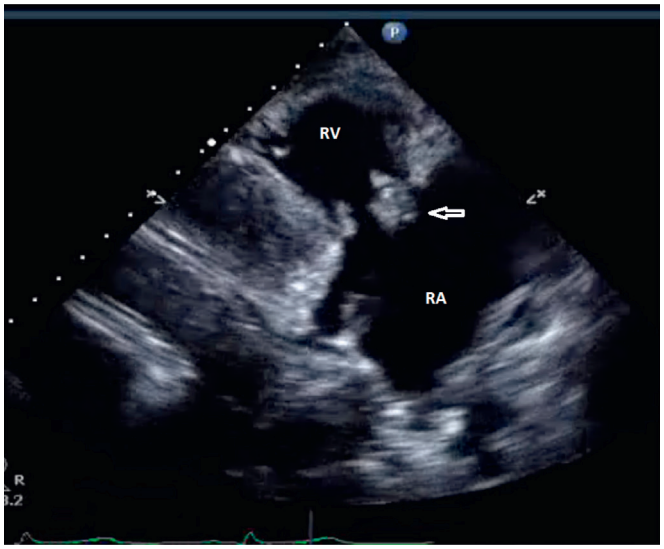
• **Fig. 8.36** Long-axis view of aortic valve vegetation *(arrowhead). Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *Veg,* vegetation.

(4) determine any extension of the infectious process, including abscesses, pseudoaneurysms, leaflet perforation, and pericardial effusion; and (5) offer prognostic information. TEE may be performed when the index for IE is high but TTE is negative and should be performed in the setting of known aortic endocarditis to assess for root abscess and extension of the infectious process to surrounding tissue. Persisting or worsening heart failure, persistent uncontrolled infection despite appropriate antibiotics, and multiple embolizations despite antibiotic therapy are indications for surgery in the active phase of the disease (Videos 8.45 through 8.48).[82]

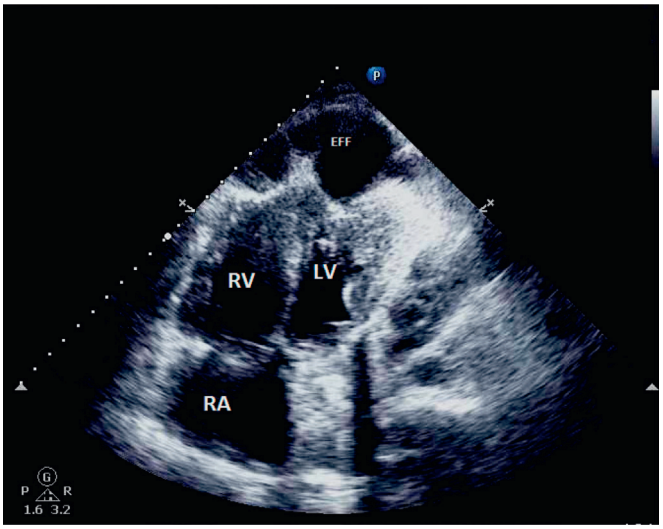
Pericardial Disease

The detection of pericardial effusion generated much of the early interest in ultrasound as a useful cardiac diagnostic tool.[83] Today, echocardiography is routinely used to diagnose and manage pericardial disease. Pericardial effusion, tamponade, and, to a lesser extent, pericardial constriction, can be readily and reliably assessed with echocardiography.

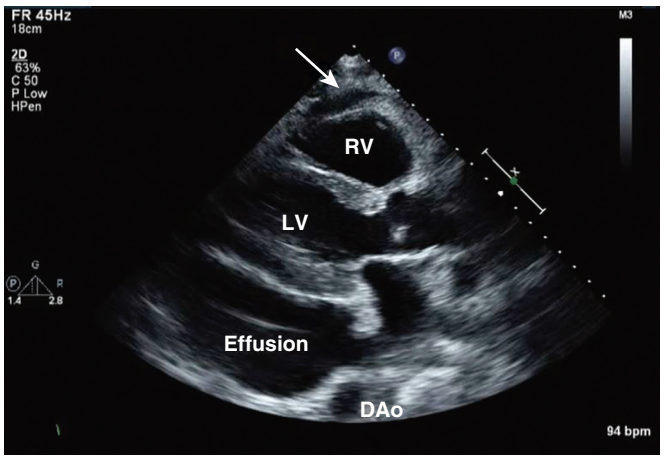
Echocardiographic findings of pericardial effusion include an echo-free space adjacent to the heart in the absence of pericardial



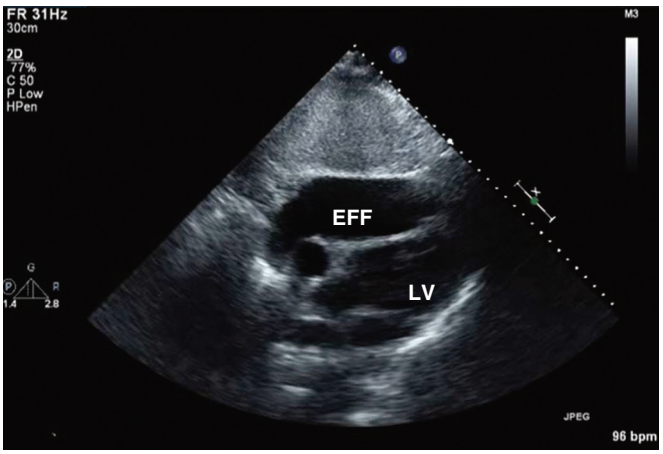
• **Fig. 8.37** Right ventricular inflow view demonstrating large tricuspid valve vegetation *(arrow). RA,* Right atrium; *RV,* right ventricle.



• **Fig. 8.39** Apical four-chamber view demonstrating unusual compression of both ventricular apices by loculated pericardial fluid *(EFF). LV,* Left ventricle; *RA,* right atrium; *RV,* right ventricle.



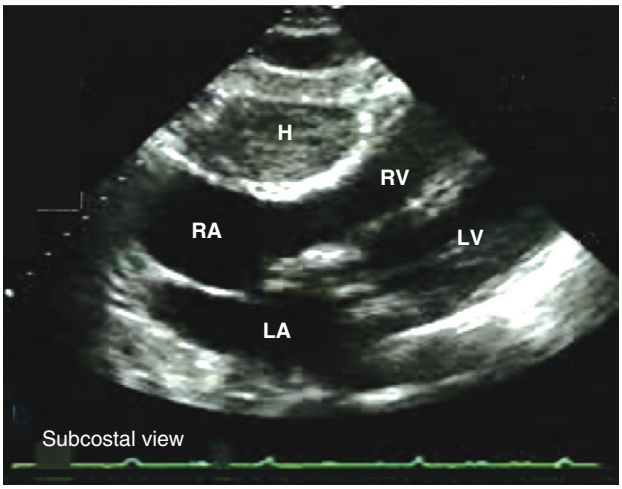
• **Fig. 8.38** Long-axis view of large postoperative loculated posterior effusion. *DAo,* Descending aorta; *LV,* left ventricle; *RV,* right ventricle.



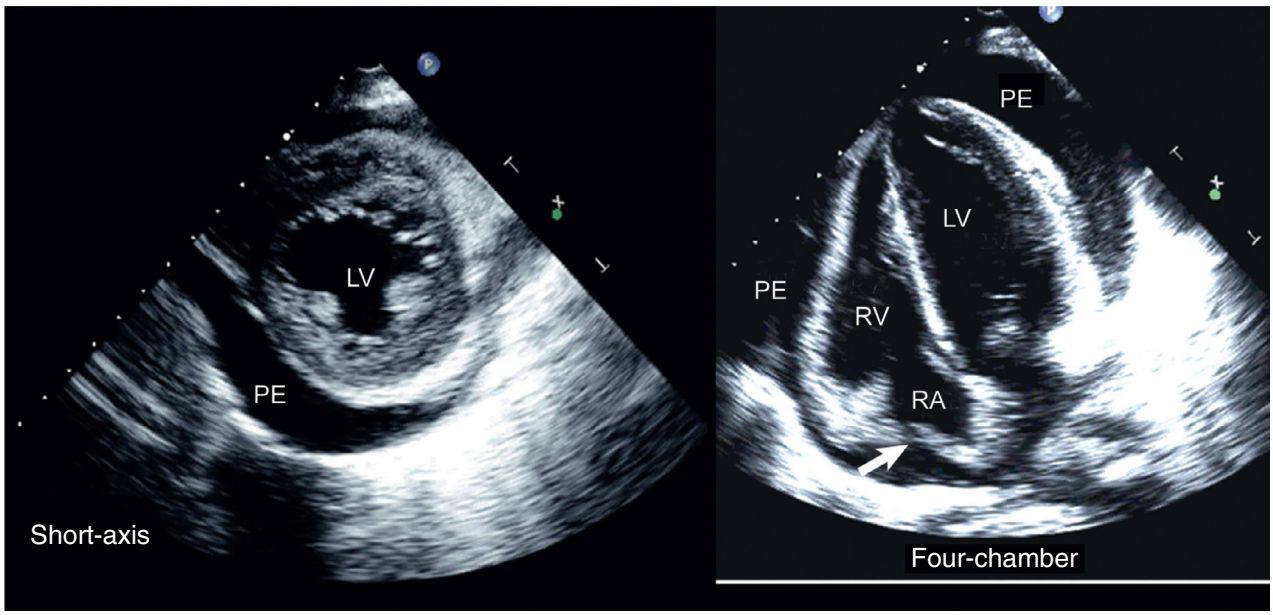
• **Fig. 8.40** Subcostal view of inferoposterior pericardial effusion *(EFF).* The right ventricle is slit-like. *LV,* Left ventricle.

motion (Fig. 8.38). Effusions are termed small, moderate, and large (Fig. 8.39) based on the visually estimated volume of fluid and its location (posterior only or circumferential). The subcostal view is particularly useful for identifying pericardial effusions (Fig. 8.40). Large effusions may occasionally result in "swinging" of the heart within the pericardial space, a phenomenon that correlates with the electrical alternans noted on the ECG.[84] Loculated pericardial effusions are seen in patients after cardiac surgery and in patients who sustain chest trauma. In these circumstances, the effusion is localized to a single area of the pericardial space. It is important to note that rapid development of a small volume of fluid in a critical location may quickly result in hemodynamic compromise. Localized hematoma in patients after cardiac surgery, percutaneous intervention, electrophysiology study, or trauma can create a compressive effect that compromises cardiac hemodynamics (Fig. 8.41).

Pericardial tamponade occurs when, in the presence of fluid accumulating in the pericardial space, the pressure in the pericardium exceeds the pressure in the cardiac chambers, resulting in impaired

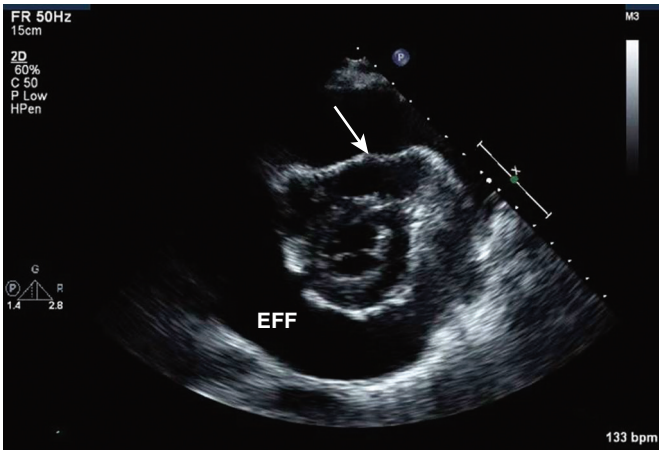


• **Fig. 8.41** Subcostal view of intrapericardial hematoma *(H). LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.



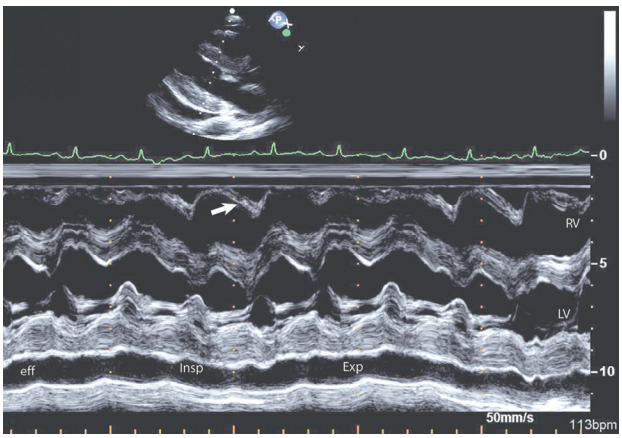
• **Fig. 8.42** Left ventricle short-axis view (A) of large circumferential pericardial effusion *(PE).* Apical four-chamber view (B) demonstrating right atrial collapse *(arrow)* and circumferential effusion. *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

filling and reduction of stroke volume and cardiac output, eventuating tachycardia, hypotension, and jugular venous distention.[85] The physiologic consequences depend on the amount of fluid, the rate of accumulation, the distensibility of the pericardium, and the compliance of cardiac chambers.[85] Tamponade may result from accumulation of fluid, pus, blood, clots, or gas within the pericardium. There are several echocardiographic features of pericardial tamponade. Pericardial effusion, usually at least moderate in volume, must be present (unless acute as described earlier). As the pressure within the pericardium increases, cardiac chamber collapse will ensue.[86] Impairment of filling is sequential: the atria will collapse before the higher-pressure ventricles.[86] The compressive effect of fluid is seen when the pressure is lowest in the chamber; RA collapse begins in late ventricular diastole (before or at the P wave) and should persist through at least one-third of ventricular systole (Fig. 8.42). RA collapse occurs early in the course of tamponade but is a less specific marker than collapse of the right ventricle because the thin-walled right atrium can invert in the absence of tamponade when there is intravascular volume depletion. RV collapse occurs in early diastole.[86] This finding will manifest later in the continuum but is more specific for significant hemodynamic compromise.[86] RV collapse is best appreciated when the ultrasound beam is perpendicular to the RV outflow tract from subcostal or parasternal views (Fig. 8.43). Timing of the onset and duration of RV collapse can be appreciated with M-mode (Fig. 8.44). Right-sided chamber collapse may be absent when tamponade occurs in the setting of severely elevated right-sided filling pressures (pulmonary hypertension).[85] When the effusion is loculated behind the left ventricle in the setting of reduced LV volumes, as might be seen in postoperative patients, diastolic collapse of the LV may be the only indicator of hemodynamic compromise. A dilated IVC that does not change dimension with respiration is also consistent with elevated intrapericardial pressures (Fig. 8.45), although this finding is nonspecific in intubated patients owing to positive intrathoracic pressures.

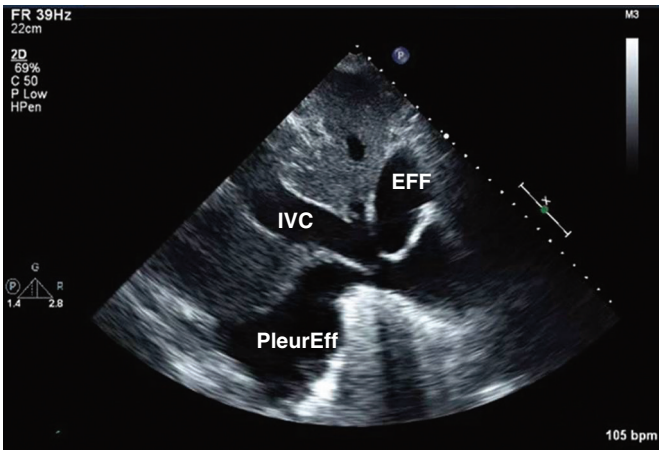


• **Fig. 8.43** Short-axis view of the left ventricle demonstrating large circumferential effusion with right ventricular collapse *(arrow). EFF,* Effusion.

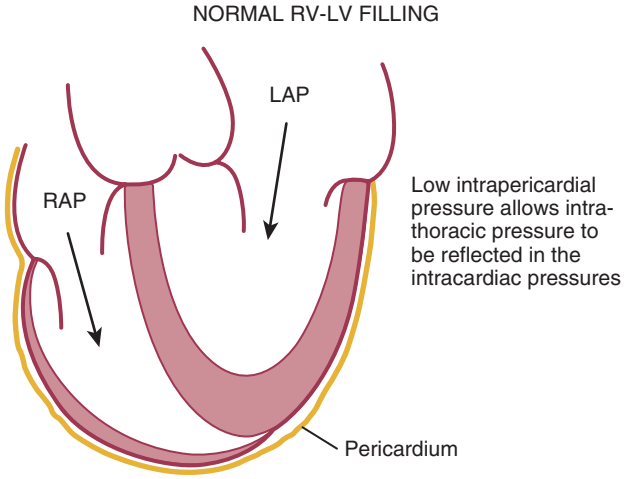
Reciprocal respiratory changes in RV and LV volumes become evident in tamponade, and increased right heart filling occurs at the expense of left heart filling in a process mediated by the pericardium. RV volume increases with inspiration, shifting the septum toward the left ventricle in diastole and toward the right ventricle in systole. RV volume decreases with expiration, normalizing septal motion as LV filling increases (Figs. 8.46 to 8.48). These findings correspond to the clinical finding of pulsus paradoxus. Transvalvular Doppler flow velocities demonstrate respirophasic changes in tamponade as well.[87] Initial transmitral velocities are enhanced with expiration and diminished (>25%) with inspiration in tamponade; transtricuspid flow augments with inspiration and diminishes with expiration (Figs. 8.49 and 8.50). Correspondingly, the RV outflow TVI increases with inspiration while the LV outflow TVI decreases. These are useful findings but can be difficult to demonstrate with precision in the acutely ill patient.



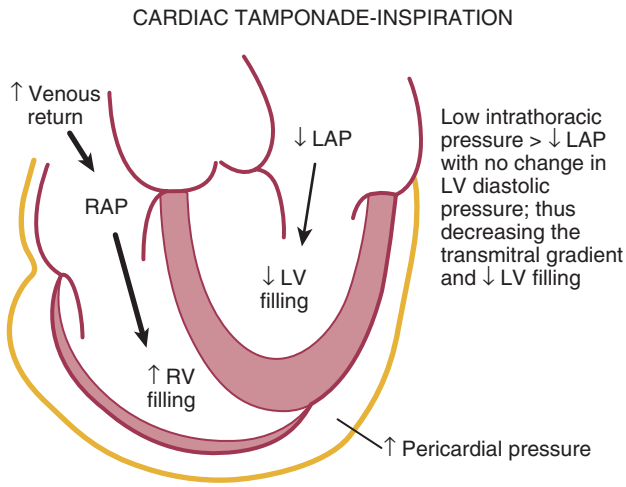
• **Fig. 8.44** M-mode through the left/right ventricles in pericardial tamponade demonstrating right ventricular diastolic collapse *(arrow).* Note that the right ventricle fills at the expense of the left ventricle. *eff,* effusion; *Exp,* expiration; *Insp,* inspiration; *LV,* left ventricle; *RV,* right ventricle.



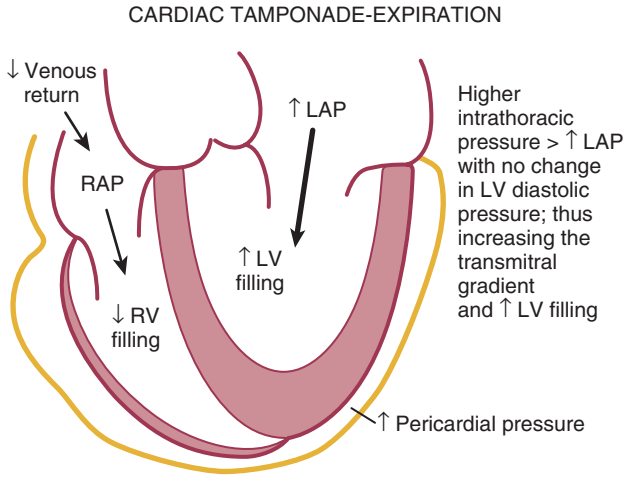
• **Fig. 8.45** Subcostal view of inferior vena cava *(IVC)* plethora in tamponade. *EFF,* Pericardial effusion; *PleurEff,* pleural effusion.



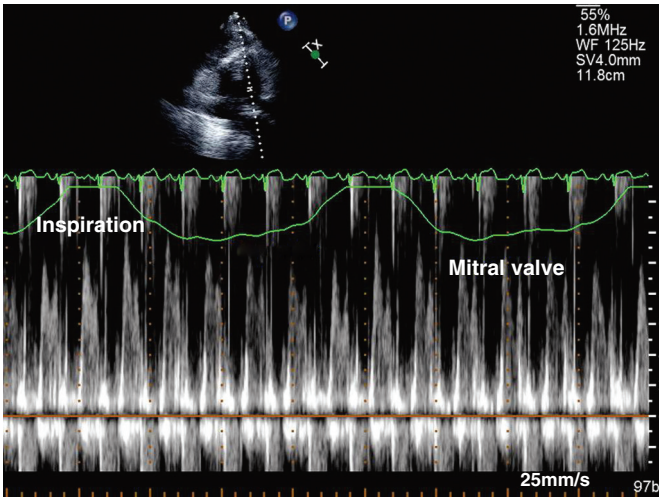
• **Fig. 8.46** Diagram of normal ventricular filling. *LAP,* Left atrial pressure; *LV,* left ventricle; *RAP,* right atrial pressure; *RV,* right ventricle. (Courtesy Miguel Quinones, MD, Houston Methodist DeBakey Heart and Vascular Center.)



• **Fig. 8.47** Alterations in left ventricular and right ventricular filling with inspiration in pericardial tamponade. *LAP,* Left atrial pressure; *LV,* left ventricle; *RAP,* right atrial pressure; *RV,* right ventricle. (Courtesy Miguel Quinones, MD, Houston Methodist DeBakey Heart and Vascular Center).



• **Fig. 8.48** Ventricular filling pattern in cardiac tamponade during expiration. *LAP,* Left atrial pressure; *LV,* left ventricle; *RAP,* right atrial pressure; *RV,* right ventricle. (Courtesy of Miguel Quinones, MD, Houston Methodist DeBakey Heart and Vascular Center.)



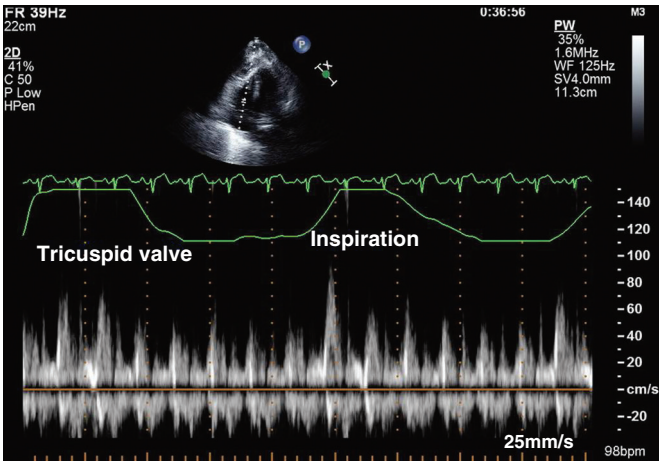
• **Fig. 8.49** Doppler inflow of mitral valve in tamponade. Note respirometer.

Echocardiography has been used to guide the percutaneous drainage of pericardial fluid.[88] Subcostal imaging is valuable in demonstrating the amount of inferior fluid in the typical location accessed by the subxiphoid needle approach, as well as determining the optimal site of puncture. Imaging from the cardiac apex in patients with large circumferential effusions can aid in determining needle position and guide advancement, although identifying the needle tip can occasionally be problematic. Once needle position is deemed appropriate and initial aspirate is obtained, an injection of a small amount of agitated saline solution confirms correct needle position within the pericardium[88] (Fig. 8.51).

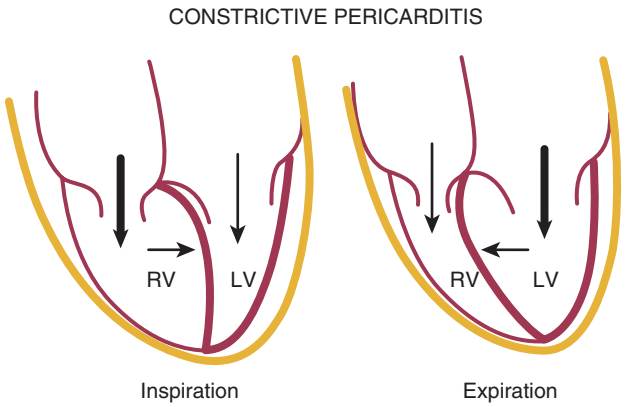
Constrictive physiology is present when the visceral and parietal layers of the pericardium become adherent and fibrotic, resulting in marked impairment of LV filling. Chronic constrictive pericarditis is usually not associated with free pericardial fluid. The echocardiographic findings in constriction include a thickened pericardium (pericardial thickening may not be uniform); normal LV size with LA dilatation; abrupt termination of ventricular filling in early diastole (best seen on M-mode); respiratory-related interventricular septal motion demonstrating a diastolic inward "bounce" in early diastole; and dilatation of the IVC. In addition, there is Doppler flow evidence of ventricular interaction with exaggerated respirophasic changes in transvalvular velocities (Figs. 8.46 to 8.48, 8.52, and 8.53). TDI is of significant value in the assessment of pericardial constriction. Typically lateral tissue Doppler velocities are higher than medial velocities. In constrictive physiology, the medial mitral annular velocities are greater than the lateral velocities because lateral expansion in CP is limited; this is a phenomenon known as "annulus reversus."[89] These observations are also valuable in distinguishing pericardial constraint from myocardial restraint; in restrictive physiology, both medial and lateral tissue Doppler velocities are less than or equal to 8 cm/sec (Videos 8.49 through 8.71).[89,90]

Aortic Disease

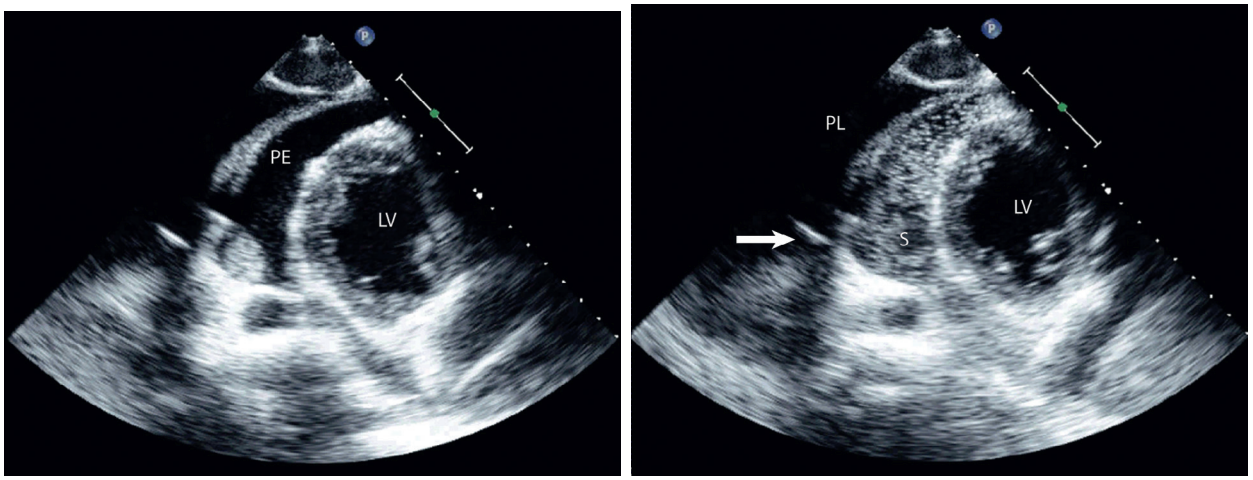
Although TEE is the preferred echocardiographic method for evaluating the aorta, transthoracic imaging can define aneurysmal



• **Fig. 8.50** Doppler inflow of tricuspid valve in tamponade. Note respirometer.

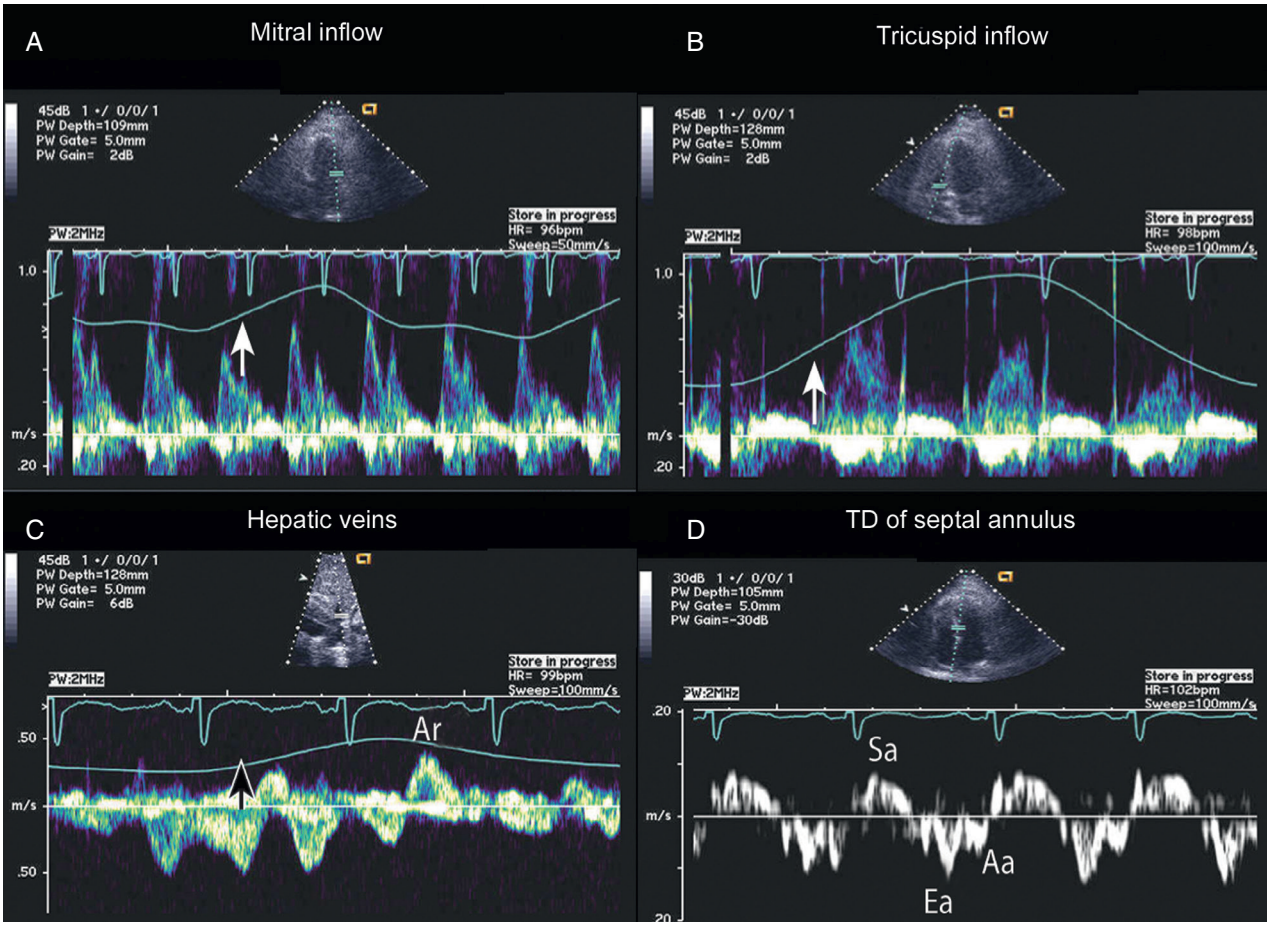


• **Fig. 8.52** Ventricular interdependence in constrictive pericarditis. *LV,* left ventricle; *RV,* right ventricle. (Courtesy Miguel Quinones, MD, Houston Methodist DeBakey Heart and Vascular Center.)

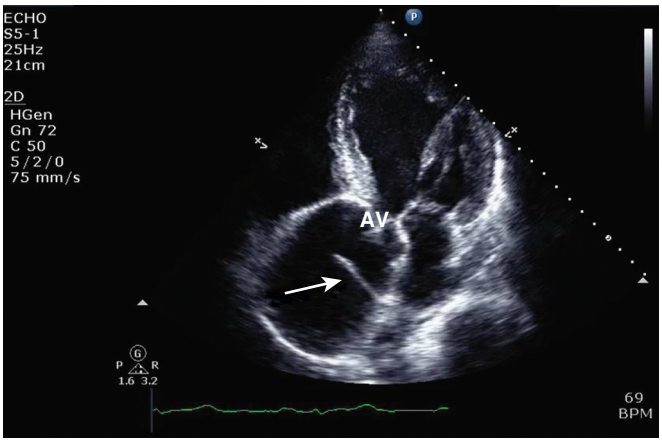


A B

• **Fig. 8.51** A, Pericardial effusion seen during pericardiocentesis before injection of saline solution, and B, after injection of saline solution to confirm correct needle location *(arrow)* within the pericardial space. *LV,* Left ventricle; *P,* pericardial effusion; *PL,* pleural space; *S,* saline solution.



• **Fig. 8.53** Doppler patterns in constrictive pericarditis. A, Respiratory variation *(arrow: inspiration)* in mitral inflow. B, Tricuspid inflow variability *(arrow: inspiration)*. C, Increase in diastolic hepatic flow reversal after expiration *(Ar)*. D, Tissue Doppler *(TD)* of septal annulus; early diastolic tissue velocity *(Ea)* 10 cm/sec, consistent with pericardial constriction. *Aa,* Late diastolic tissue velocity; *Sa,* systolic velocity.

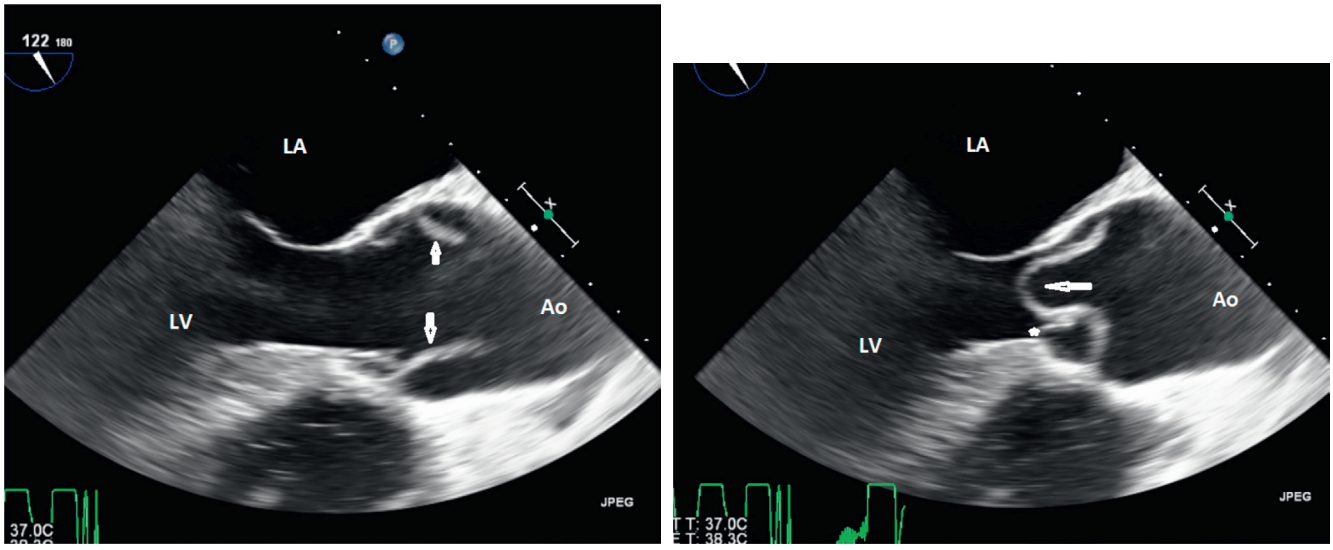


• **Fig. 8.54** Transthoracic two-dimensional image from the apex demonstrating proximal aortic dissection flap *(arrow). AV,* Aortic valve.

changes of the proximal ascending aorta and can occasionally identify an intimal flap from aortic dissection (Fig. 8.54) (Videos 8.72 through 8.74), either from the parasternal views or from the suprasternal notch. In addition, in the setting of proximal dissection, TTE can evaluate the integrity of the aortic valve and quantify the degree of AR, recognize any LV wall motion abnormalities, and identify any associated pericardial effusion. It is important to note that, as seen in aortic aneurysms, patients with dissection very often have significant aortic dilation; thus lack of aortic dilation may argue against dissection. However, overall, the sensitivity of TTE for the diagnosis of dissection in the aortic arch and descending aorta is low, and TEE (and/or computed tomography) is often indicated. The close proximity of the esophagus to the aorta makes TEE a preferred modality for the evaluation of aortic dissection, with both sensitivity and specificity of 98%.[91–94] The ascending aorta, aortic arch, and descending thoracic aorta can be visualized with excellent resolution. TEE can be performed rapidly and safely at the bedside. Common features of dissection on TEE imaging include the following:

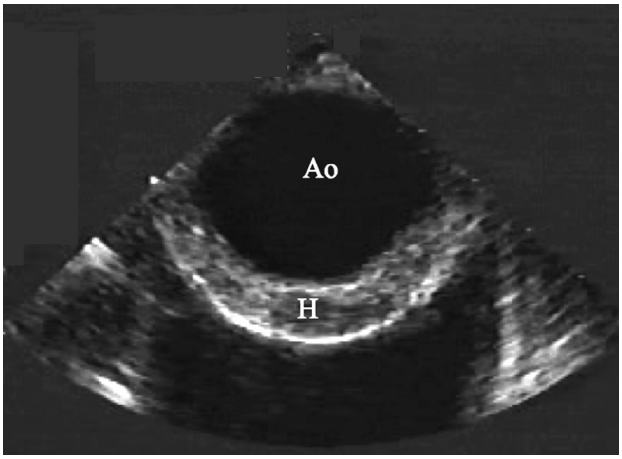
- An intimal flap that moves toward the false lumen in systole (Fig. 8.55)
- Color Doppler flow in both the true and the false lumens
- Color flow identification of entry/exit sites
- Stasis or thrombosis within the false lumen
- Intramural hematoma (IMH)

IMH, originally described as bleeding into the outer layers of the aortic media owing to rupture of the vaso vasorum without a primary tear, appears as crescentic thickening of the aortic wall greater than 0.7 cm in the absence of a frank dissection flap

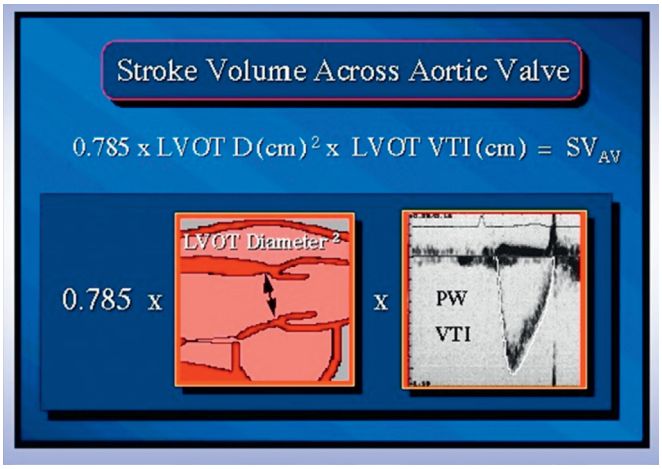


A B

• **Fig. 8.55** Transesophageal image of proximal dissection flap *(arrow)* in systole (A) and as it prolapses into the LV outflow tract *(arrow)* in diastole (B). The asterisk identifies aortic valve leaflets. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.



• **Fig. 8.56** Transesophageal image of intramural hematoma *(H). Ao,* Aorta.



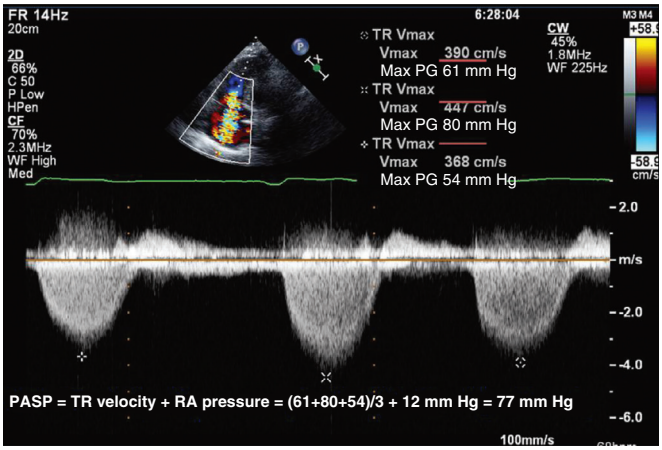
• **Fig. 8.57** Method for stroke volume *(SV)* calculation using aortic annulus and aortic time velocity integral *(TVI). D,* diameter; *LVOT,* left ventricular outflow tract; *PW*, pulsed wave Doppler; *SVAV,* stroke volume aortic valve. (Courtesy Mark Harry, RDCS.)

(Fig. 8.56).[95] Considered a variant of overt aortic dissection, IMH is an important diagnosis to make, as data suggest IMH is a lethal condition when it involves the ascending aorta, and 16% of patients with IMH have evidence of evolution to classic aortic dissection on serial imaging.[95]

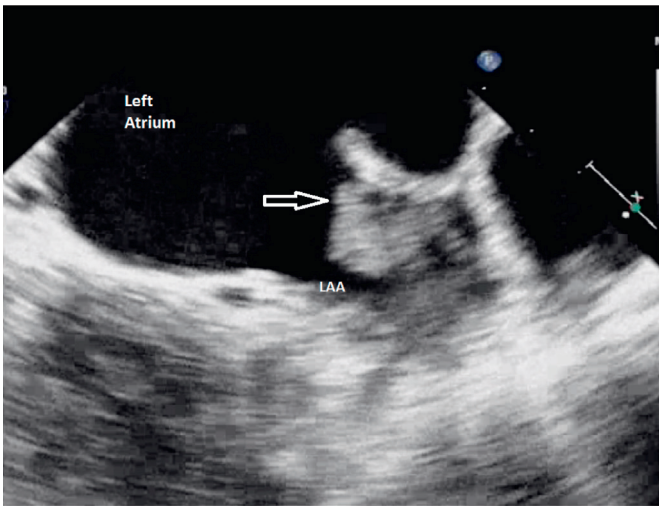
Hemodynamic Assessment

It is possible to calculate blood flow at several levels in the heart and aorta using Doppler echocardiography.[96] Such measurements of flow can be very useful in the ICU setting to derive LV stroke volume, cardiac output, regurgitant volumes, and the response to therapeutic measures such as intravenous administration of inotropic drugs or the effect of an intraaortic balloon pump on systemic output. Stroke volume in milliliters (or cubic centimeters) is calculated as the product of the cross-sectional area (in centimeters squared) of the LVOT and the TVI (in centimeters) by PW Doppler (Fig. 8.57) at this site.[96,96a] Cardiac output can then be calculated as the product of stroke volume and heart rate. A number of studies have shown good accuracy of Doppler echocardiography when compared with measurements derived by thermodilution, including data obtained from patients in the ICU. Doppler-derived stroke volume can provide important clues in situations of reduced output (whether caused by volume depletion or LV systolic dysfunction) as well as cases of high-output states such as sepsis and liver failure.

Peak PA systolic pressure is calculated from the peak Doppler velocity (v) of TR by CW (Fig. 8.58). Using the modified Bernoulli equation, the peak systolic gradient (ΔP) in millimeters of mercury between the right ventricle and the right atrium is given by $4v^2$ (where v is in meters per second). An estimate of RA pressure is then added to ΔP to estimate peak RV systolic pressure, and in the absence of pulmonary stenosis, peak PA systolic pressure.[97] RA pressure can be estimated from the change in IVC diameter with spontaneous breathing, as recorded from subcostal views. Normal collapse of the IVC with breathing (>50%) implies normal RA pressure (0–5 mm Hg); partial collapse (<50%) is generally estimated at 5 to 10 mm Hg, whereas no (or only minimal) change



• **Fig. 8.58** Method for calculation of right ventricular systolic pressure (see text). *PASP,* Pulmonary artery systolic pressure; *RA,* right atrial; *TR,* tricuspid regurgitant velocity.

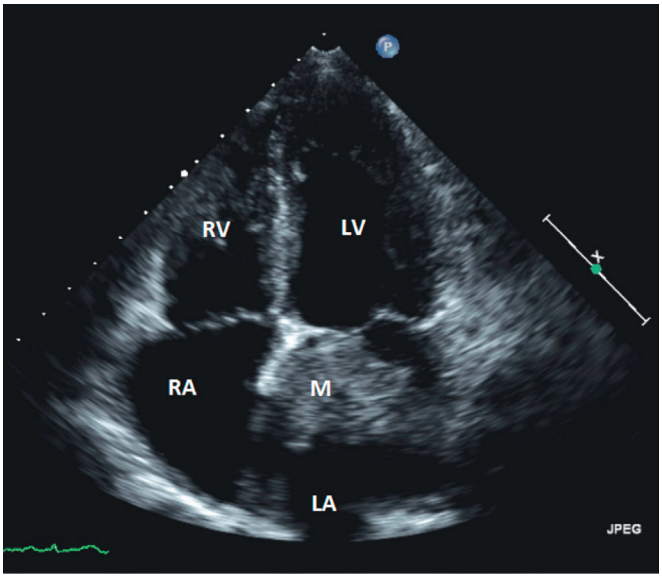


• **Fig. 8.59** Transesophageal image of a thrombus *(arrow)* in the left atrial appendage *(LAA).*

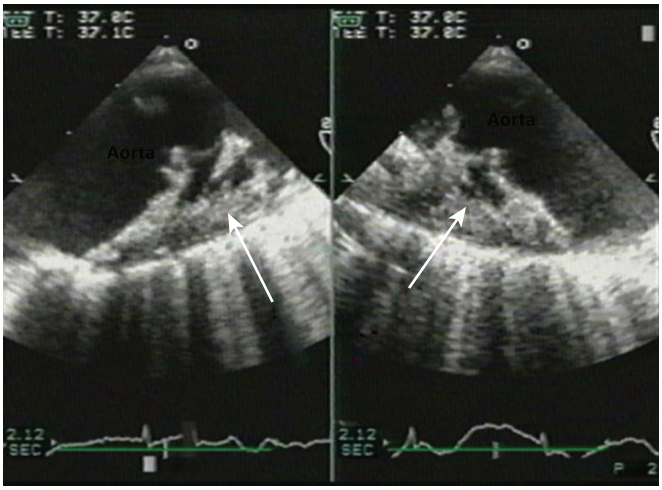
in IVC diameter implies an RA pressure of 15 mm Hg or more. When available, RA pressure should be obtained directly from a central venous pressure tracing.

Stroke and Other Systemic Emboli

Between 17% and 25% of all strokes are cardioembolic in origin.[98] Echocardiography is commonly used to search for potential cardiac sources of arterial emboli, the most common of which are LA appendage thrombus (Fig. 8.59), LA masses (Fig. 8.60, Video 8.75), valvular vegetations, atheromatous disease of the aorta (see Fig. 8.61, Videos 8.76 and 8.77), LV thrombus (see Fig. 8.11), and PFO with/without atrial septal aneurysm (see Fig. 8.3).[98,99] Atrial fibrillation predisposes to thrombus formation in the body of the left atrium and in the LA appendage, and TEE is necessary to assess the entire left atrium and the LA appendage, which is the most common site of thrombus formation in atrial fibrillation.[100,101] A significant association exists between aortic atheroma and stroke.[102] TEE reliably identifies aortic debris and can determine location, morphologic characteristics, and mobility of identified lesions (see Fig. 8.61).[98,102] The most common disorders associated with stroke identified by echocardiography are listed in Box 8.3.



• **Fig. 8.60** Apical four-chamber view of left atrial myxoma *(M). LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle;



• **Fig. 8.61** Transesophageal image of grade 5 atheromatous debris *(arrows).* This was an incidental finding.

• BOX 8.3 Echocardiographic Evaluation of Cardiac Source of Embolus

Intracardiac thrombus
- Ventricular (apex)
- Atrial (body of left atrium, left atrial appendage)
- Prosthetic material (valves, monitoring lines, pacer wires)
- Spontaneous contrast

Valvular vegetations
Patent foramen ovale/atrial septal defect
Atrial septal aneurysm
Intracardiac tumors
- Primary (myxoma, fibroelastoma)
- Metastatic (lung, breast)

Mitral valve prolapse
Mitral annular calcification
Aortic annular calcium
Atheromatous debris of the aorta

Summary

Echocardiography with Doppler is a vital tool in the assessment of patients in critical care. Ventricular function and complications of myocardial infarction can be determined; the presence and significance of pericardial effusion can be assessed; hemodynamically significant valve disease can be quantified; the presence and extent of infective endocarditis can be assessed; fundamental intracardiac hemodynamics can be calculated; cardiac complications of trauma can be noted; potential cardiac causes of stroke can be determined; and the assessment of aortic disease can reliably be accomplished. When TTE does not produce diagnostic images or when pertinent clinical questions remain unanswered, TEE can readily provide additional morphologic and hemodynamic information that can affect patient management and outcome in the critical care setting.

Key Points

- Echocardiography is an invaluable noninvasive tool for the detection of cardiovascular abnormalities in the critical care setting.
- TEE should be used to provide more detailed or more comprehensive information when transthoracic images are inadequate. TEE may be considered for the evaluation of the aorta, for the assessment of native and prosthetic valves, and for the evaluation of intracardiac shunting. Three-dimensional imaging may provide additional structural information.
- Commercially available contrast agents for LVO can now salvage many otherwise uninterpretable transthoracic studies.
- Echocardiography offers a number of reasonably accurate methods to assess global LV systolic properties, including EF using 2D imaging and tissue Doppler imaging. Stroke volume and cardiac output can also be reliably determined in most patients by echo-Doppler.
- Echocardiography now offers numerous methods to determine LV filling pressures with reasonable accuracy. A reliable assessment of LV dimensions and EF, when combined with knowledge of filling pressures, can be used to guide and assess the response to therapeutic measures.
- PA systolic and diastolic pressures can be calculated with confidence in many patients in the critical care setting.
- Mechanical complications of myocardial infarction, including acute MR, ventricular septal defect, pseudoaneurysm formation, and LV thrombus, are readily evaluated with echocardiography.
- Although the echocardiographic assessment of the right ventricle is still challenging because of its complex shape, it is possible to integrate information from multiple views to reach reasonably accurate conclusions regarding RV size and function, particularly in the setting of RV pressure or volume overload, and acute pulmonary embolus.
- Echocardiography is particularly well suited to the evaluation of cardiac valve anatomy, morphology, and motion. The integration of 2D anatomy with spectral and color Doppler methods of quantifying obstructive and regurgitant lesions provides a comprehensive assessment of valvular disease. TEE may be needed to evaluate prosthetic valves and approaches to surgical repair. Three-dimensional imaging offers great insight into the mechanism of valve dysfunction.
- Pericardial effusion can be localized and quantified, and its hemodynamic impact can be assessed, with thoughtful application of imaging and Doppler techniques. In the setting of trauma and the cardiac surgical postoperative state, opportunistic loculated effusions must be identified.

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Review Questions

1. Goal-directed (focused) echocardiography
- **a.** Should provide a comprehensive assessment of both left- and right-sided intracardiac hemodynamics
- **b.** Should determine the morphology and motion of cardiac valves
- **c.** Should provide assessment relevant to the immediate clinical situation
- **d.** Can with confidence determine patients who will benefit from intervention after an acute pulmonary embolus

Answer: c. Goal-directed two-dimensional (2D) imaging (FOCUS) is typically limited to the assessment of biventricular size and function, the presence or absence of pericardial effusion, and to the evaluation of volume status—that is, a study done to provide assessment relevant to the immediate clinical situation. A focused 2D study done by a trained individual with a handheld device has great potential for rapid triage of select patients in the emergency room or the intensive care area.[14–17] It is important to emphasize that unclear or ambiguous findings on handheld examination should be followed by a complete study on a full echocardiographic platform to obtain an accurate and comprehensive diagnosis

2. Takotsubo syndrome (or cardiomyopathy)
- **a.** Only occurs in women older than 50 years of age
- **b.** Will only manifest as an apical "ballooning" appearance on echocardiography and angiography
- **c.** Will demonstrate reversal of wall motion abnormalities, typically within 3 months
- **d.** Will demonstrate increased survival with beta blockade use while in the hospital

Answer: c. In the early experience, it was most commonly found in women older than 50 years of age, occurred after an emotional or physical stressor, and presented with ST-segment elevation and an apical ballooning left ventricular (LV) contraction abnormality. It is now recognized to be more clinically varied, identified in men and younger individuals, and importantly, diverse LV contraction patterns beyond the classic apical ballooning pattern (75%–80%) are now recognized, including midventricular ballooning (10%–20%) and basal segment ballooning (inverted ballooning; uncommon and occurring in only 1%–2%).[52,53] It can present during diagnostic procedures or during hospitalization for acute illness, and recent evidence suggests an association with sepsis. Although no single feature distinguishes Takotsubo syndrome from other conditions with a similar acute presentation, characteristic symptoms include chest pain, ischemic ECG changes with a troponin elevation, and an LV wall motion abnormality in a segment being supplied by a normal coronary artery. *Reversibility* of LV wall motion abnormalities is expected within 3 months. Hemodynamic instability requiring intervention with vasopressor agents or intraaortic balloon pumping occurs in up to 15% of patients, and in-hospital mortality is as high as 5%. The recurrence rate may be as high as 20%. Elevated catecholamine levels may be involved in Takotsubo pathophysiology. Current evidence does not suggest survival benefit with the use of β blockers in the hospital, although 1-year survival showed marginal improvement with the use of angiotensin-converting enzyme inhibitors.[54,55] A registry has been established (the International Takotsubo Registry) to improve diagnosis, treatment, and outcomes.[56]

3. Parameters of right ventricular function that *may* be associated with mortality in patients presenting with acute pulmonary embolus include all but which of the following?
- **a.** Right ventricular/left ventricular end-diastolic diameter ratio
- **b.** The "60/60" sign
- **c.** Normal pulmonary ejection acceleration time
- **d.** Right heart thrombus

Answer: c. Although it is true that as many as 70% of patients with proved pulmonary embolus (PE) have no significant echocardiographic abnormalities, recent data suggest that several parameters of right ventricular (RV) function are associated with mortality in patients presenting with acute PE.[65] These parameters include (1) the ratio of RV to left ventricular (LV) end-diastolic diameter (≥0.9); (2) RV systolic pressure derived from the tricuspid regurgitant jet velocity (≥50 mm Hg); (3) tricuspid annular plane systolic excursion (TAPSE) (<15 mm); and (4) inferior vena cava collapsibility.[64] Another study suggested that (1) the McConnell sign (hypokinesis of the RV free wall with normal contraction of the RV apex); (2) the 60/60 sign, which is the coexistence of a shortened pulmonary ejection acceleration time (AcT) (<60 msec) with midsystolic velocity deceleration ("notch") and a tricuspid regurgitation peak gradient <60 mm Hg; and (3) right heart thrombus were all strongly suggestive of pulmonary embolus.[65] Work by Dahhan et al. found an association of free wall global RV strain and the RV Tei index with mortality.[66,67] They did not find such a relationship between other measures, including TAPSE, RV size, and the RV/LV ratio; in fact, TAPSE, subjective RV dilation, and subjective RV dysfunction were not statistically different between survivors and nonsurvivors.[67] *All* studies agree, however, that there is a paucity of data from large clinical trials defining which echocardiographic parameters are actually useful in risk assessment in acute PE, and whether such parameters are of utility in identifying patients who might benefit from an intervention.

9

General Principles of Mechanical Ventilation

ISMAIL CINEL AND R. PHILLIP DELLINGER

CHAPTER OUTLINE

History

Mechanical Ventilation
- Basic Concepts
- The Ventilator Circuit
- Alarms and Safety
- Automatic Tube Compensation

Indications for Mechanical Ventilation

Mechanical Breath Generation

Ventilator Modes
- Continuous Mandatory Ventilation
- Assist Control Ventilation
- Synchronized Intermittent Mandatory Ventilation
- Stand-Alone Pressure Support Ventilation
- Dual Control Modes

Other Modes of Mechanical Ventilation
- Airway Pressure Release Ventilation
- High-Frequency Oscillatory Ventilation
- Effort-Adapted Modes of Mechanical Ventilation

Positive End-Expiratory Pressure

Monitoring the Ventilated Patient
- Hemodynamics
- Pulse Oximetry
- End-Tidal Capnography
- Transcutaneous Carbon Dioxide Monitoring
- Ventilator Waveforms

Maintaining Support of the Ventilated Patient
- Sedation and Analgesia
- Positioning
- Secretion Clearance
- Early Physical Therapy in Acute Respiratory Failure

Weaning From Mechanical Ventilation

Complications of Mechanical Ventilation
- Hemodynamics
- Ventilator-Induced Lung Injury
- Ventilator-Associated Events
- Gastrointestinal Bleeding
- Venous Thromboembolism

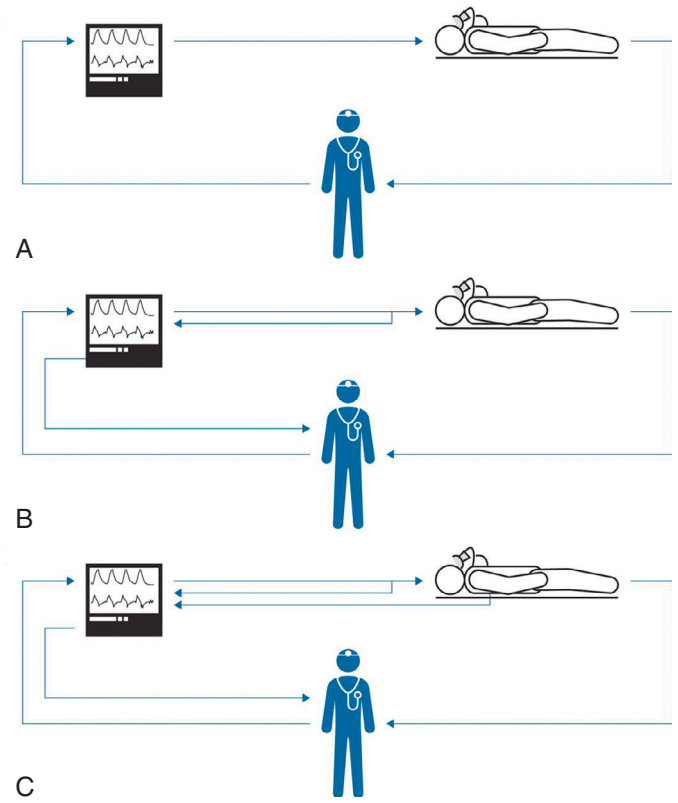
Noninvasive Positive-Pressure Ventilation
- High-Flow Nasal Cannula: A Potential Alternative to Mechanical Ventilation

The institution of mechanical ventilation can be a lifesaving measure. However, the mechanical ventilator also has potential for great harm and, in and of itself, does not reverse underlying disease. Limiting iatrogenic injury from ventilator-induced lung injury (VILI) should take high priority, along with acceptable levels of oxygenation and ventilation. The clinician should be aware of basic and advanced principles involving mechanical ventilation, allowing flexibility when applying evidence-based practices to the individual patient. Knowledge of guidelines and large clinical trials is vitally important, and the consideration of patient trajectory, individual physiology, timing of therapy, and severity of illness will make tailoring the ventilator prescription most effective.[1] The evolution of mechanical ventilation is fascinating (Fig. 9.1) with current newer modes often with complex computer interaction and automatic adjustments of ventilation parameters.[2] This chapter, which briefly discusses those modes, focuses on the traditional and still most frequently used modes of mechanical ventilation.

History

In 1530, Paracelsus (1493–1541) used a fire bellows connected to a tube inserted into a patient's mouth as a ventilator device.[3] The first known mechanical device designed specifically to provide ventilation for the patient was the foot pump developed by Fell and O'Dwyer in the 1880s.[4]

The first generation of mechanical ventilators focused primarily on the intermittent delivery of a bulk volume of gas to the patient with limited monitoring.[5] Negative-pressure ventilators were invented and applied a negative pressure around the body or chest



• **Fig. 9.1** Evolution of the concept of mechanical ventilation. A, The first mechanical ventilators were not equipped with sensors. B, Mechanical ventilators monitor all the ventilation parameters, allowing both closed-loop control of the generated waveform and providing information to the clinicians. C, Mechanical ventilators monitor the condition of the patients and automatically adjust the ventilatory parameters on the basis of patients' needs. (From Dellaca' RL, Veneroni C, Farre R. Trends in mechanical ventilation: are we ventilating our patients in the best possible way? *Breathe (Sheff).* 2017;13:85–98.)

cavity. Two classic devices that provided negative-pressure ventilation were the iron lung and the chest cuirass or chest shell.[6] Iron lungs were widely used during the poliomyelitis epidemics of the 1930s and 1940s. These devices encased the patient from the neck down and applied negative pressure around the patient to expand the lungs. The chest cuirass was intended to alleviate the problems of patient access and "tank shock" that occurred secondary to venous pooling during the application of negative pressure associated with iron lungs.[7] Although the chest cuirass improved patient access and decreased the potential for tank shock, ventilation with this device was limited by the difficulties in maintaining an airtight seal between the shell and the patient's chest wall.

After the polio epidemic of the 1960s, the era of respiratory intensive care emerged, as positive-pressure ventilation via an artificial airway became commonplace.[6] Controlled mechanical ventilation eventually led to assisted modes of support, and positive end-expiratory pressure (PEEP) was introduced in the late 1960s. The improvements in mechanical ventilators came about as understanding was gained in manipulating variables of flow and pressure for patient benefit. Further technical evolution of ventilators included advances such as intermittent mandatory ventilation and synchronous intermittent mandatory ventilation. Modern ventilators now boast microprocessors that serve both in the operating mechanism of the device and in the monitoring systems, enabling automatic adjustment of most aspects of the mechanical breath being delivered.

Mechanical Ventilation

Basic Concepts

For a breath to be generated, flow must exist. During normal spontaneous breathing, the diaphragm and other respiratory muscles create gas flow by lowering pleural, alveolar, and airway pressures relative to atmospheric pressure. Alveolar pressure is normally atmospheric at end-inspiration and end-expiration. Diaphragmatic and intercostal muscle activation during normal inspiration expands the chest and decreases intrapleural pressure from −5 cm H_2O to −8 cm H_2O. Alveolar pressure fluctuates from +1 cm H_2O during exhalation to −1 cm H_2O during inspiration.

A ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch occurs when areas of the lung are perfused but either poorly ventilated (low $\dot{V}/\dot{Q}$) or not ventilated at all (shunt). The latter is an intrapulmonary (IP) (capillary) shunt. Shunt may also be intracardiac (anatomic). Venous admixture, as a measure of less than fully oxygenated blood after passing through the lung, includes both low $\dot{V}/\dot{Q}$ areas of lung and IP shunt. Normal venous admixture is about 2% to 5%. Mechanical ventilation may increase the venous admixture to approximately 10% in the normal individual. Mechanical ventilation usually decreases venous admixture in alveolar lung disease, such as acute respiratory distress syndrome (ARDS), improving the distribution of ventilation, especially in previously underventilated lung areas. Pressures greater than alveolar opening and closing pressures expand the collapsed alveolus and prevent its collapse, respectively. However, if positive-pressure ventilation produces overdistention, redistribution of pulmonary blood flow to unventilated regions may occur, resulting in hypoxemia. *Dead space* refers to areas of the lung with a higher $\dot{V}/\dot{Q}$ ratio. *Anatomic dead space* is the volume of the conducting airways of the lungs, about 150 mL. *Alveolar dead space* refers to alveoli that are overventilated relative to perfusion; it is increased by any condition that reduces pulmonary blood flow, such as pulmonary embolism (PE) or with overdistention of the lung. *Mechanical dead space* refers to the rebreathed volume of the ventilator circuit; this volume behaves like an extension of the anatomic dead space. Mechanical ventilation can also increase dead space if it leads to overdistention.

An increased dead space fraction requires a greater minute ventilation to maintain alveolar ventilation and $PaCO_2$ (partial pressure of carbon dioxide in arterial blood). Hyperventilation lowers $PaCO_2$. Hypoventilation raises $PaCO_2$; a modest elevation (50–70 mm Hg) reduces pH and is usually not by itself injurious in the mechanically ventilated patient. It has become increasingly recognized that hypercapnia during mechanical ventilation is well tolerated and may not be harmful. An exception occurs in the presence of increased intracranial pressure.

Although modern ventilators have evolved into complex machines, the basic premise remains: a ventilator is designed to replace or augment a patient's muscles in performing the work of breathing.[8] Ventilators use input power (electricity or compressed gas) to ventilate the lungs. To generate a breath (whether it be spontaneous or positive pressure), a pressure gradient must be generated from the airway opening to the alveoli. The volumes delivered and pressures generated largely depend on the mechanical properties of the respiratory system: the lungs and chest wall as well as the abdomen.[8] Each of these components has mechanical properties that determine

the overall behavior of the respiratory system. Although the respiratory system can be quite complex, the main *variables* of interest are pressure, flow, and volume. The ventilator must generate a *pressure* to cause *flow* through an open circuit and therefore increase lung *volume*.[9] The pressure required to do this reflects a combination of the pressures to inflate the lung and chest wall. This can be illustrated by the equation of motion[9,10]:

$$\text{Musclepressure} + \text{Ventilatorpressure} = (\text{Elastance} \times \text{Volume}) + (\text{Resistance} \times \text{Flow})$$

Compliance describes the ease or difficulty of the respiratory system to expand in response to a delivered pressure and volume. Simplistically, compliance is defined by the change in volume (ΔV) divided by the change in pressure (ΔP), and the compliance of the respiratory system (C_{RS}) is $\Delta V/\Delta P_{alveolar}$. *Elastance* is the inverse of compliance, or the ratio of pressure change to volume change, and describes the tendency to recoil. *Resistance* describes the impedance to airflow through the respiratory system, or the ratio of pressure change to flow change. The *elastic load* is the pressure required to overcome the elastance of the respiratory system, and the *resistive load* is the pressure required to overcome flow resistance of the ventilator circuit, endotracheal tube (ET), and airways.[8]

The equation of motion illustrates several basic principles. To drive gas into the patient, a ventilator can directly control either the pressure or the flow and volume applied at the airway. Despite its complexity a ventilator is simply a machine controlling one of these two variables (*control* variables). For example, in pressure control and PSV, pressure is the control variable and is held constant, although flow and lung inflation vary based on the patient's respiratory mechanics and inspiratory time (I time) (the latter set directly in pressure control and patient influence with pressure support). In volume ventilation, flow is the control variable and pressure and lung inflation vary with the patient's respiratory mechanics. Flow and volume are intimately linked: volume (L) = flow (L/sec) × I time (sec).

The Ventilator Circuit

The ventilator circuit consists of plastic tubing connecting the artificial airway or mask with the mechanical ventilator. Within the circuit may reside humidifiers, devices for the delivery of aerosolized medications, filters, suction catheters for secretion clearance, and heated wires.[11] The length and compliance (2–3 cm^3/cm H_2O) of the ventilator circuit are responsible for a volume of gas contained within the circuit, termed the *compressible volume*. This is partly responsible for the discrepancy between the set tidal volume (VT) delivered and the expiratory volume measured and displayed by the ventilator. The ventilator circuit also adds resistance to the system, but it is minimal compared to either the patient's inherent mechanics or the ET. Although frequently colonized with bacterial pathogens, the routine change of the ventilator circuit for infection prevention (e.g., ventilator-associated pneumonia [VAP]) is not recommended.

In the body, inspired gases are conditioned in the airway just before the carina so that they are fully saturated with water at body temperature by the time they reach the alveoli (37°C, 100% relative humidity, 44 mg/L absolute humidity, 47 mm Hg water vapor pressure). This portion of the airway acts as a heat and moisture exchanger (HME). Under normal conditions, about 250 mL of water is lost from the lungs each day to humidify the inspired gases.

Gases delivered from mechanical ventilators are typically dry, and the upper airways of patients being ventilated are functionally bypassed by artificial airways, necessitating the use of an external humidifying apparatus in the breathing circuit. Because the upper airway is bypassed during mechanical ventilation, the inspired gas temperature should be kept close to the body temperature. Inspired gases that bypass the upper respiratory tract through ETs or tracheostomy tubes should be heated to at least 32°C to 34°C at 95% to 100% relative humidity. The temperature probe for the heated humidifier should be placed inside the inspiratory limb of the ventilator circuit as close to the patient as possible. Moisture loss and subsequent dehydration of the respiratory tract result in epithelial damage.

An HME, which is placed between the artificial airway and the ventilator circuit, may be used to replace the traditional heated humidifier. During exhalation, moisture and heat from the patient are absorbed into the honeycomb structure of the exchanger and are transferred back to the patient during the next inhalation. Ventilator circuits with bacterial-viral filtering HMEs cost less to maintain and are less likely to colonize bacteria than those with heated humidifiers.[12,13] Contraindications for use of an HME are thick or large amounts of secretions, minute volume exceeding 10 L/min, body temperature less than 32°C, and need for aerosolized medications.[14]

Alarms and Safety

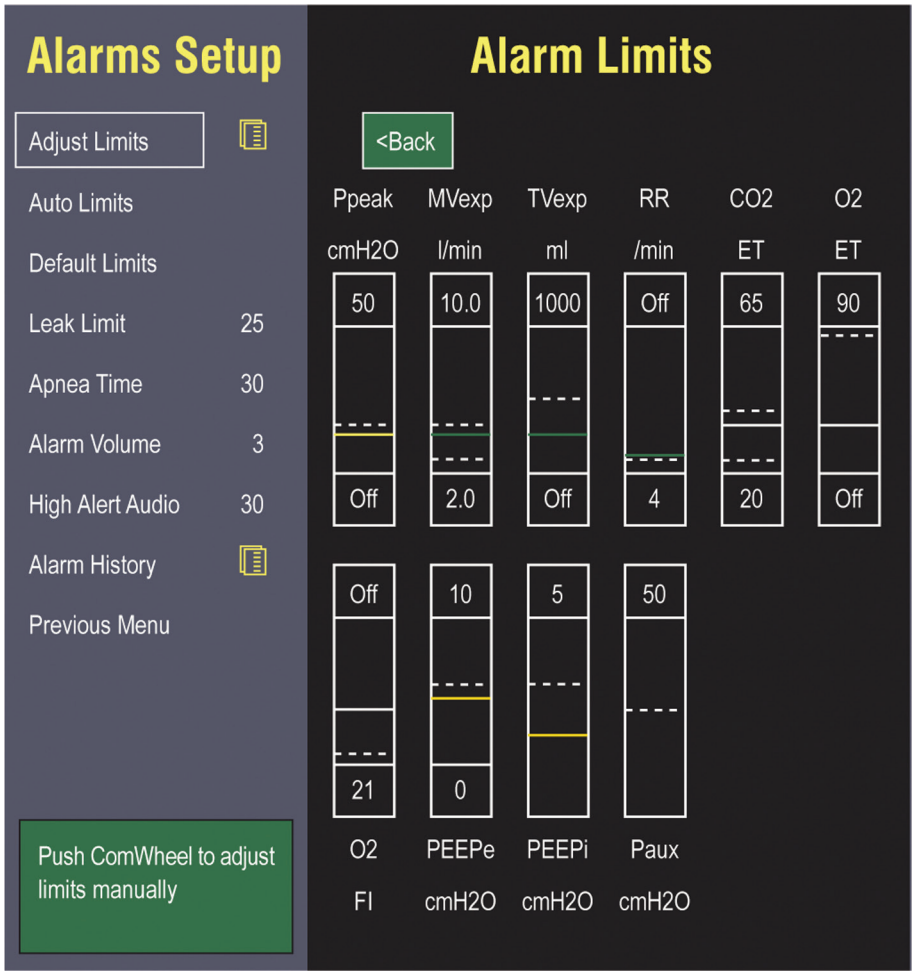
Current ventilators are equipped with monitors that constantly or periodically assess the ventilator's operation and the patient's status (Fig. 9.2). These monitors are usually associated with alarms that visually or audibly notify the operator of any variation from the preset norm. Ventilator alarms can warn of potentially life-threatening events, must have an appropriate level of sensitivity and specificity, and must be evaluated clinically and in a clinical context.[15] There are some alarms related to *power input* (e.g., low battery, loss of power, loss of air supply) and *control circuit* (e.g., nonfunctioning ventilator, incompatible settings), but most alarms are related to measured *output*, such as pressure, volume, and flow.[8]

High-pressure alarms are triggered by patient factors (such as decreased compliance and increased resistance of the respiratory system) or by ventilator circuit malfunction (obstruction or kinking of the ET). Low-pressure alarms are generally secondary to a leak in the system (ventilator circuit, ET or cuff) or patient (large pressure loss from a bronchopleural fistula). A high expired volume alarm could be seen with improved pulmonary mechanics during pressure-control ventilation. Low expired volume could be secondary to patient-ventilator disconnect or a leak in the system or patient. A high-frequency alarm is secondary to either autotriggering or hyperventilation, and a low-frequency alarm indicates bradypnea or apnea.[8,15]

Automatic Tube Compensation

Traditionally, most clinicians apply some amount of pressure support during inspiration to compensate for the increased work of breathing related to artificial airway resistance. The amount of pressure support needed to counterbalance this resistance is highly variable, depending not only on the internal diameter of the ET but also on flow, bend of the tube, and changing demands of the patient. This variability makes one level of pressure insufficient to meet these changing demands.[16]

Automatic tube compensation (ATC) compensates for ET resistance via closed-loop control of calculated tracheal pressure.



• **Fig. 9.2** The alarm panel of a Draeger Evita 4 ventilator showing the alarms typically used on current ventilators. (From Draeger Medical, Inc., Lübeck, Germany.)

A ventilator with ATC compensates for the pressure drop across the ET during inspiration by increasing the airway pressure and during expiration by decreasing airway pressure according to actual gas flow.[17–19] This technique uses a continuous calculation of the flow-dependent drop in pressure across the ET. ATC is similar to PSV, but the pressure applied by the ventilator varies as a function of ET resistance and flow demand. Most of the interest in ATC revolves around eliminating the imposed work of breathing during inspiration. During expiration, however, ATC may also compensate for that flow resistance by lowering the pressure in the expiratory limb transiently from its PEEP setting, helping reduce effective expiratory resistance and auto-PEEP.[17,20] In addition to overcoming the work of breathing imposed by the artificial airway, ATC may improve patient-ventilator synchrony by varying the flow commensurate with demand and may reduce air trapping by compensating for imposed expiratory resistance. During weaning trials, this technique may allow a more reliable prediction of patient performance when the tube is removed.

Indications for Mechanical Ventilation

Mechanical ventilation is instituted for a number of reasons (Table 9.1).[21] Most commonly, these indications are a combination of a failure to adequately oxygenate, ventilate, or meet the metabolic demands of a physiologically stressed patient. Clinical indicators, such as tachycardia, arrhythmias, hypertension, and tachypnea; use of accessory respiratory muscles; diaphoresis; and cyanosis, are used to diagnose respiratory distress. Type I respiratory failure is hypoxemic respiratory failure, defined as a partial pressure of oxygen in arterial blood (PaO_2) less than 60 mm Hg. Type II respiratory failure is hypercarbic respiratory failure, defined as $PaCO_2$ greater than 50 mm Hg, if elevated from patient baseline and associated with acidosis.[22] Blood pH is generally a better indicator than $PaCO_2$ for adjusting minute ventilation. Hypercapnia should not prompt aggressive intervention if pH remains acceptable and the patient remains alert. Hypercapnia is generally well tolerated, but this clearly depends on the underlying pathophysiology and comorbid conditions of the patient (e.g., right ventricular dysfunction). However, a sustained pH of 7.65 or greater or 7.10 or less is often considered sufficiently dangerous in itself to require control of minute ventilation by mechanical ventilation. Mechanical ventilation may also be instituted to maintain normal blood pH, decrease work of breathing, assist left ventricular function in the setting of acute decompensated heart failure, or for airway protection in the setting of toxic overdose, traumatic brain injury, or any other significant acute central nervous system illnesses. Box 9.1 suggests guidelines for setting basic operating parameters in a mechanical ventilator.

TABLE 9.1 Potential Indications for Mechanical Ventilation

Physiologic Mechanism	Clinical Assessment	Normal Range	Value(s)/Finding(s) Supporting Need for Mechanical Ventilation
Hypoxemia	$P(A\text{-}a)O_2$ gradient (mm Hg) PaO_2/FIO_2 ratio SaO_2	25–65 425–475 98%	>350 <300 <90% despite supplemental oxygen
Hypercarbia/inadequate alveolar ventilation	$PaCO_2$	35–45 mm Hg	Acute increase from patient's baseline pH <7.20 Mental status decline
Oxygen delivery/oxygen consumption imbalance	Elevated lactate Decreased mixed venous oxygen saturation	≤2.2 mg/dL 70%	≥4 mg/dL despite adequate resuscitation <70% despite adequate acute resuscitation
Increased work of breathing	Minute ventilation Dead space	5–10 L/min 0.15–0.30	>15–20 L/min ≥0.5 (acute)
Inspiratory muscle weakness	NIP VC	80–100 cm H_2O 60–75 mL/kg	<20–30 <15–20
Acute decompensated heart failure	Jugular venous distention Pulmonary edema Decreased EF		Clinical judgment combined with the listed factors
Inadequate lung expansion	V_T (mL/kg) VC (mL/kg) Respiratory rate (breaths/min)	5–8 60–75 12–20	<4–5 <10–15 ≥35

EF, Ejection fraction; *FIO_2,* fraction of inspired oxygen; *NIP,* negative inspiratory pressure; *$P(A\text{-}a)O_2$,* alveolar-arterial oxygen pressure difference; *PaO_2,* partial pressure of oxygen; *$PaCO_2$,* partial pressure of carbon dioxide; *SaO_2,* arterial oxygen saturation; *VC,* vital capacity; *V_T,* tidal volume.

• BOX 9.1 Guidelines for the Initiation of Mechanical Ventilation

1. Choose the ventilator mode with which you are most familiar. The primary goals of ventilatory support are adequate oxygenation/ventilation, reduced work of breathing, synchrony between the patient and ventilator, and avoidance of high end-inspiratory alveolar pressures.
2. The initial FIO_2 (fraction of inspired oxygen) value should be 1.0. The FIO_2 thereafter can be titrated downward to maintain the SpO_2 (oxyhemoglobin saturation) at 92% to 94%. In severe ARDS, >88% SpO_2 may be acceptable to minimize complications of mechanical ventilation.
3. Initial V_T should be 8–10 mL/kg. Patients with acute respiratory failure from neuromuscular disease often require V_T of 10–12 mL/kg to satisfy air hunger. In patients with ARDS, it is recommended to use a V_T of 6 mL/kg and to keep inspiratory plateau pressure 30 cm H_2O or less.
4. Choose a respiratory rate and minute ventilation appropriate for the particular clinical requirements. Target pH, not $PaCO_2$ (partial pressure of carbon dioxide). Initial respiratory rate is typically 10–12 breaths/min.
5. Use PEEP in diffuse lung injury to support oxygenation and reduce the FIO_2.
6. In patients with chronic obstructive pulmonary disease, avoid choosing settings that limit expiratory time and cause or worsen auto-PEEP.
7. When poor oxygenation, inadequate ventilation, or excessively high peak inspiration pressures are thought to be related to patient intolerance of ventilator settings and are not corrected by ventilator adjustment, consider initiating or increasing sedation or analgesia.

ARDS, *Acute respiratory distress syndrome;* PEEP, *positive end-expiratory pressure;* V_T, *tidal volume. Adapted from Fundamental Critical Care Support. Des Plaines, IL: Society of Critical Care Medicine; 2007.*

Mechanical Breath Generation

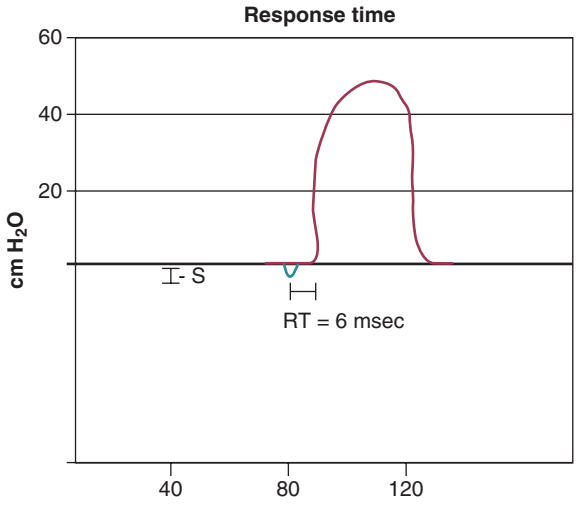
The breath generated by a mechanical ventilator can be separated into four *phases*: triggering, inspiration, cycling, and expiration.

Triggering represents the change from expiration to inspiration and occurs either because of a drop in circuit pressure or diversion of flow (when patient triggered) or because of elapsed time. Sensitivity refers to a preset threshold of pressure or flow. When this threshold is reached, a mechanical breath is delivered. This threshold can be adjusted, and is usually set at −1 to −2 cm H_2O. If sensitivity is set too low, the ventilator will be triggered by any process that causes the airway pressure to drop below the set threshold. Such processes include patient motion, external compression, gastric suctioning, and air leaks in the circuit. Conversely, if the threshold is set too high, the work of breathing increases, as the patient must make a significant effort to overcome the threshold limit for inspiratory flow to occur. In the setting of pressure triggering, airway pressure is reduced (by patient effort) in the proximal circuit, the expiratory valve closes, pressurization of the inspiratory limb of the circuit occurs, and the patient receives a breath. Flow sensing was developed as an alternative to pressure triggering to reduce the delay in response time between neural input from the patient and delivery of gas volume by the ventilator.[23,24] In the setting of flow triggering, the patient's inspiratory effort induces a disruption of the constant flow in the ventilator inspiratory circuit. This change in flow signals the expiratory valve to close and for the ventilator to deliver the next breath. Flow triggering was initially demonstrated to decrease the work of breathing compared with pressure triggering. However, with improvement in response time,

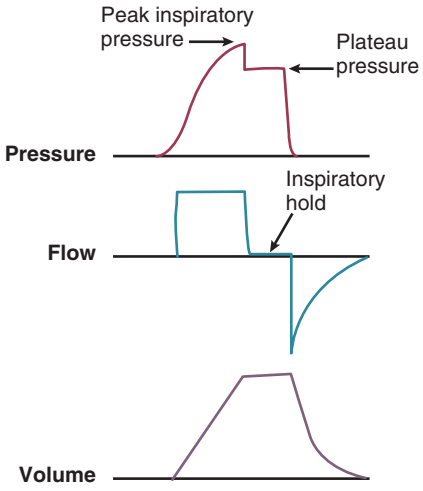
monitoring, and feedback, pressure and flow triggering are similar in this regard.[25,26] Fig. 9.3 is a representation of patient effort and ventilator response time.

During *inspiration*, flow is channeled through the open inspiratory valve of the ventilator to the patient with the exhalation valve closed. This phase can be controlled by how one sets flow or pressure in the ventilator proximal to the open inspiratory valve. For example, volume-assist control is flow controlled and pressure-assist control is pressure controlled. The choice of control variable is largely the discretion of the clinician, as either can be manipulated to achieve set goals. It should be noted, however, that in volume-targeted ventilation, excessive airway pressures can arise secondary to worsening pulmonary mechanics. In this situation, the pressure alarm will cause a pressure limit to cycle to expiration. At the end of inspiration in volume-targeted ventilation, an inspiratory hold maneuver can be performed (Fig. 9.4), which can distinguish the peak airway pressure from the plateau pressure (because flow is stopped, resistance is negligible). In pressure-targeted ventilation, minute ventilation is not guaranteed. It is a function of the compliance and resistance of the respiratory system. The clinician therefore should monitor these physiologic changes closely to avoid untoward changes in either airway pressure or $PaCO_2$ levels.

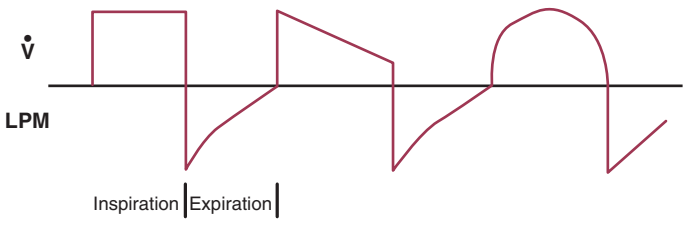
With pressure control and pressure support (PS) breaths, the pattern of inspiratory flow is a natural decelerating pattern as the pressure gradient for flow decreases as pressure rises in the patient's lungs. The pattern of inspiratory flow with a flow-controlled breath (volume cycled) is typically square with an almost instantaneous rise to a preset level (40 L/min, 60 L/min, and so on) followed by constant flow until cycling occurs. The flow pattern can be computer altered to be *decelerating* or *sinusoidal* (Fig. 9.5). Decelerating flow results in a rapid rise to a maximum level followed by a gradual decrease until cycling. Sinusoidal flow pattern most closely represents normal physiologic breathing. It results in flow that gradually increases and then decreases during inspiration. The choice of inspiratory flow pattern should be based on patient characteristics, and a few common clinical scenarios should be familiar to the clinician. Square flow over time results in a shorter inspiratory time (I time) for a given VT, and therefore longer expiratory time (E time). For this reason it may be preferred in patients with obstructive physiology (chronic obstructive pulmonary disease [COPD] or asthma).[27,28] It is also usually tolerated better in patients with demand for high minute ventilation, such as severe metabolic acidosis or elevated intracranial pressure. In this situation, there is a potential for dyssynchrony to occur during the progression of the inspiratory phase if decelerating flow is chosen. The trade-off is higher peak airway pressures with a square waveform, which may be ameliorated if it leads to a reduction in hyperinflation and iPEEP. Decelerating flow results in a longer I time and likely a better distribution of flow. With pulmonary pathophysiology involving heterogeneous distribution of injury (ARDS as the prototype example), decelerating flow is likely the best choice, as the longer I time can lead to more homogeneous distribution of ventilation. The distribution of ventilation can be quite different when the flow pattern changes. A decelerating flow pattern yields the most even distribution under most abnormal airway conditions.[29] Studies have also demonstrated that a decelerating flow pattern improves the geographic distribution of lung vibration as a presumed surrogate of airflow.[30] The length of inspiration depends on several factors. In the pressure control mode of ventilation, the clinician directly controls the I time and I:E ratio. With pressure support the patient primarily controls I time. In flow-controlled (volume-targeted) ventilation, the I time is a function of set VT and flow rate (VT/inspiratory flow rate) as well as flow wave characteristics (shape). The end-inspiratory alveolar pressure, as measured by an end-inspiratory hold, is the same for a given VT regardless of the type of ventilator breath.



• **Fig. 9.3** Pressure wave showing time relationship between patient inspiratory effort and ventilator response time *(RT)*.



• **Fig. 9.4** A plateau pressure measurement can be obtained in assist volume control mode by the performance of an inspiratory hold to better estimate the pressure in the lungs.



• **Fig. 9.5** Depicted left to right are square, decelerating, and sine inspiratory flow waveforms as options for delivery of volume ventilation. Note that the square waveform produces the shortest inspiratory time and that the decelerating waveform does not return to zero flow at end inspiration. *LPM,* Liters per minute; *V̇,* flow.

Cycling is the transition from inspiration to expiration (closing inspiratory valve and opening expiratory valve). It can occur due to a threshold of decrease in flow, elapsed time, or delivered volume. *Flow-cycled breaths* are PS breaths. With PS breaths flow rate decreases dramatically as (a) patient inspiratory effort decreases and then ceases and (b) the pressure rises in the patient's lungs as the breath is delivered. With a fixed pressure application the gradient for flow decreases. The patient often senses control not only of initiation of breath but also of its termination. When a predetermined decrement in flow occurs, inspiration is terminated and the patient cycles to expiration. This is typically set at 25% of initial flow, but can be manipulated based on different clinical conditions. For example, if a large leak occurs (bronchopleural fistula or ventilator circuit leak) it may be wise to set the cycle at a higher percentage of initial flow to terminate inspiration at the appropriate time. Strength and duration of patient inspiratory effort influence VT. For safety reasons, PS breaths can be cycled due to excessive pressures (e.g., coughing during inspiration) or elapsed time (e.g., secondary to a leak in the system which would prolong inspiration). In *time-cycled breaths* (pressure control), inspiration is terminated after a preset interval, regardless of whether preset pressure has been achieved or a desired VT has been delivered. Pressure is maintained at a preset level throughout inspiration, yielding a square pressure waveform. Pressure-targeted ventilation is time cycled, and the time can be adjusted to yield a precise inspiration/expiration (I:E) ratio. In *volume-cycled breaths* (flow controlled), the clinician has selected the targeted VT. Volume is delivered until that volume is reached. Airway pressure is directly dependent on the VT and the mechanical characteristics of the patient's respiratory system. For safety reasons, volume-cycled breaths will be pressure cycled if airway pressures exceed the pressure alarm limit. In this situation, the delivered VT will not reach the set volume target unless the pressure alarm limit is increased.

At the end of inspiration, flow from the ventilator ceases, the exhalation valve opens, and gas is allowed out from the lungs. This release occurs passively. Expiratory flow should cease prior to expiration. If this does not occur, the patient has auto-PEEP or intrinsic PEEP (iPEEP). This is most commonly seen in patients with expiratory flow limitation (COPD or asthma) or high inspiration/expiration (I:E) ratios (see later text).

Ventilator Modes

A ventilator mode describes ventilation over time and a set of specific combinations of breath characteristics delivered to a patient, including types of breaths, phase variables, and mandatory versus spontaneous breaths.[16] Clinician familiarity, unit, and institutional practice patterns determine to a large extent the mode that is used. Also, data showing definitive improvement in clinically relevant outcomes comparing one mode to another are lacking. Patient need and response to therapy should guide mode selection. Table 9.2 summarizes the features of some of the modes of mechanical ventilation, and Table 9.3 lists some of their advantages and disadvantages. Fig. 9.6 also shows some characteristic waveforms of various modes of mechanical ventilation.

Continuous Mandatory Ventilation

With continuous mandatory ventilation (CMV), the patient has no influence on mechanical ventilation, and all breaths are time (ventilation) triggered. Patient-ventilator interaction is solely from the ventilator to the patient; it is time triggered and cycled by the ventilator. Current ventilators do not have a CMV setting; this mode is essentially what is achieved when a patient using assist control (AC) ventilation has no interaction with the ventilator secondary to conditions such as heavy sedation, neuromuscular blockade, or central nervous system injury.

Assist Control Ventilation

In AC ventilation, a mandatory number of breaths are set and delivered with a set pressure or flow (assisted or unassisted), and if the patient's respiratory rate is higher than this backup setting (rate), additional assisted breaths to the preset pressure or flow are delivered. The target variable can be pressure (PC/AC) or volume (VC/AC).

Synchronized Intermittent Mandatory Ventilation

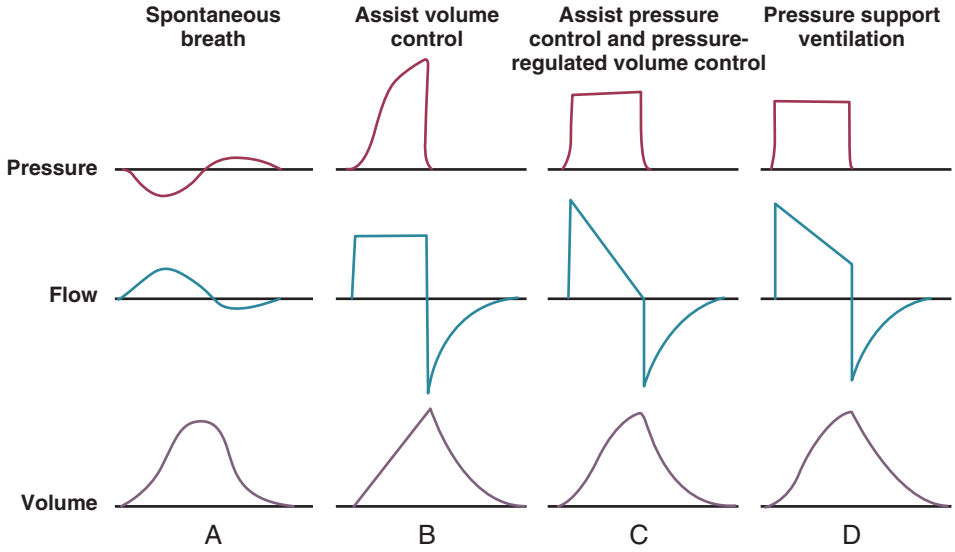
With synchronized intermittent mandatory ventilation (SIMV), the ventilator delivers a mandatory number of breaths with a set

TABLE 9.2 Overview of Features of Selected Modes of Mechanical Ventilation

Ventilator Mode	Trigger	Control	Cycling	Inspiratory Flow
Continuous mandatory ventilation	Time	Flow or pressure	Volume or time	Selected or decelerating
Volume control/assist control (VC/AC)	Patient or time	Flow	Volume	Square, decelerating, or sinusoidal
Pressure control/assist control (PC/AC)	Patient or time	Pressure	Time	Decelerating
Synchronized intermittent mandatory ventilation	Patient or time	Pressure for patient breaths Flow (VC) or pressure (PC) for ventilator breaths	Flow for spontaneous breaths Volume or time for ventilator breaths	Decelerating for spontaneous breath Square (VC), decelerating (VC or PC), sinusoidal for spontaneous breaths
Stand-alone pressure-support ventilation	Patient	None	Flow	Decelerating

TABLE 9.3 Potential Advantages and Disadvantages of Selected Modes of Mechanical Ventilation

Mode	Advantage(s)	Disadvantage(s)
Controlled mechanical ventilation	Rests muscles of respiration	Requires use of heavy sedation/neuromuscular blockade
Assist volume control	Reduced work of breathing Guarantees delivery of set tidal volume (unless peak pressure limit alarm is exceeded)	Potential adverse hemodynamic effects May lead to inappropriate hyperventilation and excessive inspiration pressures
Assist pressure control	Allows limitation of peak inspiratory pressures	Same as for assist volume control Potential hyperventilation or hypoventilation with lung resistance/compliance changes
Synchronized intermittent mandatory ventilation	Less interference with normal cardiovascular function	Increased work of breathing compared with assist control Patient may find it difficult to adjust to two different types of ventilator breaths
Stand-alone pressure-support ventilation	Patient comfort Improved patient-ventilator interaction Decreased work of breathing	Apnea alarm is only backup Variable patient tolerance



• **Fig. 9.6** Characteristic pressure-flow waveforms with breathing spontaneously and various types of ventilation. A, Spontaneous breath. Such breaths are spontaneous, and inspiratory flow is achieved by the negative pressure generated by the respiratory muscles. Expiration occurs as these muscles relax. The combination of mandatory ventilator breaths (B or C) with spontaneous breaths (with or without pressure support) is called synchronized intermittent mandatory ventilation. B, Assist volume control ventilation. The flow is constant and pressure increases throughout inspiration. C, Assist pressure control ventilation or pressure-regulated volume control (PRVC). The pressure is constant and flow decreases throughout inspiration. In PRVC, the level of applied pressure may vary from one breath to the next. D, Pressure support ventilation. The pressure is constant and flow decreases throughout inspiration. When the flow reaches one-fourth of its initial value, inspiration ends (flow-cycled). The flow and respiratory time are determined by patient effort and level of pressure support applied. The tidal volume varies from one breath to the next.

pressure or flow (assisted or unassisted), similar to AC. However, spontaneous breaths are delivered upon patient triggering during a timing window created around the delivery of mandatory breaths. These spontaneous breaths can be totally driven by patient effort or pressure-enhanced as pressure-controlled/flow-cycled (PS) breaths. The ventilator will attempt to synchronize the delivery of this mandatory breath with the spontaneous effort of the patient (if effort is present). If the patient does not trigger a breath, then the ventilator will deliver a regularly scheduled mandatory breath (time triggered).

Stand-Alone Pressure Support Ventilation

This mode of ventilation is patient triggered, pressure controlled, and flow cycled with a decelerating flow inspiratory waveform. Cycling to expiration typically occurs when the flow rate decreases

to a set percentage of inspiratory flow (typically 25% of initial inspiratory flow). However, if there is a leak in the system, inspiratory flow may never decrease to the cycle threshold. In this situation, for safety purposes, flow can be time cycled as well. During inspiration, the ventilator will adjust flow to maintain the preset pressure, and VT is dependent on patient effort and the mechanics of the respiratory system. The pressurization rate to the goal pressure is determined by the rise time, which can be adjusted on many ventilators. If the rise time is set too low, increased work of breathing can occur; if it is set too high, the preset pressure may be exceeded (overshoot), causing early cycling to expiration. PSV is effective at decreasing patient effort and work of breathing.[31–33] Data suggest that most clinicians view PSV as a weaning mode of mechanical ventilation, despite its being fully capable of appropriate full support in patients with respiratory failure and intact respiratory drive.[34]

Dual Control Modes

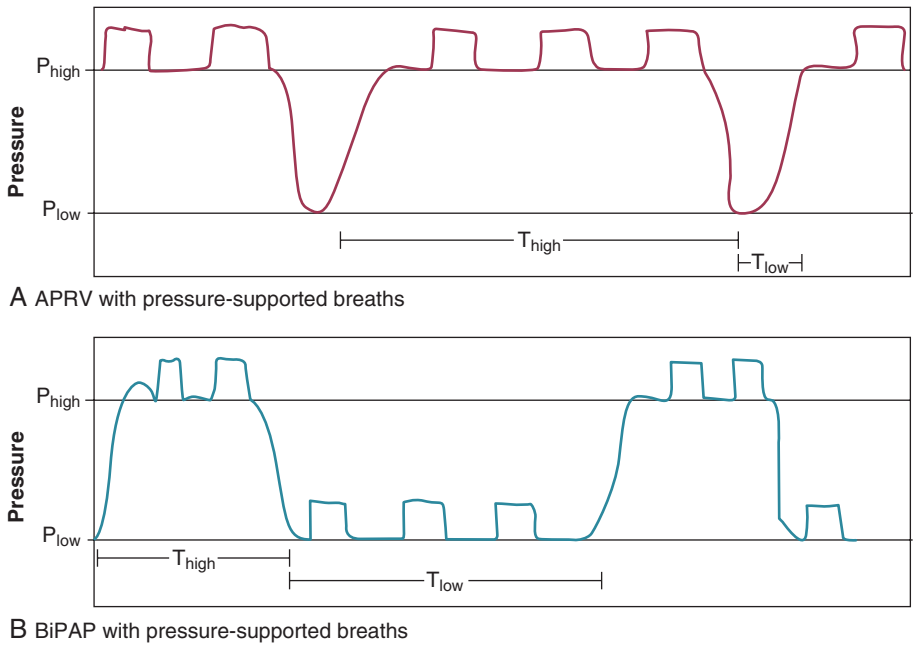
The preceding modes of mechanical ventilation are classically referred to as "conventional" ventilator modes, which is purely arbitrary. Dual control modes of ventilation manipulate pressure or volume on either a breath-to-breath basis or within the same breath. Breath-to-breath modes include volume support (VS) and pressure-regulated volume control (PRVC), also called "pressure control volume guarantee." VS is PSV (pressure limited, flow cycled) that uses VT as a feedback to adjust the pressure support level.[16] PRVC is pressure control ventilation (pressure limited, time cycled), but uses VT as a conditional variable to adjust pressure to achieve desired VT. Proportional assist ventilation (PAV) measures patient inspiratory demand while calculating compliance and resistance to offload inspiratory muscles in proportion and in synchrony with patient effort.[35] When compared to PSV it has been shown in one study to be associated with less dyschromy.[36]

Other Modes of Mechanical Ventilation

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) has been described in the literature since 1987.[37] It is a time-triggered, pressure-controlled, time-cycled mode of mechanical ventilation that exactly resembles AC/PC with very extended I:E ratios if the patient is not spontaneously breathing.[38,39] It has been described as continuous positive airway pressure (CPAP) with an intermittent time-cycled release phase to a set lower pressure. Whereas conventional modes of mechanical ventilation elevate airway pressure up from a set baseline to accomplish tidal ventilation, APRV uses very high I:E ratios to maintain mean airway pressure and brief deflations to accomplish ventilation. When APRV is used in ARDS (primary use) short time low (T_{low}) is used, whereas this mode can be used in patients without ARDS with longer T_{low} and is often called "bilevel positive airway pressure" in that circumstance (Fig. 9.7). The expiratory valve in APRV also facilitates spontaneous breathing throughout the ventilatory cycle, facilitating ventilation. Because this mode is primarily used with ARDS with long time high (T_{high}) and very short time low (T_{low}), breathing occurs primarily during T_{high}. Pressure high (P_{high}) is the baseline airway pressure that occupies most of the ventilatory cycle. Pressure low (P_{low}) is the release pressure and is set at 0 cm H_2O. T_{high} is the length of time for which P_{high} is maintained, and T_{low} is the length of time for which P_{low} is maintained. This is primarily semantics, but the term *APRV* implies longer I:E ratios than bilevel positive airway pressure, and a P_{low} setting of 0 at all times.

Although outcome data are lacking compared with conventional ventilation using protective lung strategies, the reported advantages of APRV include sustained alveolar recruitment with improved oxygenation, higher mean airway pressures accomplished with



• **Fig. 9.7** Pressure-time waveforms showing the use of airway pressure release ventilation (APRV). A, APRV as used in ARDS with pressure-supported breaths taken on T_{high} only and short T_{low} (dump time) to allow CO_2 removal and PEEP setting. B, A variant of APRV often called bilevel positive airway pressure with longer T_{low} and pressure-supported breaths allowed on both T_{high} and T_{low}. *P_{high}*, Pressure high; *P_{low}*, pressure low; *T_{high}*, time high; *T_{low}*, time low.

lower P_{peak} and P_{pl}, spontaneous breathing throughout the ventilatory cycle, and decreased use of sedation and neuromuscular blockade in severe ARDS.[39] The maintenance of spontaneous breathing may improve $\dot{V}/\dot{Q}$ matching by preferential ventilation of dependent lung regions, and the higher mean airway pressure, relative to P_{peak} and P_{pl}, may limit VILI.

Alveolar recruitment is a pan-inspiratory phenomenon and alveoli that are recruited are more compliant than recruiting or nonrecruited alveoli. With prolonged elevated pressures, APRV likely recruits alveoli, which require a longer inflation with higher threshold opening pressures.[38,39] Sustained inflation maintains recruitment, decreases shunt and dead space, and uses the more compliant expiratory limb of the pressure-volume (PV) curve. Ventilation is determined by the stored kinetic energy at the high pressure, the intermittent release phase, and is augmented by spontaneous breathing. Although minute ventilation is decreased with this mode of ventilation, ventilation is also improved by a decrease in dead space.

Clinical data are limited but have shown improved oxygenation, less shunt and dead space, as well as decreased need for sedation and neuromuscular blockade.[39–43] Data on clinically relevant outcomes, such as mortality rates, mechanical ventilation days, and intensive care unit (ICU) days, are limited. This mode remains physiologically attractive for its effects on oxygenation and potential to limit VILI, but no specific recommendations can be made given the lack of good outcome data.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is very different from conventional bulk flow ventilation and uses respiratory frequencies much higher and VTs much lower than conventional modes. It is similar to APRV in that it aims to elevate mean airway pressure to maximize recruitment and oxygenation while limiting P_{peak}.[44] Oxygenated, humidified gas (bias flow) passes in front of an oscillating membrane and generates very small VTs at very high respiratory rates. This is actively driven by a piston pump that oscillates the diaphragm. This produces sinusoidal or somewhat erratic pressure waves that are actively driven in both inspiration and expiration (unique in that expiration is not passively driven by elastic recoil). This component is created by the backward movement of the diaphragm or piston of the oscillator. Resistance valves are used to apply a constant distending airway pressure, over which small VTs are superimposed at a high respiratory frequency; in this fashion, it uncouples, for the most part, oxygenation and ventilation.

Given the fact the VT is often less than anatomic dead space, HFOV relies on gas transport mechanisms much different from those used by bulk flow ventilation. These mechanisms include some convective gas transport, but also molecular diffusion, pendelluft, coaxial flow, and Taylor dispersion.[45]

When initiating HFOV, the patient's ET should be verified to be patent, as heavy secretions or kinks in the ET will significantly harm ventilation. The mean airway pressure should be set at about 5 cm H_2O higher than that achieved with conventional settings. The bias flow delivers fresh gas into the ventilator circuit at 40 to 60 L/min and helps maintain mean airway pressure.[45] The power control allows adjustment of amplitude (Δpressure), which is set high enough to elicit vibrations of the patient to the lower abdomen or midthigh. Frequency helps determine ventilation and is set typically at 3 to 5 Hz. It should be noted, however, that at low frequencies, higher VTs and bulk flow can be achieved, which assists in ventilation (and may contribute to VILI). The percentage of I time is set at 33% or 50%, depending on ventilation goals.

This effect would be predicted to be most beneficial when applied early in the course of severe ARDS.[44,46] Clinical trials of the comparison of HFOV with ARDS net setting standard ventilation in patients at the onset of moderate or severe ARDS showed no benefit of HFOV, and one of the two trials showed an increased mortality rate in the HFOV arm.[46,47] This would imply consideration of HFOV use only as salvage therapy in ARDS. The clinician should note that patients ventilated with HFOV require heavy sedation or neuromuscular blockade.

Effort-Adapted Modes of Mechanical Ventilation

Early mechanical ventilators, such as the CMV mode setting, performed work on the patient and adapted the patient to the ventilator, with complete ventilator and physician control over breath characteristics and delivery. Although this can achieve adequate oxygenation and ventilation, it can come at a great expense to the patient, with side effects including dyssynchrony, increased work of breathing, respiratory muscle weakness, and increased use of sedative infusions. Advances in ventilator technology and increased recognition of the side effects of mechanical ventilation have led to an increased awareness to adapt the ventilator to the patient, using the patient's physiology and demand to assist the respiratory muscles in proportion to effort and need. These effort-adapted modes of mechanical ventilation include PAV, neurally adjusted ventilatory assist (NAVA), and adaptive support ventilation (ASV).

PAV is a mode of partial support in which ventilator assist is delivered in proportion to patient effort. A defined level of assist, or unloading, relieves the resistive and elastic burden of the respiratory system.[48,49] The ventilator responds to the *mechanical output* of the patient and will amplify patient effort with a preset proportional amount of pressure support. The theory behind PAV is based on the equation of motion; based on changes in flow and volume, flow-proportional and volume-proportional pressure support is given. A percentage of effort is set by the clinician, and applied airway pressure develops as a function of volume to overcome elastance or a function of flow to overcome resistance.[48] Reported benefits of PAV include improved synchrony, better physiologic breathing pattern, and improved sleep quality.[50–56] A limitation of PAV is that it relies on the mechanical output from the patient; therefore continuous knowledge of the elastic and restrictive properties of the patient is a necessity. If PAV incorrectly estimates the mechanical properties, the ventilator may overassist, causing delayed inspiratory ending ("runaway phenomenon"). This problem has been improved by the development of PAV+ (PAV with load adjustable gain).

NAVA is similar to PAV in that it is also an effort-adapted mode of partial assist. Unlike PAV, which responds to the mechanical output from the patient, NAVA responds to the *neural input* from the electrical activity of the diaphragm (Edi). Pressure is applied in a linear proportion to Edi, and this requires the placement of an esophageal electrode (similar to nasogastric tube placement). The ventilator is triggered based on Edi or conventional signals (whichever comes first), therefore improving synchrony, as the time delay from patient effort to breathe is very brief. In addition, the amount of ventilator assistance varies based on Edi. As such, to achieve greater assistance, the patient must increase Edi. Reported

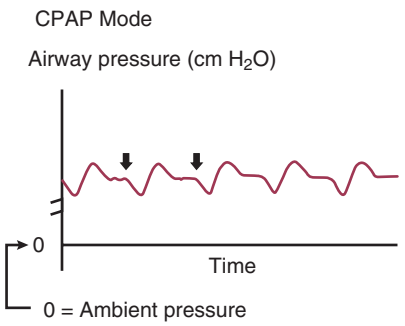
benefits include improved synchrony[57–61] and preserved variability in breathing pattern.[48,62,63] High NAVA levels and high Edi may result in high inspiratory pressures and VT delivery, especially in patients with unstable respiratory patterns or high respiratory drive.[64,65]

ASV ensures a set target minute ventilation based on measurements of the patient's E time constant and dynamic compliance, along with preset information of predicted body weight, minimum minute volume limit, and a pressure limit.[48] The ventilator attempts to minimize the work of breathing by combining the most effective combination of rate and VT, while limiting pressure support. ASV potential benefits include decreased work of breathing and improved patient-ventilator interaction.

Effort-adapted modes of ventilator assist are physiologically attractive, especially considering that most conventional modes of mechanical ventilation are decades old. The decision to use these modes should be tailored to the individual patient. Patients with a high amount of dyssynchronous breaths and iPEEP secondary to obstructive physiology may benefit from a switch to these modes. They do not, however, ameliorate iPEEP, and extrinsic PEEP should be delivered appropriately. In patients who are severely hypoxemic or hemodynamically unstable, these modes should likely be avoided. All require an intact ventilator drive, and ongoing assessments of pulmonary mechanics are a necessity. Finally, the clinician must give up a significant amount of control with these modes of ventilation (which may be unappealing to some practitioners), and outcome data are currently lacking.

Positive End-Expiratory Pressure

CPAP maintains airway pressure above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit. In mechanically ventilated patients, the purpose of CPAP is to achieve therapeutic PEEP in the presence of ARDS or pulmonary edema (Fig. 9.8). In these patients PEEP restores functional residual capacity, reduces IP shunt, shifts ventilation to a more compliant portion of the PV curve, and prevents end-expiratory volume loss (derecruitment).[66] PEEP recruits previously nonaerated lung tissue and homogenizes regional distribution of tidal ventilation. The net effect on gas exchange reflects the balance between recruitment and overdistention. In the setting of obstructive physiology or expiratory flow limitation, PEEP serves less to improve oxygenation but more to improve patient-ventilator synchrony and triggering.[27,28,67]



• **Fig. 9.8** A pressure-time waveform in a patient with continuous positive airway pressure *(CPAP)* without application of pressure support ventilation is demonstrated. The patient is breathing spontaneously at an elevated baseline system pressure. With initiation of inspiration *(arrows),* pressure becomes more negative (but remains positive), and with expiration, pressure becomes more positive.

PEEP is not without side effects. Given the heterogeneous distribution of lung injury in ARDS, PEEP can overdistend more compliant lung units, contributing to VILI.[68] If PEEP leads to overdistention, it can augment dead space, increase pulmonary vascular resistance, and cause right-sided heart dysfunction. It can also decrease venous return and, in the setting of volume depletion, decrease cardiac output.

The optimal way to set PEEP is debated and controversial, as is the optimal level of PEEP to use.[69–84] See Chapter 11 for a detailed discussion of PEEP application in ARDS.

Monitoring the Ventilated Patient

Hemodynamics

Positive-pressure ventilation causes predictable physiologic changes and cardiopulmonary function is intimately linked—respiratory function alters cardiovascular function and vice versa.[85,86] The venous system is a low-pressure reservoir that contains about three-fourths of our total blood volume.[85,87] This can be divided into the stressed and unstressed volume. The stressed volume contributes to the return of blood to the heart. The right ventricle's main function is to accept venous return and eject the optimal amount of blood into a (usually) highly compliant pulmonary vascular system.[86–89] This maintains a low right atrial pressure, thereby maximizing venous return and overall myocardial performance. A positive-pressure breath increases lung volume and increases intrathoracic pressure, which increases juxtacardiac pressure and therefore right atrial pressure. This can decrease venous return and therefore left ventricular preload several cardiac cycles later. At the same time, positive-pressure ventilation decreases left ventricular afterload by increasing the juxtacardiac pressure, therefore assisting ventricular contraction.

With respect to the mechanical ventilator, arterial blood pressure monitoring is commonplace in all ICUs. Although noninvasive cuff measurements can be adequate, invasive, continuous monitoring is much more informative when ventilator settings are dynamically changing. A fall in blood pressure temporally related to a ventilator change is a fairly specific indicator of a drop in cardiac output.[87] A narrow pulse pressure may indicate relative hypovolemia, although a widened pulse pressure may point to vasodilation or regurgitant cardiac valve disease. Pulse pressure variation (secondary to previously described heart-lung interactions) in mechanically ventilated patients is also the most accurate predictor of determining preload responsiveness.[90] Central venous pressure (CVP) is a reflection of right atrial pressure and normally is low to maximize venous return. Despite the commonality of its use in determining volume status and preload responsiveness, data and physiology have shown that to be inaccurate.[91] This does not indicate that the measurement of CVP is not of value. The absolute value and morphologic appearance (e.g., large v wave) of the CVP tracing can serve as valuable surrogates for right ventricular function, and an inspiratory fall in CVP can indicate preload responsiveness.[92] There are multiple other hemodynamic variables that could be measured in the mechanically ventilated patient, such as pulmonary artery occlusion pressure and mixed venous oxygenation, and these should be based on individual patient characteristics.

Pulse Oximetry

Pulse oximeters determine oxygen saturation by determining arterial blood light absorption at 660-nm and 940-nm wavelengths. The

ratio of absorption of these two wavelengths is then calibrated against computer-stored algorithms to determine the oxygen saturation. Pulse oximeters are quite accurate at their upper range but lose accuracy at lower oxygen saturations, require a good pulsatile signal, and have other limitations. These limitations include hypoperfusion, motion artifact, dyshemoglobinemias, ambient light, certain intravenous dyes, and deeply pigmented skin. Pulse oximetry is virtually ubiquitous in the ICU. Its use includes detection of hypoxemia, monitoring response to ventilator changes (such as PEEP setting), weaning fraction of inspired oxygen (FIO_2), and as a surrogate for pulmonary gas exchange.[93]

End-Tidal Capnography

End-tidal capnography ($ETCO_2$) is a useful way to monitor the concentration of exhaled carbon dioxide (CO_2), plotting it against time. A normal capnogram consists of a low value at baseline during inspiration and while emptying CO_2-free dead space. This is followed by a steep increase as alveolar units empty CO_2, and this increases progressively until a plateau is reached. A normal value (e.g., when ventilation and perfusion are matched) is about 5 mm Hg less than the $PaCO_2$, and a normal shape consists of a low baseline, steep ascending portion, plateau, and steep decline. The $ETCO_2/PaCO_2$ gap can widen in patients with altered $\dot{V}/\dot{Q}$ relationships or changes in cardiac output; the morphologic pattern of the waveform can be altered in patients with endobronchial intubation, expiratory flow limitation, and ventilator dyssynchrony.

Transcutaneous Carbon Dioxide Monitoring

Transcutaneous carbon dioxide ($PtCO_2$) monitoring allows noninvasive and continuous approximation of $PaCO_2$. This technique was described by Severinghaus in 1960. $PtCO_2$ monitoring uses disposable skin electrodes.[94,95] Measurement of $PtCO_2$ has been examined in patients with acute and chronic respiratory failure and as a monitoring tool. In these studies, $PtCO_2$ monitoring shows a good correlation with $PaCO_2$.[96–99] Some studies support $PtCO_2$ as superior to $ETCO_2$ monitoring in terms of reflecting $PaCO_2$.[100,101]

Limitations of the measurement for approximating $PaCO_2$ include frequency of the need for recalibrations, time needed to achieve skin warming, accuracy of measurements with thick skin, and the need for adequate tissue perfusion.[102]

Ventilator Waveforms

Modern ventilators allow continuous monitoring of pressure, volume, and flow waveforms, all of which are plotted against time. They are useful in readily identifying the mode of mechanical ventilation being used, as well as identifying physiologic abnormalities. Examination of the flow waveform can allow detection of iPEEP. A ripple-like waveform can indicate water or secretion buildup in the ventilator circuit. A prolonged expiratory flow pattern can indicate expiratory flow limitation. The pressure waveform allows calculation of compliance of the respiratory system, and an estimation of transalveolar pressure with an end-inspiratory hold maneuver to calculate plateau pressure. An initial overshoot in the pressure waveform may signal high patient effort or an overshoot on ramp speed. An upward inflection at the end of the pressure waveform could signal overdistention, and a dip in an otherwise square pressure waveform can signal patient effort and dyssynchrony.

Maintaining Support of the Ventilated Patient

Sedation and Analgesia

Critically ill patients who are mechanically ventilated often require sedative and analgesic drugs, and pain is common among ICU patients.[103] The ideal sedative and analgesic regimen would provide adequate sedation and pain control, rapid onset of action, rapid recovery after discontinuation, minimal systemic accumulation, and minimal adverse effects—without raising health care costs.[104] The primary aim of these medications is to reduce the physiologic stress of respiratory failure and to improve the tolerance of mechanical ventilation. As more patients survive acute illness, the importance of goal-oriented sedation and analgesia has emerged, and the deleterious side effects of these medications are evident.[105]

Historically, mechanically ventilated patients have been treated with continuous infusions of benzodiazepines, opiates, and propofol.[106–108] Unfortunately, emerging data point to increased side effects associated with these medications, such as delirium, increased mechanical ventilation days, increased lengths of hospital stay, and higher mortality rate.[105,109,110] This has prompted interest in novel regimens with agents such as dexmedetomidine, an α_2-agonist with sedative and analgesic properties. Data have shown that dexmedetomidine use is associated with a reduction in delirium, improved cognitive function, and a decrease in mechanical ventilation days.[111–115]

Regardless of the sedation regimen chosen, the mechanically ventilated patient should have sedation and analgesia titrated to a validated scale, such as the Richmond Agitation-Sedation Scale, and delirium should be monitored at least daily, also with a validated scale (Confusion Assessment Method-Intensive Care Unit). All patients should be assessed daily for readiness to be liberated from the ventilator (spontaneous awakening trial [SAT]), and this should be paired with a spontaneous breathing trial (SBT).

Positioning

There is no optimal position for an individual patient and certainly no evidence-based gold standard. Predictable physiologic changes occur in patients when placed in the supine position, including reduced functional residual capacity, alteration in pleural pressure, reduced lung compliance, and change in $\dot{V}/\dot{Q}$ matching. The supine position should be avoided, as it is a risk factor for VAP.[116,117] In patients with unilateral lung injury, the "good side" should be placed in the dependent position to optimize $\dot{V}/\dot{Q}$ match. Patients with severe hypoxemia (PaO_2:FIO_2 ratio <100) should be considered for prone positioning early in the course of ARDS, as this will likely improve oxygenation and may offer survival benefit in this patient cohort.[118]

Secretion Clearance

Secretion clearance is impaired in the mechanically ventilated patient owing to decreased mucociliary activity and inability to cough effectively. Removal of oral and tracheobronchial secretions is commonplace and standard care of the mechanically ventilated patient. Because of insufficient data and complications, scheduled and routine suctioning should be avoided, but the decision is based on patient assessment. The use of closed-circuit catheters is now commonplace, but data are conflicting with regard to patient benefit

when compared to open-circuit catheters. Before the suctioning procedure, the caregiver should be aware of the potential for complications, such as hypoxia, airway trauma, and cardiac arrhythmias.

Early Physical Therapy in Acute Respiratory Failure

Although overall evidence is limited and controversial, a recent clinical practice guideline "suggests" protocolized rehabilitation directed toward early mobilization for patients with acute respiratory failure and mechanical ventilation for greater than 24 hours.[35,119] It notes early physical therapy beneficial effects on duration of mechanical ventilation and ability to walk at discharge. These are mixed findings with regard to improvement in functional performance in various studies, and studies have not been able to demonstrate shortened mechanical ventilation, ICU stay, or hospital stay.[36,120] Early physical therapy is likely beneficial for select patients. Studies that inform on patient selection and dose of therapy are needed.

Weaning From Mechanical Ventilation

The five essential steps that facilitate achieving ventilation independence are (1) preparation (such as cardiovascular status, fluid balance), (2) evaluation (such as spontaneous breathing trial), (3) withdrawal of ventilation support, (4) extraction of ET, and (5) peri-extubation care.[121] (A more extensive discussion of weaning is found in Chapter 14).

Shortly after a patient is endotracheally intubated to initiate mechanical ventilation, thoughts should turn toward liberation from the ventilator. The withdrawal of mechanical support is a continuum from intubation until hospital discharge.[122,123] Depending on severity of illness, patient comorbid conditions, and critical care treatments needed, the timing of this may range from hours to weeks or months. There are several evidence-based guiding principles that shorten mechanical ventilation days across a broad cohort of critically ill patients.

A key component in liberation from the ventilator is the targeted use of sedation, limitation of sedative and opioid infusions, and the monitoring for and aggressive treatment of delirium.[105] Patients should also undergo daily interruption of sedative medications (SAT), which has been shown to decrease ventilator days and ICU length of stay.[124] After awakening, the patient should be assessed for readiness to wean. The literature abounds with weaning predictors, all of which have modest sensitivity and specificity, including the frequency/VT ratio.[123] Given this, as opposed to weaning predictors, the patient should undergo an SBT based on common sense, overall clinical trajectory, lack of hypoxia, and hemodynamic stability. The SAT should be paired with an SBT, as the SAT-SBT pairing decreases ventilator days, shortens ICU and hospital length of stay, and improves mortality rate.[125] An SBT can be conducted unassisted through a T-piece, on low-level PSV or on CPAP, once or multiple times a day and from 30 to 120 minutes; SIMV weaning is not recommended.[126–131] If a patient has an unsuccessful SBT, a reason for that failure should be sought and corrected. This could include sedation, weakness, delirium, respiratory muscle fatigue, or left ventricular dysfunction. Also, afterward the ET should be placed immediately on comfortable full mechanical support, as delaying this and prolonging the SBT to the point of respiratory muscle exhaustion can delay extubation. After a successful SBT, the patient should be extubated unless a reason exists to leave the ET in place (e.g., no cough reflex and heavy pulmonary secretions). The ability to predict successful extubation is challenging, and if the clinician never experiences a reintubation, he or she is likely not extubating patients based on the best available evidence.

Complications of Mechanical Ventilation

Hemodynamics

Blood pressure (BP) is simply the product of cardiac output (CO) and systemic vascular resistance (SVR; BP = CO × SVR). Although the transition of positive-pressure ventilation is associated with a predictable set of physiologic responses, the overall hemodynamic response is largely a consequence of underlying patient comorbid conditions (such as left ventricular dysfunction) and preload status. Immediately after endotracheal intubation, worsening hemodynamics are usually secondary to a decrease in preload, as right atrial pressure will increase, or a drop in arteriolar tone from sedation and analgesia. Any change in hemodynamics in the mechanically ventilated patient should prompt a thorough and almost algorithmic evaluation for potential causes.

Ventilator-Induced Lung Injury

Mechanical ventilation can be a lifesaving intervention. However, it has great potential for harm, and the clinician's focus should extend beyond normalization of gas exchange to providing safe and physiologically sound mechanical ventilation. Perhaps nowhere is this demonstrated more significantly than with the concept of VILI. Most patients with ARDS do not die of hypoxia, but rather multiple organ dysfunction syndrome.[132–135] Applied airway pressures in patients with ARDS distribute in a heterogeneous fashion, leaving more compliant lung units overdistended and others collapsed and nonrecruited. Respiratory system compliance is related to the amount of normally aerated lung tissue that remains, the so-called baby lung.[136] This heterogeneity leads to a maldistribution of ventilation, with some alveoli overdistended, others collapsed throughout the respiratory cycle, and others cyclically opening and closing. VILI is a spectrum, classically defined as barotrauma, atelectrauma, and volutrauma (stretch injury).[137] All of these can lead to biotrauma, or the decompartmentalization of the inflammatory response secondary to increased alveolar epithelial-capillary endothelial permeability. This results in the release of biologic inflammatory mediators and the spread of injury to distant organs, causing multiple organ dysfunction syndrome and death. VILI is much more complex than the preceding definitions and involves tissue stress and strain modifiers, complex molecular mechanisms, as well as gene activation and upregulation.[138,139]

Human studies support the concept of VILI and the importance of a protective ventilation strategy with low VTs and the use of PEEP. Low VT ventilation is the only intervention shown to consistently improve outcome in ARDS, and support for protective lung ventilation to decrease VILI from several well-conducted clinical trials exists.[73,74,140] This includes data showing a decrease in inflammatory mediators in patients ventilated with a protective lung strategy. In the absence of a patient-specific factor to suggest otherwise, a protective ventilation strategy, consisting of low VT ventilation, PEEP setting, and limitation of plateau pressure, should be attempted at all times. Emerging data suggest that these strategies should be used not only in patients with ARDS, but in all patients receiving mechanical ventilation, especially those with known risk factors for the development of ARDS.[141]

Spontaneous breathing during mechanical ventilation may lead to improved oxygenation through better aeration and ventilation-perfusion matching, reduced need for sedation, and a smaller risk of diaphragm deconditioning.[35] However, it also potentially increases transpulmonary pressure and risk for ventilation-associated lung overinflation injury.[35] It may displace gas from nondependent more-recruited areas to dependent less-recruited areas, the so-called pendelluft effect. With strong diaphragm contractions during early inspiration spontaneous breathing may lead to regional overinflation and ventilation induced lung injury. Properly applied higher PEEP may decrease this pendelluft effect.[142]

Ventilator-Associated Events

Diagnosis of VAP has been a controversial issue in the critical care setting. Problematic is that clinical findings for VAP are subjective and nonspecific. In 2013, the Centers for Disease Control and Prevention published a new algorithm for surveillance of what are called ventilator-associated events (VAEs).[143–145]

The new three-tier algorithm defines associated events as a significant and sustained worsening in oxygenation variables after an initial period of stabilization or improvement. This deterioration in oxygenation can occur from infectious and noninfectious conditions.

This three-tier definition is as follows:

1. Tier 1: Ventilator-associated condition (VAC) defined as new respiratory deterioration.
2. Tier 2: Infection-related ventilator-associated complication (IVAC) defined as VAC − clinical signs of infection.
3. Tier 3: Possible or probable VAP defined as IVAC + evidence of pulmonary infection.

Patients with VAEs have a high morbidity and mortality rate compared with patients without VAEs.[146,147] Avoiding intubation, minimizing the duration of mechanical ventilation, and targeting the specific causes of VAEs are three important approaches to improve outcome in critically ill patients.[148]

One of the most frequent complications of mechanical ventilation is the development of VAP.[149–160] VAP is discussed in Chapter 40.

Gastrointestinal Bleeding

Mechanical ventilation is a risk factor for gastrointestinal bleeding secondary to stress ulceration, trauma (especially traumatic brain injury), and major burns. Mechanical ventilation for longer than 48 hours is regarded as the most frequent risk factor.[161] The most effective treatment of stress ulceration is prevention. H_2-receptor antagonists and proton pump inhibitors have been shown to reduce the incidence of clinically important bleeding compared with sucralfate and are considered the first-line therapy among many clinicians.[162–166]

Venous Thromboembolism

Venous thromboembolism (VTE) refers to the development of deep venous thrombosis or pulmonary embolism in the critically ill patient. Patients in whom deep venous thrombosis develops have worse clinical outcomes, including prolonged mechanical ventilation.[167] Furthermore, VTE is common and frequently asymptomatic in mechanically ventilated patients. Given the adverse clinical outcomes associated with VTE, thromboprophylaxis with low–molecular-weight heparin or unfractionated heparin, both administered subcutaneously, should be given unless contraindicated.[168–170]

Noninvasive Positive-Pressure Ventilation

Noninvasive positive-pressure ventilation (NIPPV) offers the potential to provide ventilatory assistance without an invasive artificial airway. NIPPV may be accomplished using a face mask or nasal mask fitted to the face and connected through standard ventilator tubing to either a standard mechanical ventilator or smaller ventilators made specifically to deliver noninvasive mechanical ventilation.

In patients with COPD and type II respiratory failure, NIPPV reduces dyspnea, decreases intubation rates, and improves mortality rates.[171–173] Similarly, in patients with cardiogenic pulmonary edema, NIPPV decreases intubation rates and improves survival.[173,174] NIPPV may also serve a critical role in decreasing mechanical ventilation days and improving weaning success, especially in patients with COPD recovering from type II respiratory failure.[175,176] Finally, immunocompromised patients, especially those with hematologic malignancies, should be considered for NIPPV.[177] Before initiation of NIPPV, the patient should be assessed for an adequate mental status for airway protection, hemodynamic stability, and lack of excessive secretions. (See a more detailed discussion of NIPPV in Chapters 36 and 38.)

High-Flow Nasal Cannula: A Potential Alternative to Mechanical Ventilation

High-flow nasal cannula (HFNC) oxygen therapy is a noninvasive respiratory support system that delivers heated and humidified high-flow oxygen via special nasal prongs at a rate of up to 60 L/min as the F_{IO_2} is set from 0.21 to 1.0.[178]

HFNC oxygen therapy is considered to have multiple physiologic effects other than providing a high F_{IO_2}, including (1) washout of nasopharyngeal space CO_2 to reduce the anatomic dead space, (2) a therapeutic PEEP effect, (3) constant F_{IO_2} without intubation or noninvasive ventilation by mask, and (4) humidification of inspired gas. Results of these physiologic effects of HFNC reduce the work of breathing.[179–183]

In patients with acute hypoxemic respiratory failure, HFNC offers patient tolerance and comfort and has been associated with improved oxygenation, reduced need for intubation, decreased respiratory rate, decreased work of breathing, and decreased mortality.[184–191] Also, in immunocompromised patients with acute respiratory failure one study showed that patients treated with HFNC had lower intubation and mortality rates than noninvasive mechanical ventilation.[192]

HFNC oxygen therapy has potential value in postextubation respiratory failure but remains controversial.[193,194]

Key Points

- Consideration of patient trajectory, individual physiology, timing of therapy, and severity of illness will make tailoring the ventilator prescription most effective.
- High-pressure alarms are triggered by patient factors (such as decreased compliance and increased resistance of the respiratory system) or by ventilator circuit malfunction (obstruction or kinking of the ET).
- Low-pressure alarms are generally secondary to a leak in the system (ventilator circuit, ET or cuff) or patient (large pressure loss from a bronchopleural fistula).
- Closed-loop control of calculated tracheal pressure, as seen with ATC, allows compensation for ET resistance.
- The breath generated by a mechanical ventilator can be separated into four phases: triggering, inspiration, cycling, and expiration.
- With pressure control and pressure support breaths the pattern of inspiratory flow is a natural decelerating pattern as the pressure gradient for flow decreases as pressure rises in the patient's lungs.
- In AC ventilation, a mandatory number of breaths are set and delivered with a set pressure or flow (assisted or unassisted), and if the patient's respiratory rate is higher than this backup setting (rate), additional assisted breaths to the preset pressure or flow are delivered. The target variable can be pressure (PC/AC) or volume (VC/AC).
- With SIMV, the ventilator delivers a mandatory number of breaths with a set pressure or flow (assisted or unassisted), similar to AC ventilation. However, spontaneous breaths are delivered upon patient triggering during a timing window created around the delivery of mandatory breaths. These spontaneous breaths can be totally driven by patient effort or pressure enhanced as pressure-controlled/flow-cycled (PS) breaths.
- Although outcome data are lacking compared with conventional ventilation using protective lung strategies, the reported advantages of APRV include sustained alveolar recruitment with improved oxygenation, higher mean airway pressures accomplished with lower Ppeak and Ppl, spontaneous breathing throughout the ventilatory cycle, and decreased use of sedation and neuromuscular blockade in severe ARDS.
- PAV is a mode of partial support in which ventilator assist is delivered in proportion to patient effort.
- NAVA is similar to PAV in that it is also an effort-adapted mode of partial assist. Unlike PAV, which responds to the mechanical output from the patient, NAVA responds to the neural input from the Edi. Pressure is applied in a linear proportion to Edi, and this requires the placement of an esophageal electrode (similar to nasogastric tube placement).

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Review Questions

1. A patient is triggering the ventilator and is being ventilated with a pressure-controlled, time-cycled breath, using a decelerating inspiratory waveform pattern. Flash pulmonary edema develops. Which of the following statements are true?

a. Owing to a decrease in compliance, airway pressure will increase until the alarm limit is reached.

b. Owing to a decrease in compliance, flow and tidal volume will decrease, and airway pressure will stay the same.

c. Owing to a change in mechanics, intrinsic positive end-expiratory pressure (PEEP) will develop, as exhalation will be prolonged.

d. Tidal volume will stay the same, but flow will increase owing to increased work of breathing.

Answer: b. The patient is being ventilated with pressure-assist control ventilation (i.e., "pressure control"). This mode of ventilation is patient triggered, because the patient is actively triggering and can use pressure or flow triggering (like many modes). During inspiration, a clinician-set pressure is controlled, or targeted, and pressure control is always time-cycled with a decelerating inspiratory waveform pattern. In pressure-targeted breaths, if mechanics change, flow and volume will change. In the case of pulmonary edema, the problem lies in reduced compliance. As such, flow and tidal volume will decrease. Answer a would be correct if the patient was on volume-assist control, as tidal volume would stay the same, but pressure would increase. A decrease in compliance will not cause a reduction in expiratory flow; therefore answer c is incorrect. In reference to answer d, because this is a pressure-targeted breath, flow may indeed increase if the patient's work of breathing and inspiratory effort increases. However, tidal volume will decrease as a result of the decreased compliance.

2. Which one of the following is most correct concerning hemodynamic effects of positive-pressure ventilation?

a. A positive-pressure breath is always associated with a drop in arterial blood pressure.

b. During volume-assist controlled ventilation, intrinsic positive end-expiratory pressure (PEEP)-induced elevated intrathoracic pressure can be minimized by decreasing inspiratory flow.

c. The immediate effect of a positive-pressure breath is a decrease in venous return secondary to an elevation in right atrial pressure and an increase in left ventricular stroke volume secondary to increased venous return from the pulmonary veins.

d. By increasing pleural pressure, mechanical ventilation increases left ventricular afterload.

Answer: c. The physiology of a positive-pressure breath is predictable: an increase in intrathoracic pressure causes an increase in juxtacardiac and right atrial pressure. As right atrial pressure is the back pressure for venous return, right ventricular venous return decreases. At the same time, compression of the pulmonary veins causes an increase in left ventricular return and stroke volume on the left side of the heart increases. Several cardiac cycles later, the decreased venous return from the right side now presents itself to the left side (usually during expiration), and left-sided stroke volume decreases. This is one example of ventricular interdependence and is what generates pulse pressure variation. The overall hemodynamic effects, such as arterial hypotension, are typically dependent on volume status and baseline left ventricular function. Decreasing flow during volume-controlled ventilation will increase inspiratory time and worsen intrinsic PEEP. Positive-pressure ventilation always decreases left ventricular afterload.

3. All of the following statements about mechanical ventilation are correct *except*:

a. A decrease in the end-tidal carbon dioxide ($ETCO_2$)–partial pressure of carbon dioxide ($PaCO_2$) gap indicates an increase in dead space.

b. Pairing a spontaneous awakening trial (SAT) with a spontaneous breathing trial (SBT) effectively reduces ventilator time and days in the intensive care unit.

c. An SBT can be conducted through a T-piece or on low-level pressure support.

d. Mechanical ventilation in acute respiratory distress syndrome (ARDS) is approached with the knowledge that overdistention can result in alveolar injury.

Answer: a. A normal $ETCO_2$-$PaCO_2$ gap is about 5 mm Hg, with $ETCO_2$ being less than PaCO2. An increase in that gap is typically indicative of an increase in dead space, whether due to altered ventilation-perfusion relationships or an acute drop in cardiac output. Daily assessment of readiness to liberate from the ventilator, along with protocolized SATs and SBTs and targeted sedation practices, are the most effective means of safely discontinuing mechanical ventilation. The literature supports the fact that SBTs can be conducted via a T-piece, low levels of pressure support or continuous positive airway pressure (CPAP), once or twice daily, and for 30 minutes up to 120 minutes.

The literature support exists for a greater beneficial effect of PEEP when applied immediately after the onset of ARDS. Overinflation at end inspiration produces an upper deflection zone on the pressure-volume curve. Mechanical ventilation in ARDS is approached with the knowledge that overdistention can result in barotrauma, whereas allowing alveoli to collapse at the end of each expiration (below lower inflation point) may result in shearing-type airway and alveolar injury. Overdistention is a prime driver of ventilator-associated lung injury.

10

Ventilatory Management of Obstructive Airway Disease

JOHN MARINI

CHAPTER OUTLINE

Special Challenges of Patients With Severe Airflow Obstruction
- Increased Work of Breathing
- Dynamic Hyperinflation (Air Trapping)
- Increased Minute Ventilation Requirement
- Reduced Mechanical Efficiency

Problems and Hazards of Ventilation With Positive Pressure
- Interactions of Pressure-Targeted Modes With Auto-PEEP

Principles of Managing the Ventilated Patient With Severe Airflow Obstruction

Practical Management of the Ventilated Patient
- Intubation
- Initial Support
- Machine Settings
- Support Phase Management

PEEP and CPAP in Severe Airflow Obstruction
- Newer Modes of Ventilatory Support in Airflow Obstruction
- Weaning ("Liberation") Phase
- Predicting Readiness for Spontaneous Breathing
- Weaning Approaches
- Periextubation Phase

Positive pressure ventilators have been in widespread clinical use for more than five decades. Our understanding of respiratory muscle function and ventilatory failure has undergone major revision over that period, helping to gear equipment and treatment strategies more effectively to patient requirements. Some of the more important advances in this area concern the interactions of patients with obstructive pulmonary disease (airflow obstruction [AO]) with the mechanical ventilator. Improved noninvasive ventilation (NIV) has transformed both the initial rescue and weaning phases of acute episodes requiring critical care. Other advances stem from better developed understanding of physiologic principles important in safe management and withdrawal of machine support from ventilator-dependent patients, many of whom have chronic obstructive pulmonary disease (COPD) or asthma. With these advances in mind, this chapter provides an updated physiologic background for understanding mechanical ventilation in patients with AO, in addition to reviewing selected aspects of this problem that are frequently overlooked and, though noteworthy, may be unfamiliar to many practitioners. NIV and high-flow nasal cannula (HFNC), modalities of immense value in the treatment of alert patients with moderately severe obstructive illnesses, are not extensively addressed here, as they are covered in other chapters of this text.

Special Challenges of Patients With Severe Airflow Obstruction

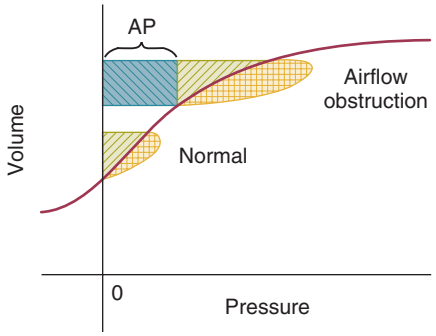
By assuming a major portion of the ventilatory workload, mechanical ventilation affords the opportunity to rest the respiratory muscles while maintaining pH homeostasis and oxygenation, thereby averting progressive ventilatory failure, respiratory arrest, or both. Unfortunately, these benefits are not cost-free—mechanical ventilation is expensive, often uncomfortable, and inherently hazardous; few would dispute the desirability of avoiding the need for airway intubation, implementation machine support, or of accelerating the process of withdrawing such interventions. Although deceptively simple in concept, the management of patients with AO who require mechanical support often proves to be a rather complex clinical undertaking. To manage respiratory failure effectively in patients with severe AO, it is important to understand their distinctive pathophysiology. Paramount among these characteristics is the dynamic hyperinflation that increases work of breathing and compromises the muscular pump that must contend with it. During acute exacerbations, such patients are also distinguished by their susceptibility to the hazards of machine support.

Increased Work of Breathing

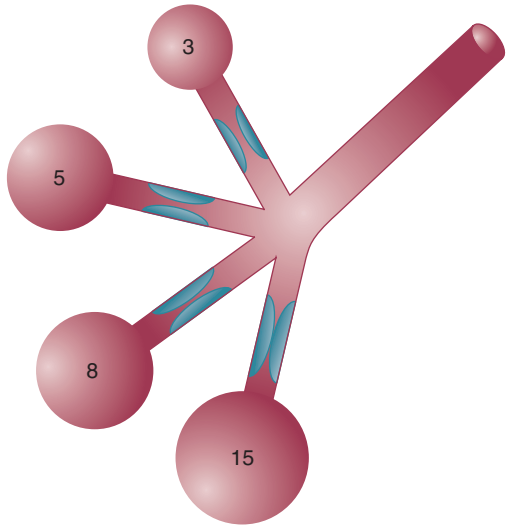
Assuming that both inspiration and exhalation proceed passively, the mechanical breathing workload can be quantified as the product of mean inflation pressure and minute ventilation. The mean inflation pressure (Pm) during constant inspiratory flow is approximated in a modification of the equation of motion of the respiratory system:

$$Pm = R\,(flow) + V_T/2C + PEEPi,$$

where R is resistance; V_T is tidal volume; C is respiratory system compliance (the inverse of elastance); and PEEPi is auto-PEEP, the positive end-expiratory alveolar pressure in excess of set PEEP because of dynamic hyperinflation (Fig. 10.1).



• **Fig. 10.1** Depiction of the elements of the inspiratory equation of motion and their associated work of breathing. The stippled area shows resistive work, and striped areas represent the elastic work associated with tidal volume and auto-positive end-expiratory pressure, respectively. *AP,* Auto-PEEP.



• **Fig. 10.2** The auto–positive end-expiratory pressure (PEEP) effect. Auto-PEEP is the positive flow driving the difference between alveolar and airway opening pressures at end-expiration. As depicted here, it can vary widely from site to site within the lung.

Increased resistance to airflow is responsible (directly or indirectly) for many of the physiologic disturbances that typify this disease. Flow resistance, an important determinant of Pm, is increased by both structural and functional narrowing of the airway. Structural changes include a reduced number of airway channels, as well as narrowed cross-sectional airway caliber. In this already narrowed tapering network of tubes, the additional reduction of airway caliber caused by mucosal edema, functional compression, increased bronchomotor tone, or secretion accumulation noticeably increases the work of breathing because resistance relates linearly to the airway length but inversely to the fourth power of airway radius. For similar reasons, resistance within these critically narrowed airways is highly volume dependent, so that loss of lung volume is accompanied by loss of elastic recoil tension, reduction of cross-sectional area, tendency for expiratory airway collapse, and major increases in the frictional workload.[1,2]

Although each factor just enumerated contributes to AO, functional compression of the airway during exhalation is of overriding importance in many patients with components of emphysema, massive obesity, or vigorous expiratory effort. Loss of elastic recoil encourages collapse of these narrowed bronchi as their transluminal distending pressure gradients decline (or reverse) during the course of exhalation. In most patients with COPD who require mechanical ventilatory support, dynamic airway collapse occurs even during tidal breathing, so the average expiratory resistance is often several times higher during exhalation than during the inspiratory phase of ventilation. This compressive mechanism underlies the phenomenon of air trapping and hyperinflation-related consequences such as loss of inspiratory muscle power and reduced compliance of the respiratory system.

Dynamic Hyperinflation (Air Trapping)

Expiration is normally a passive process that uses elastic energy stored during inflation to drive expiratory airflow. If the energy potential stored during inflation is insufficient to return the system to a relaxed equilibrium before the next inspiration begins, flow continues throughout expiration and alveolar pressure remains positive at end-expiration, exceeding the clinician-selected PEEP value applied within the external circuit (Fig. 10.2).[3–9] This positive-pressure differential distends the alveoli, enhances the pressure driving expiratory airflow, and increases lung recoil, thereby helping to offset and overcome airflow resistance. Unfortunately, such hyperinflation also places the expiratory musculature at a mechanical disadvantage. Furthermore, because the "excess" end-expiratory alveolar pressure (termed auto-PEEP or intrinsic PEEP [PEEPi]) encourages deflation even as inspiration is initiated, it must first be counterbalanced by positive pressure applied to the central airway or by negative pleural pressure before inflation can proceed.[10,11] Thus PEEPi adds to the other components of the equation of motion to elevate the mean inflation pressure and inspiratory work of breathing. The process of air trapping contributes to an increase in the respiratory work of breathing in at least two other ways. Hyperinflation drives the respiratory system upward toward the least compliant portion of the pressure volume relationship, incurring increased elastic work per liter of ventilation (see Fig. 10.1). At these higher volumes the lung approaches its elastic limit as the recoil tension of the distended rib cage becomes *expiratory* rather than inspiratory in nature. Finally, hyperinflation tends to convert more of the well-perfused (zone 3) lung into less-well-perfused tissue, thereby increasing ventilatory dead space and the minute ventilation requirement.

Generally, the resistance increase in patients with chronic AO and in many of those with severe asthma concentrates within small airways.[1] Yet for certain asthmatic patients, the central airways and larynx contribute impressively to total resistance, accounting for the helpfulness of helium-oxygen (heliox) mixtures in some (but not all) patients during exacerbated asthma.[12] According to some reports, heliox helps to reduce air trapping in patients with COPD as well. Although there is some concern regarding the generalizability and accuracy of such observations, several mechanisms can be invoked, even if the *primary* site of expiratory obstruction is too peripheral for helium to affect resistance there. These include reduced inspiratory turbulence, faster expiratory flow in non–flow-limited channels, modestly decreased carbon dioxide (CO_2) production and lower minute ventilation.

Of note, dynamically positive end-expiratory alveolar pressure can also exist without hyperinflation, provided that airway collapse does not occur. In these instances expiratory muscle contraction increases pleural pressure, alveolar pressure, and the speed of expiratory airflow, obviating the need for hyperinflation to complete

exhalation in the allotted time. Such mechanisms are used by normal subjects during heavy exercise or when faced with major respiratory workloads. Indeed, many untrained normal subjects expire to positions below the equilibrium point of the respiratory system in response to PEEP. In this way the respiratory muscles can begin contraction from a mechanically advantageous position, and the expiratory muscles can share in the ventilatory work. Using this strategy, PEEP actually provides a boost to *inspiration,* experienced early in the cycle when the *expiratory* muscles relax. This "work-sharing" strategy, although effective for a normal individual, cannot be implemented by patients who experience dynamic airway collapse during tidal breathing. Because forceful expiratory efforts succeed not only in raising alveolar pressure but also in intensifying dynamic airway collapse, flow rate is determined strictly by absolute lung volume and is not accelerated by expiratory muscle activity after the first third of expiration has been completed.

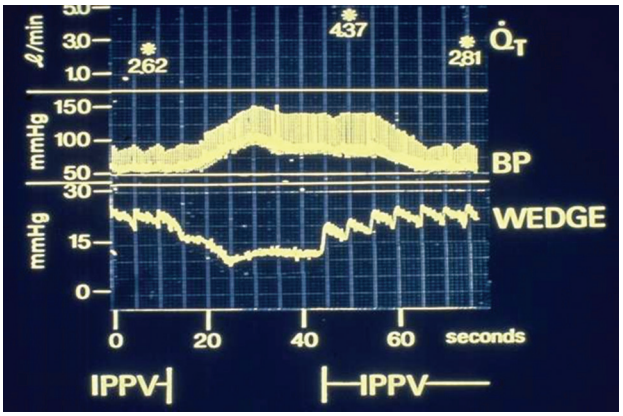
When dynamic collapse occurs during tidal respiration and breathing requirements are high, there is little alternative to hyperinflation, CO_2 retention, or both. At the chosen level of minute ventilation, maintaining the lower lung volume may be either too energy costly or physically impossible. For this reason, many patients with severe obstruction do not or cannot decrease their lung volumes when recumbent. Such considerations may help to explain the dyspnea experienced by most patients with severe AO on assuming horizontal positions. For the same recumbent angle, the lateral position may allow slightly more decompression than does the supine position.[13] Because lung volume influences airway caliber, airway resistance and tendency for collapse increase as the lung deflates.

Obesity and Airflow Obstruction

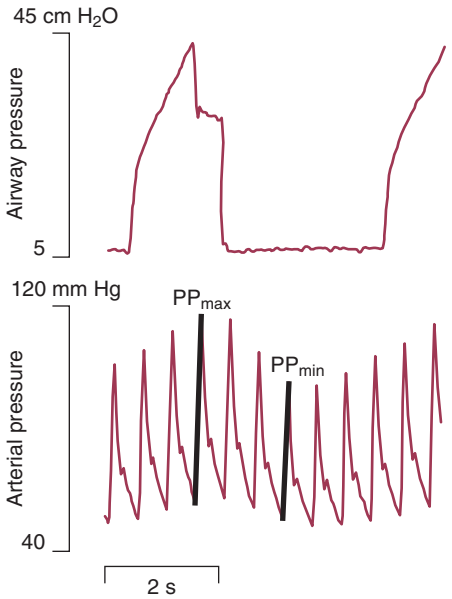
Patients with obesity normally have a lower functional residual capacity, or FRC, owing to the upward pressure of the abdomen upon the diaphragm, as well as the lower compliance of the chest cage. Consequently they exhibit higher airway resistance and a tendency for dependent atelectasis and symptoms when airways are narrowed by bronchoconstriction or disease. Likewise, patients with acute respiratory distress syndrome have higher than normal airway resistance in dependent zones. It is important to emphasize the value of upright positioning in obese bedridden patients. When the body mass index exceeds 35 kg/m^2, a transition to the horizontal position is associated with expiratory closure of dependent airways and auto-PEEP, even in otherwise healthy subjects.[14] As much as 10 to 15 cm H_2O PEEP is required to maintain airway patency throughout the breathing cycle in the horizontal position. Interestingly, assuming the horizontal prone position relieves much of the gas trapping that otherwise occurs when supine.[15]

The distribution of gas trapping in obstruction varies regionally throughout any diseased lung, depending on the local mechanical properties of the airways and the surrounding interstitial pressure. At the end of the expiratory cycle some zones remain patent, and some have sealed much earlier in the deflation cycle (Fig. 10.2). Consequently, the end-expiratory value of auto-PEEP detected at the airway opening may not reflect the magnitude of gas trapping.[16] Clues to the presence of regional closure are often seen when the airway is occluded at end-expiration; the auto-PEEP value shows an atypically slow rise to its final value as quasi-occluded small airways decompress into the common airway. In such cases, adding PEEP, a higher minute ventilation, or more upright position often eliminates or attenuates this characteristic. During volume-controlled ventilation (VCV), plateau pressure tracks hyperinflation more reliably than direct measurements of PEEPi.[5]

In some patients who passively receive ventilatory support, the problems presented by air trapping and dynamic hyperinflation are as much cardiovascular as pulmonary in nature. A relatively high fraction of the resulting positive alveolar pressure is transmitted to the pleural space, where it impedes venous return and confuses interpretation of hemodynamic pressure measurements made with pulmonary artery catheters (Fig. 10.3). Lung distention also adds to pulmonary vascular resistance, exacerbating the tendencies of patients with *cor pulmonale* to experience low cardiac output and hypotension. Marked respiratory variation of systolic and pulse pressures during passive inflation indicates phasically adverse cardiac loading and strongly implies the possibility of dynamic hyperinflation (Fig. 10.4).



• **Fig. 10.3** The hemodynamic impact of auto-auto–positive end-expiratory pressure (PEEPi) in a passively ventilated patient with severe airflow obstruction. A 40-second disconnection of the ventilator was associated with rising blood pressure and cardiac output despite a falling pulmonary artery wedge pressure. *BP,* Blood pressure; *IPPV,* intermittent positive-pressure ventilation; $\dot{Q}_t$, cardiac output.



• **Fig. 10.4** Marked respiratory variation of systemic arterial blood pressure, indicative of the relative variation in cardiac loading conditions associated with dynamic hyperinflation. *PP,* Pulse pressure. (From Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care.* 2000;4:282–289.)

Increased Minute Ventilation Requirement

Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching is widespread in patients with severe AO, reducing the efficiency of CO_2 elimination.[1] It is not uncommon for the resting minute ventilation requirement to exceed 12 L/min (twice the normal value) in patients with exacerbated asthma or extensive emphysema and strong chemical drives to breathe. Not only do such increases in ventilation requirement act through frequency as a linear cofactor in the work of breathing per minute (power), but the high minute ventilation requirement itself increases most components of inspiratory pressure *per cycle*: flow, elastance (the reciprocal of compliance), VT, and auto-PEEP. It is not surprising, therefore, that enormous increases in the oxygen consumption rate of the ventilatory muscles have been observed in distressed patients with obstructive lung disease. Moreover, during exacerbations, the oxygen consumed by ventilation and the metabolic demands associated with heightened vigilance, agitation, or anxiety may double the total body oxygen consumption observed during fully supported breathing. The combination of impaired $\dot{V}/\dot{Q}$ matching, hypoventilation, and diffusion impairment results in arterial oxygen desaturation that generally responds well to modest supplementation of inspired oxygen.

Reduced Mechanical Efficiency

In patients with exacerbated COPD or decompensated asthma, the oxygen consumed in the ventilatory task is disproportionate to the amount of mechanical work actually performed. The muscles of the hyperinflated ventilatory system are inefficiently aligned, force-length relationships of the shortened end-inspiratory fibers are suboptimal, and normally efficient coordination among the various muscles of the ventilatory group is often disrupted.[16,17] The energy cost of breathing, therefore, is greatly increased for the pressure and mechanical work accomplished during the breathing effort.

Problems and Hazards of Ventilation With Positive Pressure

When NIV is not indicated or proves unimpressive and ineffective under direct observation, intubation of the airway and invasive ventilation should not be delayed, especially in patients with severe status asthma. Yet patients with AO who require invasive mechanical ventilation present special challenges to the clinician owing to their frequently underappreciated predisposition to adverse consequences that relate only loosely to the airflow resistance. For reasons that are not entirely clear, patients with COPD have been reported to have an increased incidence of gastrointestinal ulceration and bleeding, especially during stress periods. This tendency is accentuated to an important degree by chronically poor nutrition as well as therapeutic use of corticosteroids. In modern intensive care unit practice, the incidence of ulceration has been greatly attenuated by the use of H_2 blockers, proton pump inhibitors, enteral feeding, and other means of acid suppression.

Even when able to cough with maximal force, patients with severe AO have difficulty in clearing contaminated secretions from the central and peripheral airways, encouraging bronchial and lung infections. This tendency is accentuated when the airway is intubated or when NIV is provided with poorly humidified gas mixtures. These interventions accentuate the impediment to coughing efficiency, encourage secretion thickening, and promote entry of nonsterile bio-fluids from the upper airway. In conjunction with mucus plugging, air trapping, and the tendency toward parenchymal infections, markedly inhomogeneous ventilation predisposes the ventilated patient with severe AO to the varied forms of barotrauma—pneumomediastinum, subcutaneous emphysema, and tension pneumothorax. Because the lungs cannot collapse, even a small pneumothorax in a ventilated patient with severe AO can rapidly develop a tension component, leading to ventilatory and circulatory compromise.

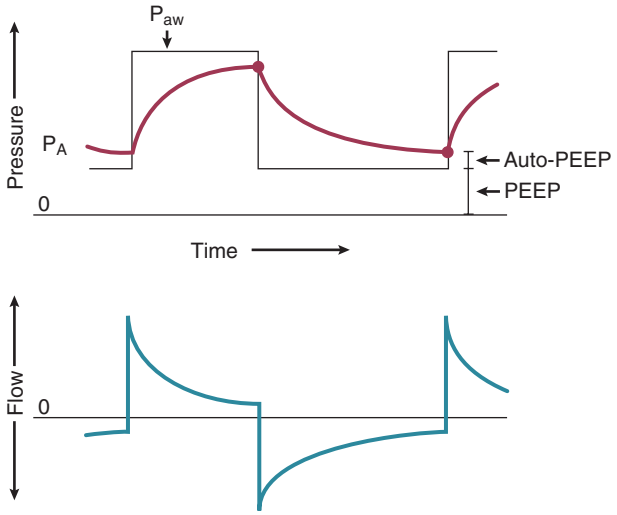
The hemodynamic sensitivity to positive-pressure ventilation of patients with AO arises from several sources.[18] The overexpanded lungs press outward on the chest wall, raising intrapleural pressure. When breathing efforts are silenced, as they are immediately after sedation and intubation, mean intrathoracic pressure abruptly changes from modestly negative to markedly positive. Increased pleural pressure raises the right atrial back pressure to venous return and encourages right ventricular dilation. Simultaneously, increased peripheral vascular capacitance (caused in part by the dilating effects of β_2-agonists) and reduced peripheral vascular tone limit the rise in mean systemic pressure, the upstream driver of venous return. Blood pressure routinely falls, and cardiac output declines disproportionately to oxygen demand. Absolute values of measured central vascular pressures (central venous and wedge) may be misleadingly high and do not necessarily reflect intravascular filling status or preload excess.[7] Marked respiratory variation of systolic and pulse pressures with the ventilatory cycle ("paradox," exceeding 12%–15%) is a hemodynamic marker of phasic alterations of preload and/or afterload (see Fig. 10.4). Either loading condition may cause such paradox, and ultrasonic assessment of the inferior vena cava as well as functional challenges may be required to determine the wisdom of adjusting fluid volume status. Depending on choice of VT, backup frequency, and set (and auto) PEEP, the afterload to right ventricular ejection may rise with any further lung expansion, coupled with the tendency for alveolar dead-space creation. Consequently, great care must be taken not to ventilate excessively and to provide adequate but carefully adjusted intravenous fluid support during this period. This advice pertains especially to patients with AO who require cardiac resuscitation.[19]

Interactions of Pressure-Targeted Modes With Auto-PEEP

Pressure-targeted modes of ventilation, exemplified by pressure control, airway pressure release ventilation, and pressure support, now occupy a central place in the care of intubated patients, as well as in those receiving NIV by face mask. Because the development of auto-PEEP reduces the pressure difference between airway opening and alveolus that drives inspiration, its rise and fall have a powerful influence on ventilation efficacy when these modes are used (Fig. 10.5). As already described, auto-PEEP varies not only with airway mechanics but also with the pattern of breathing and minute ventilation. For a fixed value of applied airway pressure, inspiratory VT in patients with AO will be more sensitive to the frequency and the inspiratory time fraction (an expression of the inspiratory:expiratory [I:E] ratio) than are normal subjects or those with restrictive disease[20,21] (Fig. 10.6). Faster breathing frequencies—for example, allow auto-PEEP to build—and this auto-PEEP must first be counterbalanced for inspiratory airflow to begin. If the patient is passive or the amount of inspiratory muscle force remains constant, delivered VT falls as the auto-PEEP builds.

This auto-PEEP/pressure differential relationship may result in an intriguing phenomenon resembling chaotic respiration during

NIV with a leaky mask interface.[21] The coupled PEEPi and VT form a "feed forward" system in which a building auto-PEEP of one cycle adversely influences the VT tidal volume of the next one. But this smaller VT also reduces the auto-PEEP that follows that restricted cycle, which in turn allows the subsequent breath—the third in the cycle—to have a larger effective airway pressure and VT, and the cycling variation continues. This may account for some of the wide variability in breathing rhythm often observed in these patients.[22] If the mask leak volume is a function of the I:E ratio, it can be shown mathematically and experimentally that fractal and chaotic VT delivery may occur, even when the patient's effort and mechanics remain unchanged (Fig. 10.7).[21] The consequences for comfort and sleep efficiency are likely to be significant, but clinical data are lacking on these issues at this time.



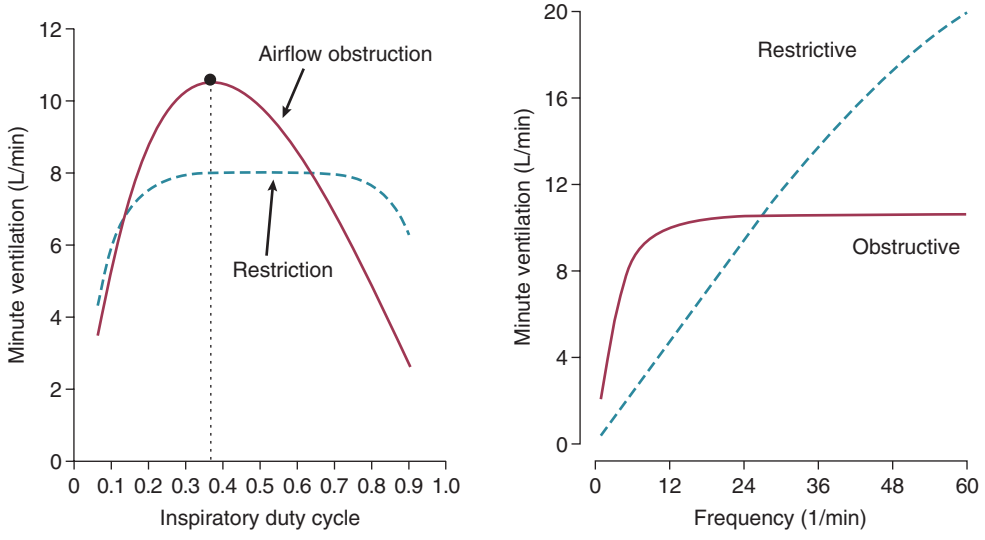
• **Fig. 10.5** Interaction of alveolar *(red line)* and applied airway *(fine line)* pressures in a patient ventilated with pressure-targeted ventilation. Auto-PEEP diminishes the driving pressure of the subsequent ventilatory cycle. P_A, Alveolar pressure; P_{aw}, airway pressure; *PEEP*, positive end-expiratory pressure.

Principles of Managing the Ventilated Patient With Severe Airflow Obstruction

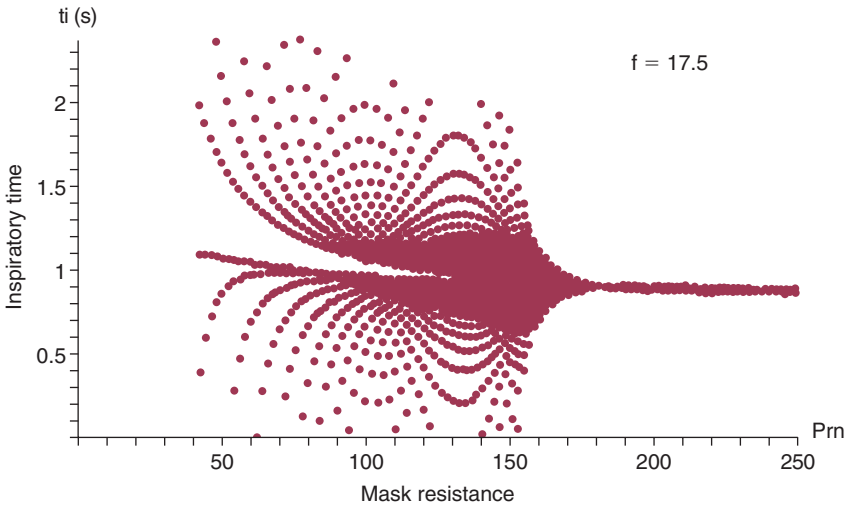
Most patients hospitalized with exacerbations of asthma or COPD can be managed effectively by regimens that incorporate aggressive secretion clearance techniques, antibiotics, corticosteroids, intensified bronchodilators, hydration, cardiovascular support, secretion lubricants (e.g., guaifenesin), and supplemental oxygen. NIV often helps as a temporizing measure for those with disease of *mild-moderate* severity, especially when cough is adequate to clear airway secretions and the patient remains both fully alert and accepting of a face mask interface.[23–28] Only a minority of such patients treated in this way need translaryngeal intubation and institution of mechanical ventilatory support unless the problem is complicated by coexisting cardiovascular, infectious, or neuromuscular problems. When invasive mechanical ventilation is required, however, the rationale underlying certain key management principles can easily be understood against a background of the physiologic derangements already described. These principles are (1) provide adequate support for muscle rest at adequate partial pressure of arterial oxygen (PaO_2) and pH; (2) do not overventilate; (3) minimize the minute ventilation requirement; (4) minimize risk of barotrauma; (5) maintain adequate bronchial hygiene; (6) prevent panic reactions; and (7) establish appropriate nutrition.

Principle 1: Provide adequate support to rest the ventilatory muscles, while avoiding hypoxemia and profound acidemia.

Poised at the edge of decompensation, the ventilatory muscles must be rested adequately before withdrawal of machine support can be considered. Rest may allow recovery of energy reserves and restore the balance between ventilatory capability and demand. Whereas sustained inactivity of the diaphragm encourages atrophy, excessively vigorous contractions of the diaphragm may eventually result in ventilator-induced diaphragmatic dysfunction.[29] Some evidence points to patient-ventilator dyssynchrony and eccentric muscular contractions as key contributors to this process. Both occur more often when ventilator demands are



• **Fig. 10.6** Relative sensitivity of patients with airflow obstruction to the settings of frequency and inspiratory time fraction for a fixed pressure target in pressure-controlled ventilation. This sensitivity is induced primarily by the impact of these settings on auto-PEEP.



• **Fig. 10.7** Theoretical behavior of tidal volume in response to pressure support by mask ventilation in a patient experiencing auto-PEEP. At a certain critical value of mask leak, there is wide cycle-to-cycle variation in tidal volume despite unchanging levels of pressure support and patient effort. Near "chaotic" behavior is a consequence of auto-PEEP. *f,* breath frequency; *PEEP,* positive end-expiratory pressure; *ti (s)*, inspiratory time in seconds. (From Hotchkiss JR, Adams AB, Dries DJ, et al. Dynamic behavior during noninvasive ventilation: chaotic support? *Am J Resp Crit Care Med.* 2001;163:374–378.)

high. Benefit may accrue to judicious muscle rest, even when it occurs intermittently on a chronic basis. Sufficient oxygen and mechanical support must be provided to permit restorative sleep and to avoid significant hypoxemia (arterial oxygen saturation <85%) and acidemia (pH < 7.2)—derangements that increase pulmonary vascular resistance; stimulate vigorous breathing; and inhibit mental, cardiac, and skeletal muscle functions.

Principle 2: Do not overventilate.

Profound respiratory acidosis and hypoxemia accentuate pulmonary hypertension, impair the right ventricle, and demand reversal. Nevertheless, although it is important to provide adequate ventilation and to reverse hypoxemia, overventilation is detrimental on several counts. Rapid reduction in the alveolar CO_2 tension tends to promote bronchoconstriction and impair neuromuscular and cardiovascular function. Furthermore, excess ventilation exacerbates dynamic hyperinflation and auto-PEEP, whereas moderate arterial partial pressure of carbon dioxide ($PaCO_2$) elevations are generally well tolerated.[30] Generally, it is a mistake to depress the $PaCO_2$ below the level that the patient chronically maintains. Such a strategy may temporarily reset chemical drives, effectively increasing respiratory workload intensity once spontaneous breathing resumes. If $PaCO_2$ falls sufficiently, the patient will not maintain unassisted breathing without intolerable effort, potentially delaying discontinuation of mechanical breathing assistance.

Principle 3: Minimize minute ventilation requirement.

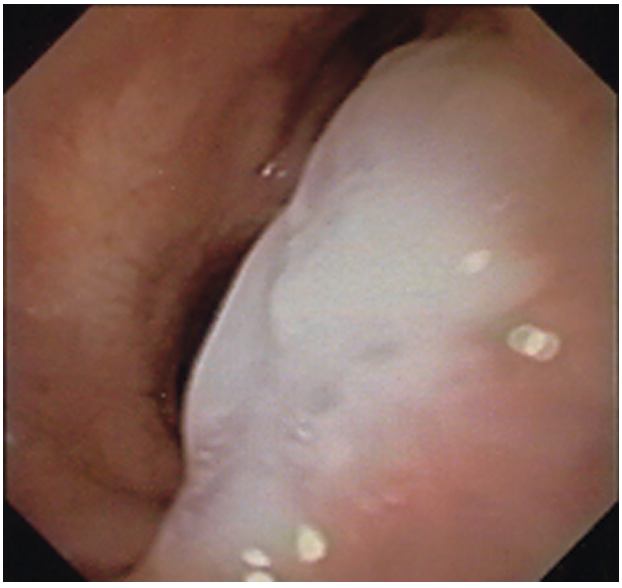
Because hyperinflation, mean inflation pressure, and the adverse cardiovascular consequences of mechanical ventilation are intimately linked to the minute ventilation requirement, ventilatory dead space and CO_2 output must be minimized while both metabolic acidosis and iatrogenic hyperventilation are avoided or addressed. Relief from discomfort, anxiety, fever, and metabolic acidosis help achieve these objectives.

Principle 4: Minimize the risk of barotrauma.

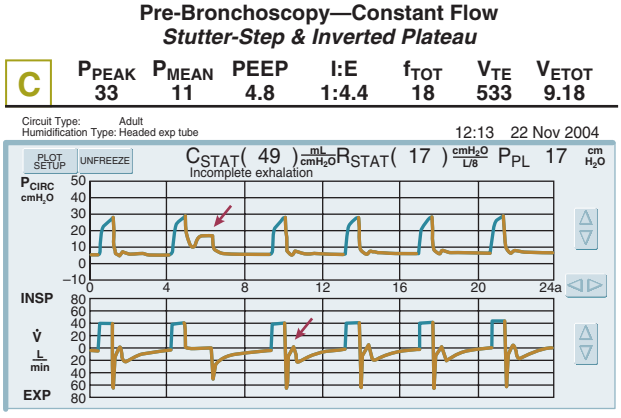
The predisposition of patients with severe AO to barotrauma must be combated by intelligent choices for VT, ventilation frequency, PEEP, and machine settings of trigger sensitivity and flow. Reduction of the minute ventilation requirement decreases the mean or peak alveolar pressures, or both, reducing the incidence of barotrauma. The relative contributions of mean alveolar pressure, PEEP, dynamic cycling pressure, and peak static (plateau) ventilatory pressure to the risk of barotrauma are not clear. Based on epidemiologic evidence, however, peak airway pressures in a passively inflated lung should be kept below 40 cm H_2O whenever possible. Selecting a VT within the recommended range (6–8 mL/kg of predicted body weight) is probably best. The question of optimal flow setting is of no small importance: auto-PEEP and mean alveolar pressure are reduced by selection of relatively rapid flow settings when minute ventilation is high. If minute ventilation is normal, however, rapid inspiratory flow rates are much less effective in reducing gas trapping, at least in asthmatic patients.[31] Using less rapid inspiratory flows may improve ventilation-perfusion matching, as well. Finally, higher peak *dynamic* airway pressures engendered by unnecessarily rapid flows are not entirely without risk. Units served by low-resistance pathways are in jeopardy from associated overdistention. For the same tidal inspiratory time, a constant ("square") flow waveform often serves better than a decelerating one in patients with severe AO. The risk of barotrauma can also be minimized by maintaining the lungs free of infection and the airways clear of secretions.

Principle 5: Maintain effective bronchial hygiene.

Secretion retention may dramatically increase airflow resistance and effectively seal off entire banks of functional alveoli, preventing their effective participation in ventilation. Thickened central airway secretions are a particular risk during mechanical ventilation, whether invasive or noninvasive (Fig. 10.8).[32] Apart from raising the end-inspiratory pressure, the resulting dynamic hyperinflation can detrimentally affect cardiovascular function, work of breathing, and respiratory muscle function. In addition to effective suctioning, bronchodilators, adequate hydration, corticosteroids, mucolytics, mucolubricants, and infection control, frequent repositioning, mobilization, and tolerated forms of physiotherapy are fundamental to secretion management. Percussive ventilation or vibropercussive vest treatments often complement mobilization effectively when tolerated. Whether vibratory delivery of inhaled bronchodilators enhances their therapeutic effects has not been conclusively established. Tracheotomies not only reduce resistance and provide improved access to the lower airway but also eliminate the direct connection between the pharynx and trachea established by tracheal intubation. Yet because of their associated morbidity, tracheostomy is best avoided unless mandated by the ineffectiveness of other measures.[33]



A



B

• **Fig. 10.8** A, Central airway mucus retained in a ventilated patient with severe airflow obstruction. B, The resulting inverted plateau and stutter step deformations of the airway pressure and flow tracings during controlled, volume-cycled ventilation. (From Zamanian M, Marini JJ. Pressure-flow signatures of central-airway mucus plugging. *Crit Care Med.* 2006;34:223–226.)

Principle 6: Prevent panic reactions.

In patients susceptible to dynamic airway collapse, an abrupt need to augment ventilation often precipitates a downward spiral in which the capability of the patient is overwhelmed by the imposed workload. Not only is minute ventilation increased during such episodes, but the resulting augmentation of dynamic hyperinflation also impairs muscle strength and endurance. Respiratory acidosis, dyspnea, and anxiety unbalance the ventilation demand/capability relationship to encourage the need for aggressive intervention. Cardiac decompensation owing to increased demands, adverse loading conditions, and diastolic dysfunction is another potential consequence, especially in the elderly. Anxiolytics, although hazardous to use in patients who are not invasively ventilated, may be extremely helpful in carefully selected circumstances.

Principle 7: Maintain appropriate nutrition, ensure adequate hemoglobin concentration, and prevent obstipation.

In stressed and often malnourished patients, the nature and quantity of nutritional support can make the difference between expedient recovery and continued ventilatory insufficiency. Although reasonable caution is advisable, severe anemia (hemoglobin <8 gm/dL) should be reversed and an adequate number of calories should be provided, via the enteral route whenever possible. Care must be taken to ensure that bowel motility is normal. Patients with AO frequently develop breathing discomfort because of raised abdominal pressures within a compartment bounded by a hyperinflation-depressed diaphragm. Along a similar line, attention to upright positioning is also important to relieve infradiaphragmatic hydrostatic pressures.

Practical Management of the Ventilated Patient

Intubation

An understandable reluctance to initiate mechanical ventilation in patients with COPD or perennial asthma exists because ventilatory assistance may be needed for prolonged periods and because a minimalist palliative approach may be appropriate for individuals who are so chronically disabled as to be miserable or despondent at home—even when everything is going as well as possible from a physiologic viewpoint. The development of comfortable noninvasive systems, coupled with supportive trials and clinical experience, has given rise to the initial use of mask ventilation and HFNCs in those who are alert and can tolerate such approaches. However, the most severely affected patients, especially those with copious, thick, and retained secretions; claustrophobia; anxiety; cardiovascular decompensation; or irreversible somnolence continue to require intubation to stabilize their deteriorating conditions.[34]

A mounting load of secretions audibly retained within the central airways generally indicates that the patient is too weak or breathless to expectorate and often portends an imminent crisis. Hence, when this sign arises and cannot be easily reversed, most physicians consider it strong evidence favoring intubation for secretion management and ventilation support. Overt disorganization of the breathing rhythm and gasping or ataxic respirations strongly suggest approaching exhaustion.

Initial Support

Postintubation Problems

The first 24-hour period after tracheal intubation and initiation of positive-pressure ventilation may be highly dynamic for the patient with AO. Many of these individuals have depleted intravascular volume and impaired cardiovascular reflexes—features that prepare them poorly to compensate for the suddenly increased pleural pressure and impediment to venous return that usually accompany initiation of mechanical support. In this postintubation phase there is an understandable but unfortunate tendency for the physician to intentionally overventilate the patient, and asynchrony often develops as patients cough vigorously or fight against the rhythm imposed by the machine.

One reason for the agitation that some patients experience is a sudden rise of positive intrathoracic pressure through the process of dynamic hyperinflation. When these intubated patients are deeply sedated and paralyzed, respiratory efforts cease and vasodilation occurs related to hypercapnia and sedation. The consequent buildup of intrathoracic pressure, coupled with a fall

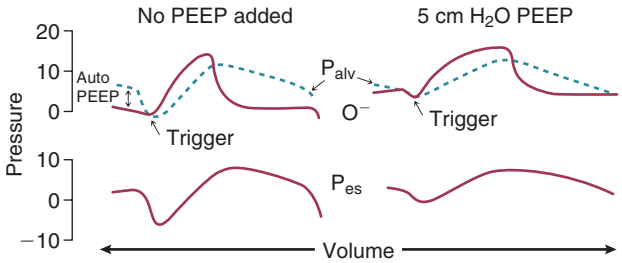
in mean systemic vascular pressure, almost routinely depresses venous return and cardiac output (see Fig. 10.3). Therefore the physician is well advised to remain alert to the predictable development of cardiovascular depression and hypotension after intubation or sedation and be prepared to intervene to reduce ventilation or to support the circulation at the initially selected level, or both. A catastrophic error is to misinterpret the development of sudden hypotension as the uncloaking of tension pneumothorax and then to undertake needle puncture of the chest wall. In such individuals it is also wise to remember the potential contribution of auto-PEEP to hypotension during cardiopulmonary resuscitation attempts.

Shortly after intubation there may be agitation, coughing, and retching related to tube insertion. When this interferes with comfort or ventilation, many lightly sedated patients benefit from 3 to 5 mL of 1% to 2% lidocaine instilled through the endotracheal tube. Instillation may be repeated one or two times, but care should be exercised, as lidocaine is easily absorbed via the lung. Fortunately, intolerance of tube placement gradually abates with sedation and the passage of time.

Machine Settings

As a general rule, ventilation should be adequately supported during this initial phase, but it is better to underventilate cautiously than to overventilate the patient. One reasonable approach is to use assisted flow-regulated volume-controlled mechanical ventilation, delivered with a square wave profile, with the backup rate set to provide about two-thirds of the estimated minute ventilation requirement. Although the flow setting is adjusted empirically to coordinate the cycle lengths of the patient and the ventilator, an initial peak flow setting of approximately four to six times the minute ventilation requirement (depending on whether the flow profile is square or decelerating, respectively) usually suffices to meet expiratory time requirements and minimize auto-PEEP without imposing undue risks that attend extraordinarily high peak cycling pressures. Assuming a minute ventilation of 10 L/min, a constant flow setting of about 40 to 60 L/min is usually appropriate. This yields an I:E ratio of approximately 1:4, which is considerably shorter than customary in a patient with normal mechanics who breathes at this level of minute ventilation. Reducing the I:E ratio still further may not improve gas trapping noticeably at modest levels of ventilation, as terminal rates of airflow are predictably very low.[5] On the other hand, increasing airflow carries a high airway pressure cost in patients with such severe AO. For similar reasons, a constant inspiratory flow is preferable to a decelerating one when flow-controlled, volume-cycled ventilation is in use. Pressure-targeted ventilation is a sensible choice only when it is monitored closely or adjusted automatically by the ventilator to maintain VT in response to changing airflow impedance.

The triggering threshold of the ventilator is set to be as sensitive as possible, and the auto-PEEP level is estimated when feasible to do so. (Measurement typically requires passive inflation to allow predictable occlusion of the circuit at end-expiration.) If auto-PEEP exceeds 5 cm H_2O and expiratory flow is limited during tidal breathing (which is almost invariably the case during the initial phase), an uncomfortable patient who makes spontaneous breathing efforts may benefit from the addition of a low level of end-expiratory pressure to counterbalance auto-PEEP, reduce the incidence of ineffective triggering efforts, and reduce the breathing workload (Fig. 10.9). PEEP levels in excess of 15 cm H_2O may be necessary in some unusual instances to reestablish patency of some air channels.



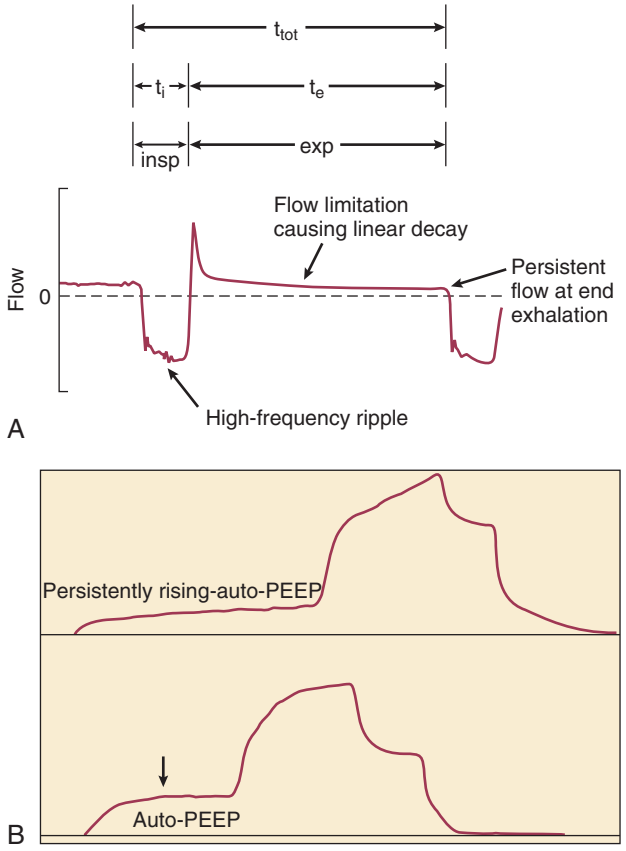
• **Fig. 10.9** Work of breathing and ventilatory effort are improved in patients with tidal flow limitation by the addition of PEEP marginally less than the original value of auto-PEEP. Airway pressure *(top)* and intrapleural pressure *(bottom)*. P_{alv}, Alveolar pressure; P_{es}, esophageal pressure.

The plateau pressure is a better guide to the degree of hyperinflation than is the measured level of auto-PEEP, for reasons of heterogeneous mechanics already discussed. First, most machines do not allow estimation of auto-PEEP in a patient who is spontaneously triggering the ventilator and varies the length of the respiratory cycle. On the other hand, a plateau pressure estimate is usually recordable during triggered, as well as during controlled, volume-cycled breathing. Just as importantly, the auto-PEEP estimated by central airway occlusion is simply the volume-weighted average of those airways that remain open at end-expiration, which generally have shorter time constants and better mechanical properties than those that seal earlier in the expiratory period at higher pressure (see Fig. 10.2).

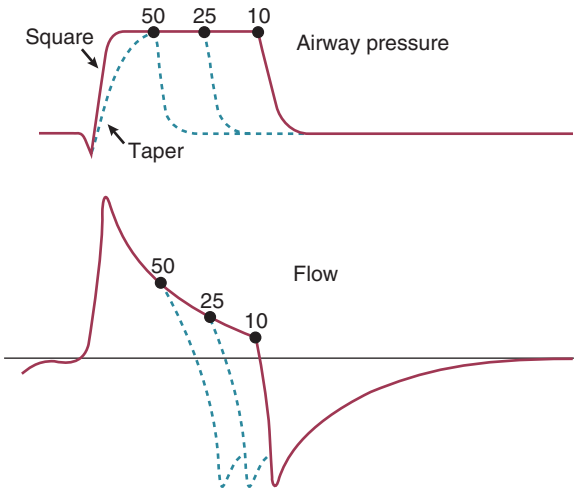
The flow tracing gives some indication of the underlying presence of gas trapping but does not indicate its severity. For example, a severely obstructed airway may be totally occluded and therefore unable to transmit its high pressure to the pressure sensor located within the machine circuitry. Similarly, a severely narrowed airway may give rise to almost imperceptible flow at end-expiration. Several features of the flow tracing are of value: high-frequency variations of the flow tracing during exhalation suggest the presence of retained central airway secretions or water in the external tubing. An abrupt transition between the earliest part of expiration and what follows ("hockey-sticking") indicates a flow limitation during tidal breathing and the potential value of added PEEP if flow persists to the onset of the next breathing cycle (Fig. 10.10). Several signs appearing in the monitored airway pressure and flow signals have been reported to be signatures of partial central airway occlusion, as by mucus plugging (see Fig. 10.8).[32]

Support Phase Management

After the first hours of ventilatory support, rational management focuses not only on reversal of the underlying problems of infection, bronchospasm, secretion retention, and cardiac insufficiency, but also on replenishing spent nutritional reserves and building endurance. It makes sense to support ventilation fully in patients intubated for ventilatory failure while fundamental pathologic processes and precipitating causes are being addressed—at least for the initial 24 to 48 hours. Because it is not known what intensity of ventilatory effort is best for patients with AO to undertake during the support phase of the illness, controversy exists as to the optimal mode of ventilation. During the support phase, the major ventilation objective while the acute problems causing deterioration are being addressed should be to provide sufficient breathing assistance to alleviate discomfort while not risking deconditioning of the



• **Fig. 10.10** A, Typical flow tracing of a patient demonstrating flow limitation during tidal breathing. High-frequency ripple suggests secretions or circuit fluid, whereas "hockey-sticking" and linear flow decay during expiration characterize flow limitation. B, Configurations of airway pressure tracing after end-expiratory airway occlusion for heterogeneously (upper), and homogeneously (lower) distributed auto-PEEP. *exp,* Expiration; *insp,* inspiration; *PEEP,* positive end-expiratory pressure.



• **Fig. 10.11** Adjustment of the expiratory flow trigger during pressure support can help to compensate for a slowly decelerating inspiratory flow profile that typifies patients with severe airflow obstruction. The appropriate adjustment in this schematic drawing might be from 25% to 50%.

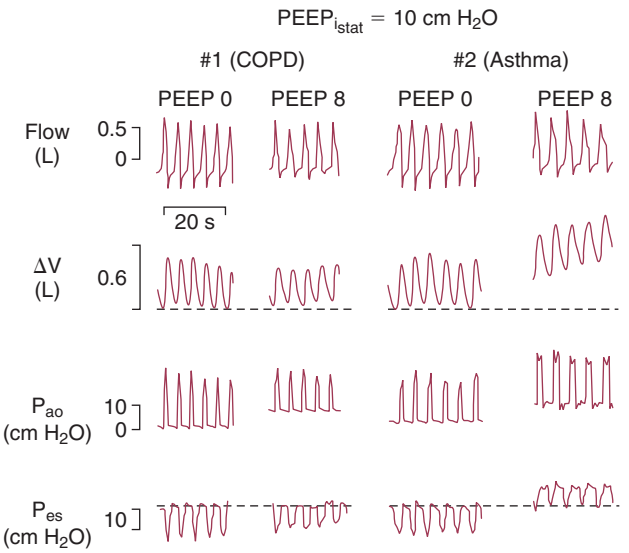
ventilatory muscles. To this end, it is reasonable to use volume- or pressure-targeted assist-control (assisted mechanical ventilation) or even synchronized intermittent mandatory ventilation (SIMV). Although the latter has seen decreasing use in recent years, it still proves helpful when a consistent back-up rate is needed while reducing the asynchrony otherwise encountered with purely time-cycled modes such as VCV or pressure-controlled ventilation (PCV). In patients who are not deeply sedated and who breathe chaotically, the latter mode applied with pressure support sufficient to replicate the VT of the mandated breaths may reduce the number of dyssynchronous "collisions" between the rhythms of patient and machine. Adequate sedation must be provided to ensure comfort and reduce the minute ventilation requirement as other fundamental elements of ventilatory therapeutics are addressed (e.g., antibiotics, corticosteroids, regulation of intravascular volume, secretion expulsion or extraction, cardiovascular support).

Ensuring adequate oxygenation, ventilatory muscle rest, and restorative sleep deserve emphasis. Deep sedation and muscle relaxants, although occasionally necessary in achieving therapeutic objectives early in the ventilatory process, may prove detrimental when their use is prolonged unnecessarily. Not only does sedation present risks of muscle deconditioning and even neuromyopathy, but secretions tend to pool in dependent areas when breathing efforts and coughs are suppressed. As a general rule, deep sedation and paralysis should not be continued for longer than 40 to 72 hours after intubation.

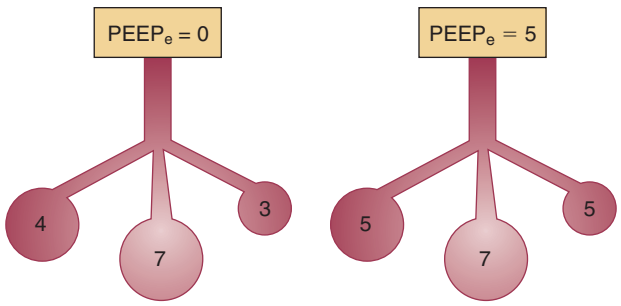
Decelerating flow profiles are often poorly tolerated by the patient with severe AO who makes spontaneous efforts, because the latter half of the inspiratory period may require higher flows than imposed by the tightly regulated and stereotyped flow waveform of the ventilator. Raising the flow criterion off-switch that triggers expiration can help manage this problem during pressure-supported ventilation (Fig. 10.11).

PEEP and CPAP in Severe Airflow Obstruction

The deliberate use of PEEP in patients with AO historically has been considered undesirable, but there is now ample reason to believe that most of these patients benefit from the application of low levels of PEEP or continuous positive airway pressure (CPAP).[5,10,11] When applied downstream of airways that collapse dynamically during the exhalation phase of tidal breathing, PEEP helps to improve the effective triggering responsiveness of the machine without significantly increasing the alveolar pressure or hyperinflation (Fig. 10.12). Most benefit is provided to patients receiving VCV who do not experience proportionate increases of peak static or peak dynamic cycling pressures after PEEP application.[10,11,35] When using a fixed level of targeted pressure (pressure control or pressure support), VT may increase after PEEP is applied. This occurs because the added PEEP counterbalances auto-PEEP to allow the applied inspiratory pressure to more effectively drive inspiratory flow. In effect, PEEP improves the pressure gradient that drives *inspiratory* flow and delivers VT. (Should minute ventilation increase with PEEP application, total PEEP may also rise.) Applied PEEP may also help to keep airways more widely patent, and thereby improve secretion clearance and bronchodilator deposition. Finally, the application of external PEEP theoretically may help to even the distribution of ventilation among multiple units with heterogeneous time constants, but this potential benefit has not been definitively shown (Fig. 10.13).



• **Fig. 10.12** Differing responses of a flow-limited patient with chronic obstructive pulmonary disease *(COPD)* and a non–flow-limited patient with asthma to the application of PEEP. The increases of lung volume *(V)* and airway opening pressure (P_{ao}) in asthma and the relative absence of these features in the patient with COPD are demonstrated. *PEEP,* Positive end-expiratory pressure. (From Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis.* 1993;147:5–13.)



• **Fig. 10.13** PEEP evens the flow distribution by counterbalancing auto-PEEP in flow-limited channels with differing levels of gas trapping. *PEEP,* positive end-expiratory pressure; *PEEP$_e$,* external PEEP.

Newer Modes of Ventilatory Support in Airflow Obstruction

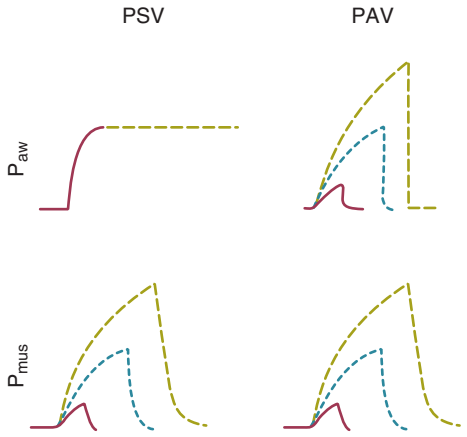
Currently the majority of ventilatory support of AO is still provided with modes of ventilation that are now decades old—flow-controlled, volume-cycled ventilation ("assist-control"); pressure assist control (pressure control, PCV); pressure support (PSV); and SIMV. When combined with PEEP/CPAP and an attentive provider, these time-tested options suffice for the majority of patients. Increasingly, however, practitioners have recognized the need to offload to the ventilator responsibility for minute-by-minute and even intrabreath adjustment of settings for flow and pressure delivery in response to changing conditions of mechanics or ventilatory demand. Patients with dyspnea generally need a faster rise of pressure and flows to their target values, unimpeded inspiratory flow, and precise termination of the ventilator's inspiratory phase to avoid collisions between the patient's neural and the ventilator's mechanical cycling rhythms. Once set, however, a specified flow pattern regulates the ventilator's gas delivery, whereas pressure control caps airway pressure at the targeted value. Just as importantly, these time-cycled assist-control modes (whether flow or pressure regulated) disregard the duty cycle rhythm variations of the patient's own drive center; therefore asynchrony occurs commonly in these modes, and asynchrony may result not only in dyspnea but also in adverse outcomes.[36,37] Avoidance of the triggering, power, and cycling dyssynchronies that are so common among acutely ill patients has now become a key focus of optimized ventilator care. Appropriate moment-by-moment intracycle adjustment of flow or pressure is not an option with "traditional" modes of ventilation. Logic dictates that better synchrony between patient and machine would require continuously monitored feedback and flexibility to adjust to the vagaries of patient need. Of the newer modes of ventilation, four with implications for AO have garnered considerable attention and have been incorporated into some of the latest equipment.

Airway Pressure Release Ventilation and Bilevel Ventilation

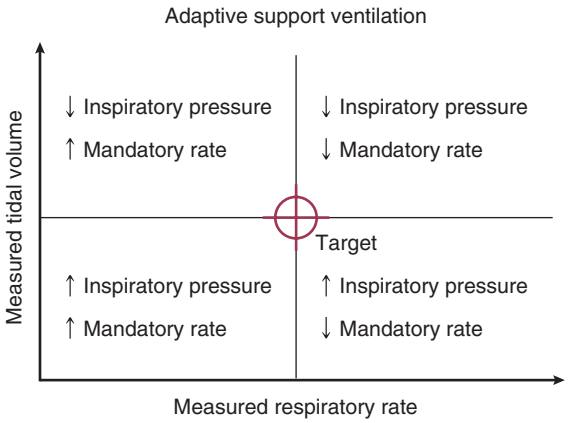
These modes were neither designed nor intended for patients with lengthy expiratory time constants. Airway pressure release ventilation does not take full advantage of its release phase in patients with lengthy expiratory time constants and therefore ineffectively ventilates unless the release frequency is high. At the same time, maintaining mean alveolar pressure relatively high is a priority. The machine's inspiratory phase pressure is generally higher than that encountered during conventional ventilation, introducing the problems associated with sustained hyperinflation in patients with relatively flexible lungs. Wide variations of auto-PEEP and of release cycle volumes are to be expected. The addition of PEEP to airway pressure release ventilation may not prove effective in mitigating this variation during release cycles unless the release phase had been prolonged sufficiently to encounter flow limitation during tidal breathing. Bilevel ventilation alternates ventilation around two levels of CPAP and may take better advantage of PEEP's work-offsetting effect. Again, however, this mode holds little advantage over more conventional options for patients with AO.

Proportional Assist Ventilation

Proportional assist ventilation (PAV)—a mode based on the equation of motion of the respiratory system that regulates delivered pressure in proportion to externally sensed inspiratory flow and volume—effectively mimics the actions of an auxiliary muscle in patients without gas trapping.[38–40] Quite unlike pressure support, which targets the same pressure for every breath, PAV takes resistance and compliance into account and is meant to provide help breathing in proportion to patient effort according to a percentage designated by the provider (Fig. 10.14). Unfortunately, ventilatory impedance varies considerably in patients with AO, and a considerable fraction of inspiratory muscle effort is spent in counterbalancing variable auto-PEEP, an event that precedes the onset of inspiratory flow. Given the strong dependence of dynamic hyperinflation on minute volume ($\dot{V}E$) and the expiratory time constant, the original version of PAV could not easily fulfill its intended function in patients with severe OA and changing mechanics or minute ventilation needs. Despite these theoretical disadvantages, a modern adaptation of PAV (e.g., PAV+)—which monitors respiratory mechanics several times or more per minute on an ongoing basis—has shown at least equivalent comfort in patient trials, as well as no greater incidence of missed triggering events and greater V_T variability



• **Fig. 10.14** Comparison of pressure support ventilation *(PSV)* and proportional assist ventilation *(PAV)* in response to muscular efforts of varying intensity. The machine pressure mirrors the patient's muscular effort during PAV but not during PSV. P_{aw}, Airway pressure. (From Younes M. Proportional assist ventilation, a new approach to ventilatory support. Theory. *Am Rev Respir Dis.* 1992;145:114–1120.)



• **Fig. 10.15** Regulation of ventilation by adaptive support. By changing the number of mandated pressure-controlled breaths and by regulating the pressure applied to each triggered cycle, adaptive support aims to keep breathing frequency and tidal volume within acceptable physiologic ranges (see text).

than pressure support, both in invasive and noninvasive settings.[41] Although reassuring, no outcome advantage over PSV has yet been convincingly demonstrated in any AO setting.

Neurally Adjusted Ventilatory Assist

Neurally adjusted ventilatory assist (NAVA) is similar in concept to PAV in that it attempts to regulate the machine's power support moment by moment by sensing inspiratory effort from the patient.[40,42] The difference is that the diaphragmatic electromyogram provides the pressure-controlling signal for the machine, so that the electrical intensity of phrenic nerve traffic regulates the amplitude and the pattern of the inflation pressure delivered. NAVA depends on the patient's drive to breathe, not the lung's mechanical response. A thin, multielectrode esophageal catheter is used to pick up the strength and contour of the electromyogram signal, and failure to detect it has not proven a major problem. The dynamic hyperinflation drawbacks of PAV in patients with AO are theoretically nullified by placing the "effort detector" closer to the respiratory drive controller—inspiratory efforts related to auto-PEEP are tracked and supported before inspiratory flow actually begins. Inherent protective reflexes are believed to help the patient avoid overdistention, even if the machine's power boost factor is set inappropriately high. Despite its intuitive appeal, NAVA is still too recently deployed in the clinical arena to confirm its theoretical advantage over other options.

Adaptive Support Ventilation

Adaptive support ventilation (ASV) regulates machine output with pressure-targeted breaths delivered at a variable frequency and with variable pressure in accordance with the clinician-set minute ventilation target and the breathing pattern across a sequence of multiple breaths (Fig. 10.15). It can be used during triggered (pressure-supported) or controlled (pressure-controlled) ventilation. Its intent is to minimize the work of breathing and auto-PEEP while avoiding both hypoventilation and hyperventilation. ASV attempts this by optimizing the VT and frequency combination that comprises the targeted minute ventilation. As such, ASV is one step closer to "closed-loop" ventilation, in which clinical goals are set, monitored, and accomplished automatically. Once the clinician has determined the PEEP, fraction of inspired oxygen, and cycling ramps and triggers for pressure support, he or she must input the patient's predicted body weight or height and age as well as the fraction of the estimated "normal" minute ventilation (approximately 100 mL/kg per minute) the machine should provide for that disease state. It then varies the mandatory breath number and the pressures of a pressure-regulated SIMV algorithm to stay within the desired breathing pattern zone. All the while, the machine tries to nudge the patient toward the ventilatory pattern optimum that *should* minimize dead space, work of breathing, and auto-PEEP.

In observational studies ASV appears to regulate VT and total breathing frequency effectively, without the need for clinician intervention.[43] As with all advanced modes, however, its performance in severely stressful settings has not been validated and no convincing outcome benefit has yet been reported. As originally implemented, ASV lacked gas exchange feedback, did not calculate total physiologic dead space, and did not account for adjustment to the ideal optimum breathing pattern incurred by disease or deformity.

A refinement of ASV (Intellivent-ASV, Hamilton Medical, Reno, NV) incorporates end-tidal CO_2 and pulse oximetry data and is somewhat more complicated to set up as the ranges for three controllers must be specified. Nonetheless, it is a promising approach that modifies machine output in response to changing need and patient response and may prove to reduce the gas trapping that dysfunctional patterns of AO engender.

Extracorporeal Carbon Dioxide Removal

While still in its initial stage of clinical deployment, extracorporeal CO_2 removal by intravascular catheter holds undeniable logical appeal for use in the most severely ill and/or refractory patients with AO.[44] Because blood flowing through the external circuit can be virtually scrubbed free of its CO_2 content, relatively low blood flows are required in exchange for considerable benefit regarding the pulmonary workload associated with any given metabolic state. In turn, reduced ventilating burden attenuates dyspnea and conceptually may spare the need for airway intubation and invasive mechanical ventilation, especially when used in conjunction with NIV. Moreover, in patients with adequate hemodynamics, blood flow through the external CO_2 exchanger may be driven by the

arteriovenous pressure gradient. Mechanical pumps are clearly more effective and would be required in patients with limited cardiac reserve, but the associated apparatus is inherently more complex. Although the hazards of this methodology currently remain very significant and reliability needs further enhancement, recent improvements in anticoagulation, catheters, exchangers, and circuitry suggest that variations of this promising methodology will offer a viable as well as logical consideration for many severely ill patients with life-threatening ventilatory failure in the relatively near future.

Weaning ("Liberation") Phase

Protracted ventilator dependence is perhaps the most feared consequence of intubating patients with exacerbated COPD and perennial asthma. Not only are breathing workloads high, but the ability of the patient to sustain them is compromised by muscle weakness, hyperinflation, disadvantageous thoracic geometry, blunted ventilatory drive, and abnormal cardiovascular function. Rational management of the patient with AO includes provision of adequate rest and nutritional support; enhancement of mental, neuromuscular and cardiovascular function; and minimization of the breathing workload. Maintenance of positive mental attitude and avoidance of sedation excess can greatly speed the weaning process. It has been argued that few if any patients benefit from the gradual removal of ventilator support.[45] Although this argument holds validity for many patients, those with life-threatening exacerbations of AO are among those most likely to benefit.

Patients remain dependent on mechanical ventilation for a wide variety of reasons (failure to wean). Among these are hypoxemia, cardiac arrhythmias, hemodynamic instability, and psychological dependence. However, imbalance between ventilatory capability and demand is perhaps the most common reason for failure to wean in patients with ventilatory failure either of itself or because it provokes worsening of one or more of the other factors just mentioned.[46,47]

Predicting Readiness for Spontaneous Breathing

In clinical practice a panel of indices has long been used to predict the outcome of the weaning trial. Most individual elements of these demand and/or capability panels can be classified as indicators of either one or the other, but not both. Some capability indicators depend on voluntary effort as well. Thus a maximal inspiratory pressure measurement exceeding negative 30 cm H_2O and a minute ventilation requirement of less than 10 L/min are standard components of the traditional predictive battery. Although minute ventilation has been criticized as unreliable when used alone, it is still a highly useful observation, particularly when referenced to blood gas measurements, body size, gender, and integrated into an evaluation of other panel elements. When the patient is calm, a high degree of variation of minute ventilation suggests some degree of ventilatory reserve.[48] Because the product of minute ventilation and the average inspiratory pressure per breath are the main components of the breathing workload, minute ventilation must not be disregarded, even when more integrative indices are in use, such as the frequency-to-VT ratio (rapid shallow breathing index [RSBI]).[49] For example, a high RSBI does not necessarily portend failure if the patient has restrictive physiology of lung or chest wall and/or minute ventilation rises from the baseline value as well. Such an observation may simply reflect the most efficient breathing pattern during tolerable exercise. A steadily rising RSBI during the trial is more concerning, especially if the patient exhibits signs of distress. Published criteria for RSBI lose some reliability in the presence of neuromuscular weakness, severe restriction, or chronic illness requiring ventilator support.[47]

Numerous other weaning outcome indices have been suggested over the years, but none stands alone as infallible, including the RSBI. The most successful of these indicators reliably relate power requirement for ventilation to the ability of the patient to sustain it. Certain physiologic measurements such as the $P_{0.1}$ (a measurable indicator of ventilatory drive now offered on some of the newest ventilators) have predictive appeal. These are not universally available, however, and cannot be relied on for definitive judgment in every case. Because many factors may limit the patient's ability to be removed from the ventilator, more than one single indicator is usually necessary to observe. Alertness, degree of cardiovascular compensation, clinical trajectory over the preceding days, oxygenation status, secretion load, upper airway patency, coughing efficiency, and psychological well-being are as important as any single predictive measure based on mechanics and muscle strength. Successful weaning protocols take all such factors into account.[46,47,49]

Repeated failure to wean is often explained by cardiovascular factors such as ischemia and diastolic dysfunction, particularly among elderly patients with COPD. This is especially true when parameters based on ventilation appear favorable. Clues may appear in the form of cardiac dysrhythmias and an unfavorable excess of fluid intake over output. In part for such reasons, weaning protocols must be constructed and applied carefully; failure to meet weaning criteria must be considered a cue to undertake a careful review of all potential factors that prevent success, not necessarily an indication to allow a bit more time with unchanging therapy.

Weaning Approaches

Preparations

Preparations for ventilator withdrawal should include ensuring adequate nocturnal rest with fully supported breathing, adequate nutrition, good circulatory reserve, avoidance of excessive intravascular volume and edema, treatment of infection, appropriate body positioning, and judicious sedation.[46,49] Obstipation, urinary retention, pleural effusions, gastric distention, musculoskeletal pain, severe anemia, and chemical imbalances must be avoided or reversed. During the full support phase of ventilation, care must be taken not to allow sedatives to accumulate or secretions to collect within the airways. Intermittent "as-needed" dosing is preferred to steady infusion or scheduled dosing of sedatives, and if used at all, interruption of sedation should be implemented daily. Heat-moisture exchangers do not hydrate the airway secretions reliably, especially in low humidity environments or when high inspired concentrations of oxygen have been in use. Active humidification often proves the better choice when secretion load or clearance is problematic. Inspection of the central airway before attempted extubation may be rational in tenuous patients when intubation has continued for more than a few days, as thickened or inspissated secretions may not have been adequately removed by routine suctioning. The patient must not depend on high levels of PEEP for either oxygenation or comfort. It must be remembered that PEEP and CPAP aid ventilation in patients with flow limitation and auto-PEEP.

The use of frequent wake-ups, intermittent dosing, and short-acting sedatives (especially in the hours before spontaneous breathing trials and weaning attempts) has helped to avoid the common problem of benzodiazepine metabolite hangover; lingering sedative

effects may persist for up to a week after the last benzodiadepine dose was given. As a complement or alternative to minimized and low-dose benzodiazepines, dexmedetomidine (Precedex), a sedative agent with relatively little hypnotic action, has proved helpful when calm alertness is desired but difficult to otherwise achieve.[41] In well-selected cases, alertness-enhancing drugs such as modafinil (Provigil) have been helpful. Delirium should be addressed to the extent possible by nonpharmacologic means, such as verbal redirection, restoration of diurnal wake and sleep schedules, minimized sedation, repositioning, and mobilization. Delirium that interferes with weaning occurs commonly and may benefit from such agents as quetiapine and olanzapine.[50,51] The highly effective interventions of noninvasive ventilation and high-flow nasal cannulas often act as effective "bridges" to fully spontaneous breathing once the tube is removed.

Specific Modes for Weaning

Considerable effort has gone into the delineation of the optimal weaning technique. It is generally true that the majority of patients do not need a lengthy period of gradual machine withdrawal once the primary problems that brought the patient to medical attention have been treated and the adverse effects of fluids and drugs given during their acute problems have been addressed.[52] It is also true, however, that a distinct subset of these patients with underlying AO or other chronic impairments not amenable to therapy cannot tolerate abrupt transitions to spontaneous breathing. More graded reloading is sometimes necessary because of fragile cardiovascular status, neuromuscular weakness, or psychological factors. Pressure support ventilation is generally to be preferred to SIMV, as the muscle and cardiovascular reloading process tends to be less sudden and more predictable. Use of intermittent T-piece weaning makes little sense in patients like this; each transition to fully spontaneous breathing abruptly imposes a full stress workload. All patients, however, should be *tested* with low-level pressure support or T-piece breathing before any gradual withdrawal of support is undertaken, as the latter may not be necessary.[53] Once the patient is breathing with a low level of pressure support or from an oxygenated T-piece, observation should be continued at least 30 minutes, but generally less than 2 hours before decannulation of the airway is attempted. During the attempt at spontaneous breathing, the patient must be watched carefully and not allowed to fatigue because recovery from that condition may require more than a day to restore energy reserve.[54] Although careful implementation of weaning protocols by a dedicated team is highly effective, it is worth noting that two modes that have recently been introduced to accelerate and automate weaning—namely, Smartcare/PS (Draeger Medical, Lübeck, Germany) and ASV—have met with some success in facilitating that process. For settings in which appropriate protocols are not rigorously applied or patient surveillance not closely maintained, both approaches hold strong appeal.[55]

Periextubation Phase

In intubated patients in whom upper airway obstruction is suspected, a cuff deflation test should be conducted before decannulating the airway. This is performed by elevating PEEP to 10 cm H_2O immediately in advance of deflation. An audible leak should be heard if the glottic space is not prohibitively tight. With the tube cuff deflated and no audible leak, the sitting position, manipulation of head position, slight (1–2 cm) caudal displacement of the tube, and a temporary increase of PEEP during ventilation may help break a "mucus seal" that otherwise prevents gas leakage. In questionable cases, advance preparations should be made for urgent intervention, should that prove necessary after tube extraction.[33]

The immediate postextubation phase should be as carefully managed as the ventilated one. The first 24 hours off the ventilator are often difficult, but in successful cases there should be progressive improvement. Coughing, deep breathing, adequate oxygenation, avoidance of arrhythmias, adequate bronchodilation, airstream hydration, maintenance of a clear central airway, and a mechanically efficient posture are crucial. Oral refeeding must be undertaken with extreme caution because swallowing difficulty and dysfunction can persist days to weeks after extubation in patients who have been ventilated for lengthy periods. CPAP and intermittent NIV may be especially helpful in selected patients,[33,56] especially in the nighttime hours. Interfaces for NIV have improved remarkably in recent years, facilitating NIV use. In some patients with AO who require only modest ventilation assistance, well-hydrated high flow nasal cannulas (HFNCs) (30–50 L/min of blended gas) can provide a well-tolerated and effective option.[57,58] The mechanisms for therapeutic ventilation effect with this modality may include (1) an modest upper airway CPAP effect that helps dilate the upper and lower airways; (2) CO_2 washout from the pharynx and upper trachea; (3) reflexes that reduce the sensation of dyspnea, slow the breathing rate, and improve ventilating efficiency; and (4) an expiratory retard similar to the effect of pursed lips breathing (HFNC physiology). This comparatively comfortable methodology allows for speech, eating, and expectoration.

NIV (often referred to by its now generic but once commercial designation of Bi-pap [biphasic positive airway pressure]) affords greater ventilating power than HFNC, helps maintains patency of an edematous upper airway, and provides ventilation support during all phases of sleep. This often proves important in patients who have received sedating medications and/or are sleep deprived. It must be used judiciously, however, and carefully applied. Ventilation by pressurized mask impedes secretion clearance, and if a humidifier is not used, mouth-breathing during Bi-pap dries secretions and encourages displacement of oral material into the central airway. Therefore it is not uncommon for patients who receive mask ventilation after extubation to require reintubation for clearance of thickened airway mucus.

Key Points

- By assuming a major portion of the ventilator workload, mechanical ventilation affords the opportunity to rest the respiratory muscles while maintaining pH homeostasis and oxygenation, thereby averting progressive ventilatory failure or respiratory arrest, or both.
- Increased resistance to airflow and gas trapping is responsible (directly or indirectly) for many of the physiologic disturbances that typify AO.
- When dynamic collapse occurs during tidal respiration and breathing requirements are high, there is little alternative to hyperinflation, CO_2 retention, or both.
- Ventilation-perfusion mismatching is prevalent in patients with severe AO, reducing the efficiency of CO_2 elimination but allowing for hypoxemia reversal by relatively low levels of oxygen supplementation.

- Pressure-targeted modes of ventilation, exemplified by pressure control and pressure support, have become increasingly popular in the care of intubated patients, as well as those receiving NIV by face mask.
- Most patients hospitalized with exacerbations of asthma or COPD can be managed effectively by regimens that incorporate aggressive secretion clearance techniques, antibiotics, corticosteroids, intensified bronchodilators, hydration, cardiovascular support, and supplemental oxygen.
- The first 24-hour period after tracheal intubation and initiation of positive-pressure ventilation is a highly dynamic one for many patients with AO.
- The majority of ventilatory support of AO is still currently provided effectively with modes of ventilation that are now decades old—flow-controlled, volume-cycled ventilation (assist-control); PCV; PSV; and SIMV. However, newly developed ventilator modes and nonventilatory innovations point the way toward more effective and comfortable life support.
- Careful attention to the nature and quantity of sedation, coupled to daily attempts to awaken and test spontaneous breathing, accelerates liberation from mechanical ventilation.
- The postextubation phase should be as carefully managed as the ventilated one. The first 24 hours off the ventilator are often difficult and tenuous. During this phase, close attention to secretion clearance, quality sleep, upper airway patency, appropriate upright positioning, and fluid management help avert the need for reintubation.
- NIV and HFNC are valuable adjuncts to care both before and after intubation.

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Review Questions

1. For patients with chronic obstructive pulmonary disease (COPD), dyspnea during exertion best correlates with which one of the following?
- **a.** Heavy secretion load
- **b.** Dynamic hyperinflation
- **c.** Elevated airway resistance
- **d.** High tidal driving pressure

Answer: b. Many patients with airflow obstruction experience low levels of dyspnea until the tidal volume approaches the inspiratory capacity. Breaths taken from high chest volumes require more work to perform and inspiratory muscles are mechanically disadvantaged. Dynamic hyperinflation reduces the reserve between end-expiration and total lung capacity. Further increases of lung volume cannot be accomplished without encroaching on total lung capacity. Although secretion load, elevated airway resistance, and high tidal driving pressures all increase the breathing workload, dyspnea depends most directly on the workload-to-work capacity ratio.

2. For hospitalized patients with massive obesity which one of the following is most correct?
- **a.** Lung volume is predictably increased.
- **b.** Gas trapping is reduced by upright positioning.
- **c.** External positive end-expiratory pressure (PEEP) increases regional gas trapping in the supine position.
- **d.** Gas trapping seldom occurs in those without COPD or asthma.

Answer: b. Patients with massive obesity tend to collapse airways and gas trap upon assuming the horizontal position. The upward thrust of the abdominal pressure is reduced by assuming an upright posture, relieving the tendency for expiratory collapse. Adding PEEP to the supine patient helps keep the airways open and also relieves tidal gas trapping. Although positional gas trapping may occur, the overall tendency is for overall lung volume (as measured by FRC) to decline.

3. In patients who are passively inflated by volume-controlled mechanical ventilation, changes in gas trapping are best indexed by which one of the following?
- **a.** Difference between peak dynamic and static airway pressures
- **b.** End-expiratory esophageal pressure
- **c.** End-inspiratory plateau pressure
- **d.** End-expiratory flow rate

Answer: c. The extent and severity of regional auto-PEEP vary from site to site, influenced by local variations in pleural pressure. Thus some airways seal at relatively high airway pressures, whereas others remain open throughout the entire respiratory cycle. Measurements made at end-exhalation tend to underestimate the pressures in the units that closed earlier in the expiratory cycle. During inflation, reversibly closed units reopen as the airway pressure builds. Therefore the end-inspiratory plateau pressure during volume-controlled ventilation is influenced by the pressures in all lung units and will better reflect the difficulty of inflation owing to dynamic hyperinflation. End-expiratory flow is influenced by airway resistance in the units that remain in communication with the airway opening as well as by the auto-PEEP in those units. The end-inspiratory difference between peak dynamic and plateau pressures will reflect the end-inspiratory resistance of open channels but does not index auto-PEEP.

11

Mechanical Ventilation in Acute Respiratory Distress Syndrome

LUCIANO GATTINONI, ELEONORA CARLESSO, AND PIETRO CAIRONI

CHAPTER OUTLINE

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- Force-Bearing Structure of Lung Parenchyma
- Concept of Stress and Strain
- Driving Pressure

Patient Characterization
- Gas Exchange

Respiratory Mechanics, Chest Wall Elastance, and Lung Volume
- Severity of Lung Injury and Lung Recruitability
- ARDS Classification

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History

Extensive reviews on the history of mechanical ventilation of acute respiratory distress syndrome (ARDS) can be found elsewhere.[1,2] In the 1970s mechanical ventilation was recommended and performed with low positive end-expiratory pressure (PEEP) and high tidal volume (VT): "larger tidal volumes (10–15 per kilogram) are preferable, having been used in several thousand ventilated patients with no evidence of development of pulmonary damage."[3] Today this advice seems inconceivable. At that time, the main concerns were the putative harm of high inspiratory oxygen fraction and the hemodynamic impairment. It was later recognized in experimental and clinical settings[4–6] that high-volume/high-pressure mechanical ventilation could severely damage the lung parenchyma. Such lesions, primarily attributed to the excessive airway pressure, were collectively classified as *barotrauma*. In the same period, Suter and colleagues[7] published a report that, for the first time, systematically described the interaction between PEEP, lung mechanics, gas exchange, and hemodynamics.

In the 1980s, based on the work of Dreyfuss,[8,9] the focus progressively shifted from the potential harm of pressure to the harm of volume (overdistention), a concept that was popularized as *volutrauma*.[10] In the mid-1980s the application of computed tomography (CT)[11,12] and the quantitative approach to CT analysis[13] led to the concept of *baby lung*,[14,15] which accounted for most of the previous observations on respiratory mechanics, gas exchange functionality, and potential harm of mechanical ventilation. The premise of this line of thought is that high pressure or excessive distention applied to a small fraction of the lung parenchyma (with a size similar to the lung of a baby) unavoidably leads to structural lesions of the lung regions open to ventilation. Total *lung rest* was achievable with the use of extracorporeal carbon dioxide (CO_2) removal, targeted to prevent the damages of high-pressure/high-volume ventilation.[16–18] The target of mechanical ventilation shifted toward lung protection, rather than normal gas exchange functionality. Hickling and associates[19] proposed the "permissive hypercapnia" strategy for ARDS, providing "gentle treatment" of the portion of the lung that remains open to ventilation (the baby lung) through less aggressive mechanical ventilation, at the acceptable price of an abnormally higher arterial partial pressure of carbon dioxide ($PaCO_2$).

Substantial experimental and clinical data over the years have supported the approach of a *lung protective strategy*.[20–24] Low VT prevents the excessive global stress and strain of the baby lung, whereas higher PEEP prevents the regional excessive stress and strain by avoiding alveolar collapse and reopening during mechanical ventilation.[25] These mechanical events are associated with an inflammatory reaction of the epithelial and endothelial lung cells *(biotrauma/atelectrauma)* as shown by the seminal study of Tremblay and colleagues[26] (see also work of Dreyfuss and Saumon[10] and Tremblay and Slutsky[27]). The literature supports the thought that the harm of mechanical ventilation is due to excessive global or regional stress and strain.[28] This situation leads to two results—a physical rupture of the lung and a mechanically induced inflammation of the lung parenchyma, constituting ventilator-induced lung injury (VILI). The best "mechanical ventilation" would provide adequate gas exchange with the lowest amount of VILI.

Up until recent times, little consideration has been dedicated to the flow and the respiratory rate, although both may have a significant role in the generation of VILI. Flow may be considered as the rate at which a given strain occurs into the lung, proportional to the energy dissipated into the lung parenchyma. Theoretical considerations[29,30] and experimental evidence[31] suggest that during mechanical ventilation the importance of flow cannot be neglected. Moreover, the effects of respiratory rate are quite intuitive. In a series of experiments on healthy pigs, Cressoni et al. found that a strain considered lethal (i.e., >2) was only fatal when delivered at 15 breaths/min, not at rates of 3 to 6 breaths/min. In addition, the tidal strain was more related to injury than the static strain.[32] In this scenario, the concept of ergotrauma has been recently introduced.[33] Given these data, it can be concluded that the cause of VILI could be described as a single physical entity, which combines volume, pressures, flow and respiratory rate, the mechanical power.

Physiologic Basis of Mechanical Ventilation

Driving Force

Force is required to ventilate the respiratory system. The driving force for ventilation under normal circumstances is provided by the respiratory muscles. During spontaneous breathing, the thoracic cage expands. This causes a decrease in intrathoracic pressure (pleural pressure, Ppl) relative to the atmosphere (in normal conditions approximately 2 mm Hg of ΔPpl is sufficient to expand the thoracic cage by 0.5 L). Because the lungs are connected in series with the thoracic cage, their volume is expanded to a nearly equal extent (not considering the blood shift[34]). The force that distends the lung is the pressure difference between the alveoli and the pleural cavity (the transpulmonary pressure, PL). As the lung expands, the alveolar pressure becomes subatmospheric and gas flow is generated (*inspiration*). When the respiratory muscles relax, the potential energy accumulated in the respiratory system (lung and chest wall) returns the chest wall and the lung parenchyma to the resting position (*expiration*). In spontaneously breathing subjects, the driving force (muscular pressure, ΔPmusc) is spent partly to expand the chest wall (ΔPpl), partly to expand the lung (ΔPL), and partly to overcome the resistances to the gas flow. In *quasi-static* conditions, in which the resistances to gas flow are negligible,

$$\Delta Pmusc = -\Delta Ppl + \Delta PL$$

During positive-pressure mechanical ventilation, the rules are exactly the same, with the exception that ΔPmusc is substituted by the force provided by the ventilator, and the force is applied to the lung parenchyma and not to the chest wall. The airway pressure at plateau during an end-inspiratory pause (in quasi-static conditions), is spent first to expand the lung and second to expand the chest wall:

$$\Delta P_{aw} = \Delta PL + \Delta Ppl,$$

where ΔP_{aw} is the change in airway pressure.

In spontaneous breathing and during positive-pressure mechanical ventilation, the distending force of the lung is the transpulmonary pressure. During spontaneous breathing, pleural pressure is negative (facilitating venous return), whereas during mechanical ventilation it is positive (impairing venous return). What matters from the pulmonary perspective is the distending force (i.e., the transpulmonary pressure [ΔPL]), whereas what matters from the hemodynamic perspective is the pleural pressure (ΔPpl).

Transpulmonary Pressure

At the same driving force applied to the whole respiratory system (lung and chest wall), the resulting transpulmonary pressure may be extremely variable. If the lung is relatively "stiff" and the chest wall is relatively "soft" (e.g., during pulmonary fibrosis or ARDS of pulmonary origin), a greater fraction of the airway plateau pressure is spent to distend the lung (high transpulmonary pressure). In contrast, if the lung is relatively soft but the chest wall is relatively stiff (e.g., in the presence of an abdominal disease or severe obesity), most of the driving force is spent to move the chest wall (high pleural pressure).

To express this phenomenon quantitatively, it is convenient to consider the concept of *elastance*. The elastance of the whole respiratory system is the driving force (ΔP_{aw}) required to increase the lung and the chest wall 1 L above their resting position (total elastance of the respiratory system [Etot] = ΔP_{aw}/1 L). Part of this driving force is spent to increase the lung volume of 1 L (lung elastance [EL] = ΔPL/1 L), and part is spent to increase the chest wall by the same amount (Ecw = ΔPpl/1 L, where Ecw represents the chest wall elastance). Transpulmonary pressure (ΔPL) can be expressed as the driving force times the ratio between lung elastance and total elastance of the respiratory system:

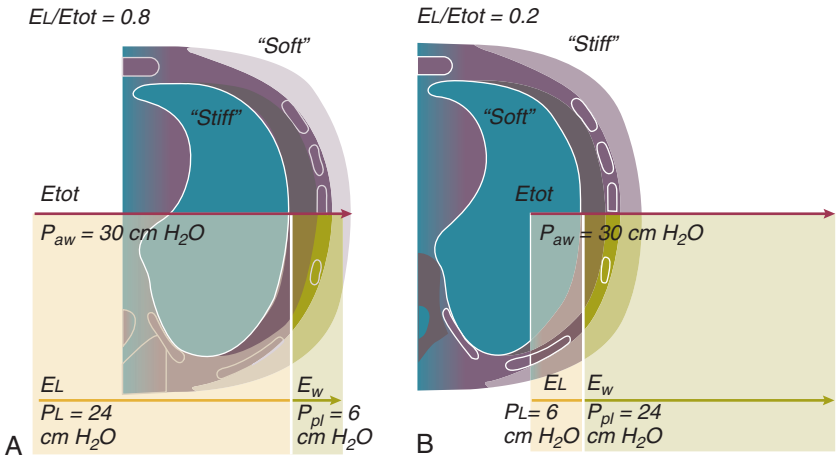
$$\Delta Pl = \Delta Paw \times EL/Etot$$

The transpulmonary pressure for a given plateau pressure uniquely depends on the ratio of lung elastance to respiratory system elastance. In normal subjects EL/Etot is approximately 0.5, whereas in patients with ARDS it may range from 0.2 (e.g., in obese patients or in patients with high intraabdominal pressure) to 0.8 (e.g., in patients with a very small baby lung and a normal chest wall elastance). This variability implies that for the same driving force applied and read on the ventilator display (e.g., 30 cm H_2O), the resulting transpulmonary pressure may range from 6 to 24 cm H_2O (Fig. 11.1).

Force-Bearing Structure of Lung Parenchyma

The transpulmonary pressure is applied to the force-bearing structure of lung parenchyma, the extracellular matrix, which constitutes the *lung skeleton*.[35] The lung skeleton is a complex and metabolically active structure that includes a network of several components—elastin, collagen, and proteoglycans. All these molecules are involved in determining the mechanical characteristics of the respiratory system. The elastin may be considered as an elastic spring, whereas the inextensible collagen, which is folded at end-expiration and completely unfolded at a lung volume equal to total lung capacity, acts as a stop-length fiber.[36,37] The proteoglycans stabilize the collagen-elastin network, contributing to lung elasticity and alveolar stability at low and medium lung volumes.[38]

The matrix of elastin, collagen, and proteoglycans is arranged in two main fiber systems: (1) the *axial* system, which originates from the pulmonary hilum and runs deeply into the lung parenchyma down to the alveolar level, where it joins (2) the *peripheral* system, which originates from the visceral pleura and runs centripetally within the lung parenchyma.[35] The lung skeleton may be considered a continuous elastic structure that reaches its extension limits at total lung capacity, a lung volume equal to about threefold the lung resting volume. At this level of alveolar distention, the collagen is completely unfolded and further expansion is prevented. The epithelial and endothelial cells do not directly bear the applied forces because they are anchored to the extracellular matrix by a



• **Fig. 11.1** Two examples of EL/Etot variability in patients with acute lung injury/acute respiratory distress syndrome. A, EL/Etot = 0.2. B, EL/Etot = 0.8. This variability implies that for the same airway pressure applied (e.g., 30 cm H_2O), the resulting transpulmonary pressure (PL) may range from 6 to 24 cm H_2O. *EL,* Lung elastance; *Etot,* total elastance of the respiratory system; P_{aw}, airway pressure; *Ppl,* pleural pressure.

series of structural proteins (integrins), which are connected to the cytoskeleton. During lung expansion, the epithelial and the endothelial cells modify their shape.

It is well documented that mechanically induced cellular deformation activates a series of mechanosensors with the production of several inflammatory mediators, such as cytokines (interleukin 6, tumor necrosis factor α, and interferon γ),[26,39] metalloproteinases (enzymes involved in the remodeling of the matrix),[40] leukotrienes,[41] and interleukin 8,[42–44] the most powerful attractor of neutrophils.[45] Gross barotrauma (e.g., pneumothorax) is due to the stress at rupture of the lung skeleton, whereas intrapulmonary inflammation is primarily due to the excessive strain of the epithelial and endothelial cells.

Concept of Stress and Strain

Stress is the applied force, and strain is the linear deformation of material. In the whole lung, the rough approximation of stress is the transpulmonary pressure, whereas the approximation of the average strain is the change in volume relative to the lung resting volume. The ratio between alveolar stress and strain is defined as *lung-specific elastance* (Espec), which is mathematically defined as

$$\Delta P_L = Espec \times \Delta V / V_0,$$

where ΔV is the volume variation applied to the lung (i.e., the VT), and V_0 is the lung resting volume (i.e., the functional residual capacity at atmospheric pressure [without any application of PEEP]). The lung-specific elastance is the transpulmonary pressure required to double the lung resting volume (i.e., the ΔP_L when $\Delta V/V_0$ is equal to 1). In ARDS, lung-specific elastance is similar to normal,[15,46] reinforcing the concept of the baby lung (lung is small and not stiff), and questions the use of normalizing the VT to the ideal body weight. The same VT per kilogram may result in completely different strain according to the size of the baby lung (the V_0 of the previous equation). For example, a 70-kg man with ARDS may have, according to the severity of the lung injury, a residual baby lung equal to 60%, 40%, or 20% of his normal lung size. If the ventilator is set to deliver 10 mL/kg, the actual delivered VT would generate an alveolar strain, which would result from the application, in normal lung, of a VT equal to 17 mL/kg, 25 mL/kg, and 50 mL/kg, values associated with a significant lung injury in laboratory studies.[10,28]

Recently we attempted to quantify the relationship between stress-strain and VILI in healthy animals. We found that edema formation was a threshold phenomenon, induced by mechanical ventilation when the global strain reaches a critical value of about 2.[47] This threshold roughly corresponds to the point where the stress-strain curve loses its linearity and starts an exponential growth, indicating that some lung regions reach their own total capacity and cannot expand any further. At this level of strain, in a period of 24 to 48 hours the mechanical ventilation is lethal and the increased lung weight (two to three times the baseline) is associated with a striking impairment of respiratory mechanics, gas exchange, hemodynamics, inflammation, distal organs damage, and 100% mortality rate. This lethal strain and associated stress, however, are rarely applied in clinical practice. To explain VILI in a diseased lung, therefore, alternative phenomena must be taken into account as the lung dishomogeneity and the presence of stress rise, which is discussed later.

Driving Pressure

Recently it has been suggested that VT should be scaled to compliance, introducing the concept of driving pressure (ΔP = Pplat – PEEP, where Pplat indicates the plateau pressure). Indeed, driving pressure is the ratio of VT to compliance, the latter indicating the "functional" size of the lung.[48,49] It is important to remember that driving pressure is one of the causes of VILI included in the computation of mechanical power, a single physical entity that combines volume, pressures, flow, and respiratory rate.[50]

Patient Characterization

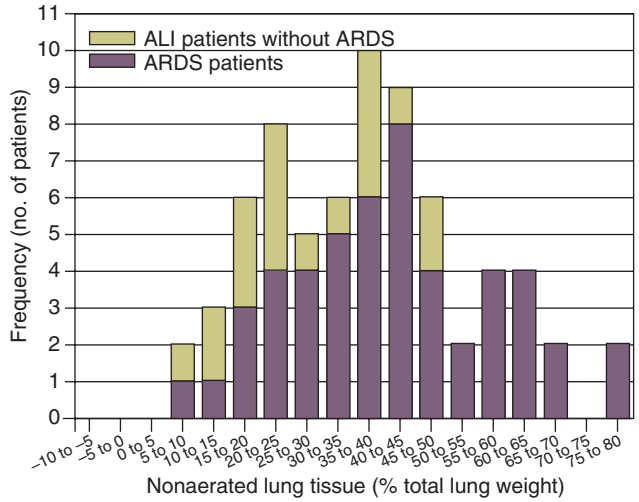
Using the least harmful mechanical ventilation setting requires a preliminary knowledge of the main pathophysiologic characteristics of the patient. The most relevant characteristics are the kind and amount of the lung injury, the chest wall elastance, and the lung recruitability.

Gas Exchange

Oxygen

The partial pressure of arterial oxygen (PaO_2), PaO_2-to-fraction of inspired oxygen (FIO_2) ratio (PaO_2/FIO_2), and Riley's shunt fraction[51] are the most commonly used variables to assess the severity of lung injury. In particular, the PaO_2/FIO_2 thresholds of 300 and 200 were originally used to define acute lung injury (ALI) (300) and ARDS (200) according to the 1994 American-European Consensus Conference on ARDS.[52] Consequently, the PaO_2/FIO_2 ratio is perceived as a key variable by most intensive care unit (ICU) physicians: The lower the PaO_2/FIO_2 ratio, the greater the lung injury. This equivalence is highly questionable. First, in most large studies on ARDS, no association was found between hypoxemia and outcome.[53] In the large study showing a better outcome with low VT compared with higher VT, the PaO_2/FIO_2 ratio was significantly lower in the low VT group despite ending with better outcome.[24] Finally, the PaO_2/FIO_2 ratio was not different in patients with early, intermediate, and late ARDS, suggesting that oxygenation was not dependent on the structural changes of lung parenchyma occurring with time.[54] In a study[55] in which the lung severity was assessed by CT scan (and defined as a fraction of the gasless tissue), we did not find significant changes of PaO_2/FIO_2 ratio over a wide range of nonaerated tissue (Fig. 11.2), and the PaO_2/FIO_2 ratio was not associated with outcome.

Most data suggest that PaO_2/FIO_2 ratio is a weak indicator of the overall lung severity, with compensatory rearrangement of perfusion during ARDS limiting the deterioration of oxygenation. The same limits apply when PaO_2/FIO_2 ratio changes are used to assess lung recruitment. Because this maneuver is unavoidably associated with changes of perfusion (global or regional), the increase of the PaO_2/FIO_2 ratio may be partly due to decrease of perfusion, as shown in the 1980s.[56–58] Most data suggest that the use of oxygenation variables alone to assess lung severity is misleading.



• **Fig. 11.2** Frequency distribution of nonaerated lung tissue, expressed as a proportion of the total lung weight, recorded at 5 cm H_2O positive end-expiratory pressure in 68 patients with acute lung injury/acute respiratory distress syndrome *(ALI/ARDS)*. *Green columns* represent patients with partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FIO_2) ratio less than 300 (ALI without ARDS), whereas *purple columns* represent patients with PaO_2/FIO_2 ratio less than 200 (ARDS). The nonaerated lung tissue was defined as the lung tissue with a physical density at computed tomography scan image analysis between +100 Hounsfield units (HU) and −100 HU, representing the portion of lung parenchyma that is consolidated or collapsed or both (i.e., the lung injury severity). (From Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1775–1786.)

Carbon Dioxide

Although less considered, the variables derived from CO_2, as the total or alveolar dead space, seem to be of greater value in assessing lung severity. It has been shown in patients with ALI/ARDS that dead space at entry is a strong predictor of outcome,[59] and that $PaCO_2$ for the same total ventilation steadily increases from early to intermediate and to late ARDS, reflecting the lung structural changes.[54] The PCO_2 response to prone position (in contrast to the partial pressure of oxygen [PO_2] response) is a strong prognostic index of mortality.[60] Most data suggest that CO_2-related variables (dead space), more than PaO_2/FIO_2 ratio, reflect the severity of lung injury (and associated mortality rate) at the time of presentation and the structural changes of lung parenchyma occurring with time (fibrosis, *Pneumocystis* infection, and possibly perfusion defects).

Respiratory Mechanics, Chest Wall Elastance, and Lung Volume

In the original description of ARDS,[61] the low compliance (i.e., high elastance) of the respiratory system was a landmark of the syndrome. The respiratory system compliance is not considered in the current definition of ARDS, however.[52] For years, the low compliance was attributed uniquely to the lung component (lung stiffness and lack of surfactant). Quantitative CT shows, however, that the respiratory system compliance primarily reflects the size of lung open to gases (the baby lung[13,15]), suggesting that the intrinsic functioning lung elasticity in ARDS is close to normal (the lung is "small" rather than "stiff"). More than gas exchange, the respiratory system compliance indirectly assesses the lung injury severity (the smaller the baby lung, the greater lung injury),[62] as confirmed in animal experiments.[63] Another variable also must be taken into account—the elastance of the chest wall. It has been shown in a significant portion of patients with ALI/ARDS that the chest wall elastance is greater than normal because of increased intraabdominal pressure, obesity, or severe edema.[64] In patients with extrapulmonary ARDS[65] and in obese patients,[66] the high elastance of the respiratory system may be due to the chest wall and to the lung derangement. Measurement of intraabdominal pressure should be considered when selecting mechanical ventilator settings.

Severity of Lung Injury and Lung Recruitability

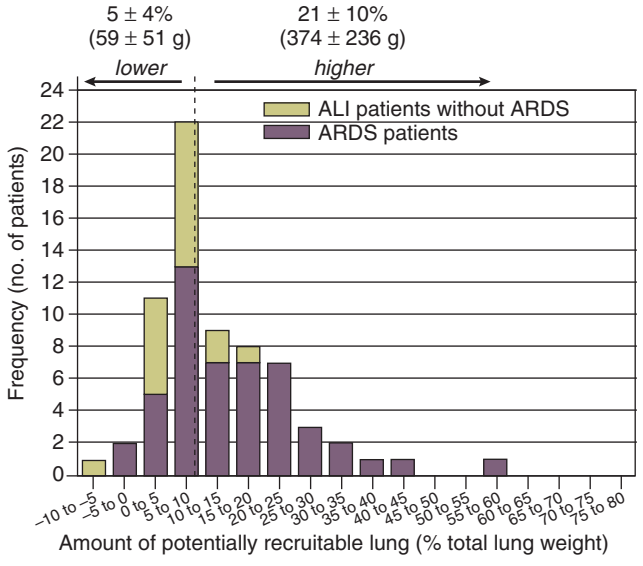
CT can be used to assess the severity of lung injury by measuring the fraction of nonaerated lung tissue at end-expiration (end-expiration pause at 5 cm H_2O). This fraction includes the lung tissue that is "consolidated" (i.e., not openable at 45 cm H_2O airway pressure) and the tissue that is collapsed but openable at 45 cm H_2O. These values were chosen to produce a minimal risk during the maneuver and because this is the most frequently used in the literature for recruitment maneuver.[67] In patients with elevated chest wall elastance, the resulting transpulmonary pressure could be insufficient, however, to overcome the opening pressure of some pulmonary units.

The total fractions of nonaerated lung tissue (consolidated plus recruitable) and the recruitable tissue alone (tissue that regains aeration at 45 cm H_2O airway pressure) are strongly associated with mortality rate. The data of Fig. 11.2 show the inadequacy of the

term ALI/ARDS, as currently defined, to describe the lung injury.[55] The data refer to a population of ALI/ARDS patients, classified according to the American-European Consensus Conference on ARDS (AECC),[52] in which a CT-based quantitative analysis of the whole-lung parenchyma at 5 cm H_2O PEEP was performed. As shown in Fig. 11.3, the fraction of the nonaerated lung tissue (consolidated or collapsed or both) may range from 5% to 70% of the entire lung parenchyma. Patients meeting ALI/ARDS criteria may have a baby lung size very close to that of normal subjects, or a baby lung that is just a small fraction of the expected normal lung. When the distending force is applied to the lungs by the mechanical ventilator, previously collapsed lung regions may open. Lung recruitability may be expressed as the amount of lung tissue regaining aeration when increasing the applied driving force from 5 to 45 cm H_2O. As shown in Fig. 11.3, in some patients lung recruitability was almost negligible, whereas in others it was equal to 25% to 35% of the entire lung parenchyma. Lung recruitability was strongly associated with the fraction of nonaerated tissue, suggesting that the greater the inflammatory edema, the greater the lung collapse. It seems that the best way to assess the overall lung severity and the related lung recruitability, both strongly associated with mortality rate, is the CT scan analysis. Physiologic variables are poor indicators of the severity of the lung injury. This relationship is shown in Fig. 11.4—that for a large variation of lung injury ranging from 20% to 60% of the lung parenchyma—the values of PaO_2/FIO_2 ratio, lung compliance, and $PaCO_2$ greatly overlap.

ARDS Classification

Although, in our opinion, the definition of ARDS should include a quantitative estimate of the lung edema, because this is not feasible in most of the ICU, alternative ways for defining ARDS have been sought. ARDS was first defined by Ashbaugh and coworkers in 1967.[61] Several other definitions have been introduced afterward, up to the AECC in 1994.[52] This conference defined ARDS as the acute onset of hypoxemia ($PaO_2/FIO_2 \leq 200$) with bilateral infiltrates seen at x-ray study and no evidence of left atrial hypertension, and these parameters were largely used for the enrollment of patients in clinical trials. In 2011 a panel of experts, under the initiative of the European Society of Intensive Care Medicine endorsed from the American Thoracic Society and Society of Critical Care Medicine, convened to develop what has been called the "Berlin definition."[68] The final Berlin definition is reported in Table 11.1. Stages of mild, moderate, and severe ARDS were related to increased mortality rates and increased median duration of mechanical ventilation in survivors.

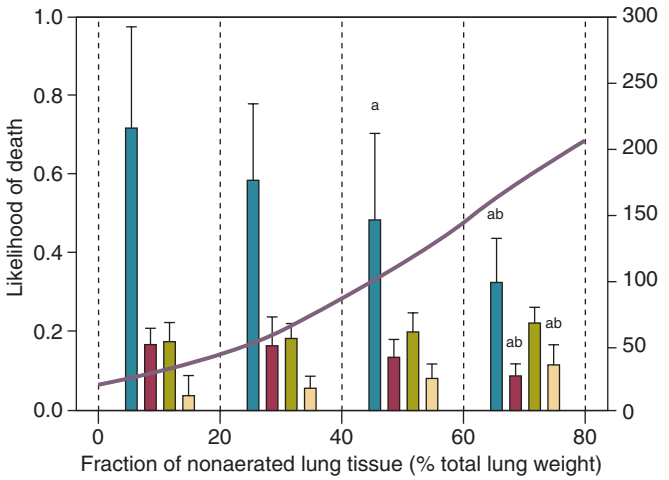


• **Fig. 11.3** Frequency distribution of 68 patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) according to the percentage of potentially recruitable lung, expressed as the percentage of total lung weight. ALI without ARDS was defined by a PaO_2/FIO_2 ratio less than 300, but not less than 200; ARDS was defined by a PaO_2/FIO_2 ratio less than 200. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration was restored at airway pressures between 5 and 45 cm H_2O. *FIO_2,* Fraction of inspired oxygen; *PaO_2,* partial pressure of arterial oxygen. (From Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1775–1786.)

Mechanical Ventilation in ARDS: Available Evidence

Setting Tidal Volume

The main results of several outcome studies specifically designed to compare different VTs are summarized in Table 11.2. A survival benefit was found in the study comparing 6 mL/kg VT versus 12 mL/kg, the highest VT range tested,[24] whereas no survival



• **Fig. 11.4** Mean ± standard deviation values of respiratory variables of a population of 68 patients with acute lung injury/acute respiratory distress syndrome. *Blue columns* represent PaO_2/FIO_2 ratio at positive end-expiratory pressure (PEEP) 5 cm H_2O (mm Hg). *Red columns* represent respiratory system compliance at PEEP 5 cm H_2O (mL/cm H_2O). *Green columns* represent dead space fraction (%), *Gold columns* represent alveolar dead space fraction (%). [a]$P < 0.05$ versus patients with a fraction of nonaerated tissue recorded at 5 cm H_2O PEEP less than 0.2. [b]$P < 0.05$ versus patients with a fraction of nonaerated tissue recorded at 5 cm H_2O PEEP ranging from 0.2 to 0.4. The *continuous purple line* represents the likelihood of death predicted by the fraction of nonaerated lung tissue recorded at 5 cm H_2O PEEP ($P = 0.015$). Weight is a poor surrogate of strain because ARDS patients with similar body weights may have completely different lung sizes and consequently different levels of strain at equal tidal volumes. This is confirmed by the plateau pressures measured in these different studies (see Fig. 11.5). As shown for the same tidal volume per ideal body weight, the plateau pressures are widely distributed with huge overlap between the studies. This reflects a wide distribution of the respiratory system compliance and consequently of the lung size.

differences were found in the other studies, which compared intermediate values of VTs.[20,22,23] As previously discussed, the VT per ideal body weight is a poor surrogate of strain because ARDS patients with similar body weight may have completely different lung sizes and consequently different strain at equal VT. This is confirmed by the plateau pressures measured in these different studies (Fig. 11.5). As shown for the same VT per ideal body weight, the plateau pressures are widely distributed with huge overlap between the studies. This reflects a wide distribution of the respiratory system compliance and consequently of the lung size.

Despite the lack of information about stress and strain in each individual patient, most available data strongly suggest that a gentle ventilation is safer than the application of high volumes and pressures. This evidence does not mean that 6 mL/kg ideal body weight represents the ideal VT. In a patient with a very small baby lung, it still may be harmful, inducing excessive strain, whereas if applied to a lung characterized by a large ventilatable area, it may be low. There is little doubt, however, that 12 mL/kg ideal body weight is excessively high and unnecessary. It is evident that low VT ventilation, decreasing the global alveolar stress and strain, is advantageous compared with high VT ventilation in different patients.

It has been suggested that a plateau pressure of 30 cm H_2O represents the safe limit for plateau pressure.[69] In a retrospective analysis, such a safe limit has been challenged, however.[70] A safe upper limit for plateau pressures in patients with ALI/ARDS could not be identified. This is understandable if we consider that the airway plateau pressure is a poor surrogate of stress owing to the high variability of the chest wall compliance. The same plateau pressure, 30 cm H_2O, may result in completely different stress values in different patients.

TABLE 11.1 The Berlin Definition of ARDS

Defining Features	Criteria
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need for objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor is present
Oxygenation[b]	
Mild	200 < Pao_2/FIo_2 ≤ 300 with PEEP or CPAP ≥ 5 cm H_2O[c]
Moderate	100 < Pao_2/FIo_2 ≤ 200 with PEEP ≥ 5 cm H_2O
Severe	Pao_2/FIo_2 ≤ 100 with PEEP ≥ 5 cm H_2O

[a]Chest x-ray study or computed tomography scan.
[b]If altitude is higher than 1000 m, the following correction factor should be used: Pao_2/FIo_2 × (barometric pressure/760).
[c]This may be delivered noninvasively in the "Mild" group.
ARDS, Acute respiratory distress syndrome; *CPAP*, continuous positive airway pressure; *FIo_2*, fraction of inspired oxygen; *Pao_2*, partial pressure of arterial oxygen; *PEEP*, positive end-expiratory pressure.
From The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–2533.

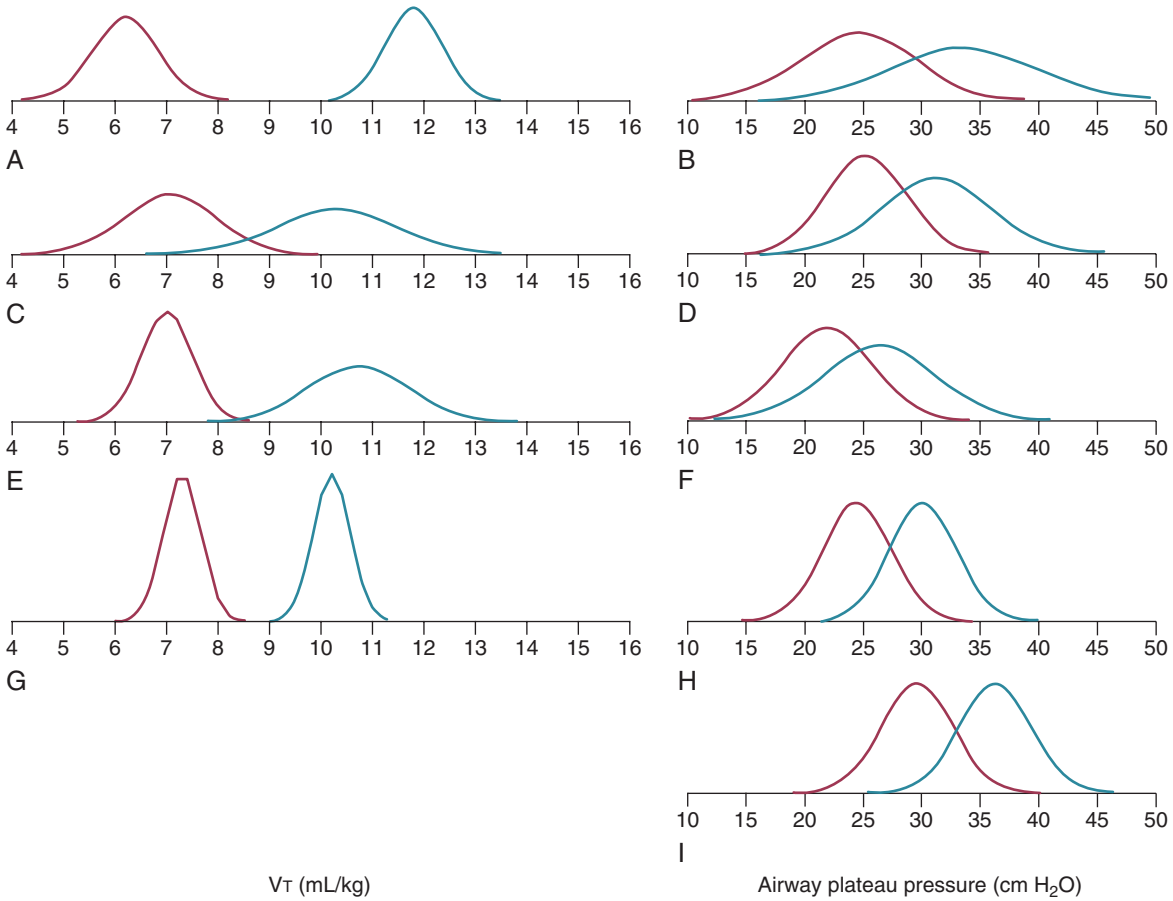
Setting Positive End-Expiratory Pressure

The available evidence on the effects of higher versus lower levels of PEEP in ALI/ARDS with ALI/ARDS is summarized in Table 11.3. As shown, despite the fact that the experimental data provide striking evidence that PEEP may reduce the damages of mechanical ventilation, the largest studies comparing higher versus lower PEEP levels in unselected patients with ALI/ARDS were unable to find any difference in outcome.[71–74] It has been suggested that PEEP should be of benefit in patients with higher lung recruitability and useless or harmful in patients with low lung recruitability.[75] Patients with greater severity are those with a lower PaO_2/FIO_2 ratio and higher recruitability as well as greater lung weight and, in general, worse CT scan findings. Two meta-analyses seem to confirm this

TABLE 11.2 Different Tidal Volumes per Ideal Weight and Airway Plateau Pressures Investigated in Other Studies

Study	Group	No. of Patients	Tidal Volume (mL/kg)	Plateau Pressure (cm H_2O)	Mortality Rate (%)	*P* (Outcome)
Acute Respiratory Distress Syndrome Network[24]	Control	429	11.8 ± 0.8	33 ± 9	39.8	.0007
	Treatment	432	6.2 ± 0.9	25 ± 7	31	
Brochard et al.[22]	Control	58	10.3 ± 1.7	31.7 ± 6.6	37.9	NS
	Treatment	58	7.1 ± 1.3	25.7 ± 5	46.6	
Stewart et al.[20]	Control	60	10.7 ± 1.4	26.8 ± 6.7	47	NS
	Treatment	60	7 ± 0.7	22.3 ± 5.4	50	
Brower et al.[23]	Control	26	10.2 ± 0.1	30.6 ± 0.8	46	NS
	Treatment	26	7.3 ± 0.1	24.9 ± 0.8	50	
Amato et al.[21]	Control	24	12 (768 ± 13)[a]	36.8 ± 0.9	71	<0.001
	Treatment	29	<6 (348 ± 6)[a]	30.1 ± 0.7	38	

[a]Mean ± standard error values of tidal volume (mL/kg) were not provided in the report by Amato et al. The value set by the physician and the mean ± standard error values of tidal volume in milliliters (over the first 36 hours) have been provided.
Studies cited in this table can be found in the complete list of references for the chapter, available online at www.expertconsult.com.



• **Fig. 11.5** Distribution of tidal volume *(VT)* per ideal body weight (mL/kg) *(left column)* and of plateau pressure *(right column)* (the *red line* indicates the treated group; the *blue line* indicates the control group) in five randomized trials (computed from the reported mean ± standard deviation assuming a Gaussian distribution). Data from the following studies: A and B, Acute Respiratory Distress Syndrome Network[24]; C and D, Multicenter Trial Group on Tidal Volume Reduction in ARDS[22]; E and F, Pressure- and Volume-Limited Ventilation Strategy Group[20]; G and H, Brower et al.[23]; I, Amato et al.[21] (From Gattinoni L, Carlesso E, Cadringher P, et al. Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J.* Suppl 2003;47:15s–25s.)

hypothesis—that is, that higher PEEP improves outcome in more severe ARDS. The meta-analysis by Phoenix and associates[76] showed a trend toward improved survival in more severe ARDS treated with high PEEP group with no evidence of increase in barotrauma. The other meta-analysis by Briel and colleagues[77] of the largest three trials reported no treatment effect on hospital survival between higher and lower PEEP groups, whereas a significant improved survival rate was found in patients in presence of ARDS defined as PaO_2/FIO_2 ratio equal or less than 200. In contrast, in patients with mild and moderate ARDS, higher PEEP seemed harmful. These results roughly account for what we know about the ARDS pathophysiology. In fact, the putative beneficial effect of PEEP on survival should be related to the prevention of excessive regional stress and strain by keeping open lung regions that would otherwise collapse.[25,78] When we studied lung recruitability in an unselected ALI/ARDS population, we found that it varied from 0% to more than 50% of the whole lung.[67] We found that severity of lung injury was associated with higher lung recruitability and more severe hypoxemia, greater dead space, and lower compliance of the respiratory system. By arbitrarily dividing the study population into patients with higher or lower lung recruitability, we first observed that in the latter group, the amount of recruitable lung was almost negligible, amounting to about 50 g of tissue weight. The response to the application of higher levels of PEEP was minimal and much lower than that observed in patients with higher lung recruitability. This suggests that correct patient characterization is needed before PEEP setting. Selection criteria may include lung recruitability, end-expiratory transpulmonary pressure, respiratory system compliance, and driving pressure. A large randomized trial[79] tested the open lung approach performed by aggressive recruitment maneuvers followed by PEEP selection according to the compliance changes measured during the deflation. Surprisingly, the mortality rate was significantly lower in the control group in which the PEEP was selected according to a National Institutes of Health table than in the patients treated according to the open lung approach. These results cast serious doubts on the application of high PEEP level. Moreover, a high PEEP level may contribute to explaining the high-frequency oscillatory ventilation trial failure, in which the PEEP applied was close to the pressure needed to reach total lung capacity (i.e., >30 cm H_2O).

TABLE 11.3 Summary of Available Evidence on the Effects of Higher PEEP in Patients With ALI/ARDS

Study	Population	Group	No. of Patients	PEEP (cm H_2O)	Tidal Volume (mL/kg)	Plateau Pressure (cm H_2O)	Mortality Rate (%)	*P* (Outcome)
Brower et al.[71]	Unselected	Lower PEEP	273	8.9 ± 3.5 (first day)	6.1 ± 0.8 (first day)	24 ± 7 (first day)	27.5 (hospital discharge)	0.48
		Higher PEEP	276	14.7 ± 3.5 (first day)	6 ± 0.9 (first day)	27 ± 6 (first day)	24.9 (hospital discharge)	
Meade et al.[72]	Unselected	Control	983	9.8 ± 2.7	6	<30	40.4 (hospital discharge)	0.19
		LOVS Group	983	14.6 ± 3.4	6	<40	36.4 (hospital discharge)	
Mercat et al.[73]	Unselected	Minimal distention strategy	382	7.1 ± 1.8	6.1 ± 0.4	21.1 ± 4.7	31.2 (28 day)	0.31
		Increased recruitment strategy	385	14.6 ± 3.2	6.1 ± 0.3	27.5 ± 2.4	27.8 (28 day)	
Villar et al.[139]	Selected	Control	45	9 ± 2.7 (first day)	10.2 ± 1.2 (first day)	32.6 ± 6.2 (first day)	55.5 (hospital discharge)	0.41
		P flex	50	14.1 ± 2.8 (first day)	7.3 ± 0.9 (first day)	30.6 ± 6 (first day)	34 (hospital discharge)	
Ranieri et al.[74]	Unselected	Control	19	6.5 ± 1.7	11.1 ± 1.9 (first day)	31.0 ± 4.5 (first day)	58 (28 day)	0.19
		Lung Protective Strategy	18	14.8 ± 2.7	7.6 ± 1.1	24.6 ± 2.4	38 (28 day)	

ALI/ARDS, Acute lung injury/acute respiratory distress syndrome; *LOVS,* Lung Open Ventilation Study; *PEEP,* positive end-expiratory pressure; *P flex,* lower inflection point of the pressure-volume curve of the respiratory system. *NS,* not significant.
Studies cited in this table can be found in the complete list of references for the chapter, available online at www.expertconsult.com.

Setting Respiratory Rate

Although extensive work has been devoted to understanding better how to set VT and PEEP in ARDS, the potential importance of respiratory rate in the development of VILI has been scarcely investigated. Technology allows the use of respiratory rate from near zero breaths per minute using extracorporeal techniques to remove CO_2 to 2000 to 3000 breaths/min by using high-frequency oscillation. Each VT delivered may be considered as a stress cycle. Increasing the number of stress cycles may increase the lung damage. In experimental ARDS models, it has been observed that decreasing the respiratory rate decreases edema formation in isolated rabbit lung,[80] whereas an increase in respiratory rate during spontaneous breathing leads to an increase in edema formation.[81] It is conceivable that the respiratory rate may play a role in the pathogenesis of VILI when associated with a harmful VT or inadequate PEEP. A different issue is the use of high-frequency oscillatory ventilation (HFOV), a technique that uses very high respiratory frequencies in association with very low VTs and very high mean airway pressure, minimizing inspiratory overdistention and end-expiratory lung collapse.[82] Most patients treated with HFOV improved PO_2/FIO_2 ratio and reduced oxygenation index over time. Clinical trials were not able to prove a survival benefit; however, a recent meta-analysis of six randomized controlled trials comparing HFOV to conventional ventilation suggested a survival benefit at 30 days.[83] Two recent trials—the OSCILLATE (Oscillation for Acute Respiratory Distress Syndrome Treated Early) and OSCAR (Oscillation in ARDS) trials—did not show survival benefits. The OSCILLATE trial was stopped because of increased in-hospital mortality and found that, in adults with moderate to severe ARDS, early application of HFOV, compared with a ventilation strategy of low VT and high PEEP, does not reduce, and may increase, in-hospital mortality.[84] The OSCAR trial concluded that the use of HFOV had no significant effect on 30-day mortality in patients undergoing mechanical ventilation for ARDS.[85] The editorial accompanying the two trials suggests that "for now clinicians should be cautious about applying HFOV routinely in patients with ARDS."[86] A recent meta-analysis suggested that HFOV may be of potential advantage in patients with very severe ARDS (PaO_2/FIO_2 < 70 mm Hg).[87]

Setting Inspiratory-to-Expiratory Ratio

Mechanical ventilators provide a wide range of inspiratory-to-expiratory (I:E) ratios. Setting an adequate I:E ratio may be of great importance when ventilating patients with structural alterations of lung parenchyma, such as chronic obstructive pulmonary disease and emphysema, and during asthmatic exacerbation. In these conditions characterized by a time constant of the respiratory system greater than normal, a longer expiratory time must be provided to allow deflation of gas from the lungs before the next respiratory cycle, avoiding dynamic hyperinflation and intrinsic PEEP.[88] During ALI/ARDS, no convincing evidence has been provided for the advantages of setting an I:E ratio different from 1:1.

In the past, inverse ratio ventilation[89] was advocated as a tool to improve the effects of mechanical ventilation in ARDS.[90–92] Studies primarily showed an improvement of arterial oxygenation. Increased mean airway pressure, intrinsic PEEP, and a decrease in

cardiac output were problematic.[93] Extreme forms of manipulating I:E ratio are not recommended; an I:E ratio in ALI/ARDS of 0.5 to 1.5 is appropriate.

Individualizing Mechanical Ventilation in Patients With ARDS

General principles underlying the application of mechanical ventilation in patients with ALI/ARDS have been discussed. We now present the sequence of interventions that we believe are most appropriate for tailoring mechanical ventilation in an individual patient.[94]

The first intervention after admission to the ICU is to determine whether the patient has the criteria for ARDS diagnosis, keeping in mind that this syndrome consists of diffuse inflammatory lung edema. Patient history (research for possible etiologic factors leading to ARDS) and clinical observation (cyanosis, higher respiratory rate, use of accessory respiratory muscles, inspiratory crackles at lung auscultation mainly in the dependent lung regions) may suggest a possible lung inflammatory edema. Blood gas analysis and chest x-ray studies may confirm the initial diagnosis of the syndrome. The choice between an attempt of noninvasive respiratory support (face mask continuous positive airway pressure or noninvasive ventilation) or endotracheal intubation should be made on a clinical basis, according to the severity of illness, and whether the patient's condition is stable or deteriorating. We pay particular attention to the improvement of PaO_2 after oxygen administration and to $PaCO_2$. The lack of remarkable response in oxygenation to increased FIO_2 indicates a remarkable fraction of right-to-left intrapulmonary shunt, which is typical of ARDS. Low $PaCO_2$ suggests that the respiratory muscles of the patient are still able to deal with the decreased compliance of the respiratory system (i.e., sustaining the increased respiratory effort), whereas normal or high levels of $PaCO_2$ suggest a near exhaustion of the respiratory muscles and need of immediate ventilatory support.

Clinicians should be aware of the immediate possible consequences of intubation and initiation of mechanical ventilation. Sedation, either by itself or in association with muscle paralysis, produces a loss of respiratory muscle tone and a cranial shift of the diaphragm, promoting further lung collapse with immediate consequences in gas exchange. Mechanical ventilation produces an increase in intrathoracic pressure and decreased venous return. The intravascular volume status of the patient should be assessed before intubation, and hypovolemia should be corrected. The rate and the amount of fluid replacement should be decided for each individual patient. Inadequate fluid replacement may lead to a severe hemodynamic impairment immediately after beginning positive-pressure ventilation. An excessive fluid replacement in an inflamed lung with leaking capillaries may result in a dramatic increase of pulmonary edema with devastating consequences on gas exchange. Wiedemann and coworkers,[95] in a study published in the *New England Journal of Medicine,* compared a conservative and a liberal strategy of fluid management in 1000 patients with ALI. Although the primary endpoint (60-day mortality) was not significantly different, patients treated with the conservative strategy had better lung function and shorter duration of mechanical ventilation and intensive care without increasing nonpulmonary organ failures. For these reasons, we prefer to tailor fluid replacement according to the results of a fluid challenge test. Echocardiography also may be helpful in assessing the volumetric status.[96] After endotracheal intubation, the initial ventilatory setting used is blind because the pathophysiologic characteristics of the patient have not yet been assessed. We usually set the ventilator (volume-controlled) with a VT equal to 6 to 8 mL/kg ideal body weight, FIO_2 equal to 0.7, and a respiratory rate of 15 breaths/min, with an I:E ratio of 1:1. As soon as hemodynamic stability is obtained, a PEEP trial (preceded by a recruitment maneuver) is performed by applying in a random sequence of 5 to 15 cm H_2O PEEP with the patient under sedation and, sometimes, muscle paralysis. At each level of PEEP, we maintain VT, respiratory rate, FIO_2, and I:E ratio constant for about 20 minutes, after which we measure (1) arterial oxygenation, (2) respiratory system compliance, and (3) alveolar dead space. Patients who, after the application of higher PEEP, show improvement in at least two of these three parameters have a greater likelihood of having a higher lung recruitability. Alternatively, it is possible to target a specific saturation on the basis of pulse oximetry, if available, aiming at a hemoglobin oxygen saturation of 90%.

The improvement in arterial oxygenation alone, although commonly used, may be misleading for the assessment of lung recruitment because it may be the result of a slight decrease in cardiac output or a modification of regional distribution of pulmonary blood flow or both. It has been shown that improvement in respiratory physiologic variables from a PEEP trial has low sensitivity (71%) and specificity (59%) in assessing lung recruitability[67]; we prefer to obtain whole-lung CT scanning. In the CT scan facility, while maintaining the baseline ventilator setting, whole-lung CT scanning is performed at 5 cm H_2O PEEP at end-expiration and 45 cm H_2O at end-inspiration. The subsequent quantitative analysis of the CT scans allows us to obtain a precise assessment of lung recruitability. In patients with higher recruitability we apply PEEP greater than 15 cm H_2O, up to 20 cm H_2O and exceptionally greater than 20 but not exceeding 25 cm H_2O, whereas in patients with lower lung recruitability we apply a PEEP level not greater than 10 cm H_2O.

If CT scan is unavailable and only the PEEP trial has been performed, we assign to the high-recruitment group patients with either a baseline PaO_2/FIO_2 ratio less than 150 when measured at 5 cm H_2O PEEP or patients who respond to 15 cm H_2O PEEP compared with 5 cm H_2O with a positive response of two of the following three variables: increased PaO_2, decreased alveolar dead space, or increased compliance of the respiratory system.

We attempt to keep the plateau pressure less than 30 cm H_2O by modifying VT and respiratory rate. As discussed earlier, however, VT and plateau pressure are inadequate surrogates for alveolar stress and strain. We now measure, in each patient with severe ARDS, the transpulmonary pressure by helium dilution technique using an esophageal balloon (lung resting volume of 0 cm H_2O or 5 cm H_2O PEEP). With mechanical ventilation, a global pulmonary strain greater than about 1.5 (strain is dimensionless because it is the ratio of two volumes), or an end-inspiratory transpulmonary pressure greater than 20 cm H_2O, may cause VILI, with irreversible respiratory failure to follow.[10,28] These values of alveolar stress and strain are the ones at which the residual ventilatable lung reaches its near-total lung capacity, with a full extension of the collagen fibers of the lung skeleton.

In some patients, we have observed that a VT of 8 to 10 mL/kg ideal body weight determines a lung strain value less than 1 and a transpulmonary pressure value less than 14 cm H_2O. In these patients, we use a VT greater than 6 mL/kg ideal body weight, avoiding excessive hypercapnia or need for sedation. In contrast, in the patient with the most severe disease, in which the baby lung

is extremely small, even a ventilation with 6 mL/kg ideal body weight may result in values of alveolar stress and strain higher than those required to reach total lung capacity. Evidence from the literature and physiologic reasoning strongly indicate that for these patients a safe form of mechanical ventilation does not exist.[97,98] We reserve to them the use of extracorporeal support. We acknowledge that measuring alveolar stress and strain may seem to be a physiologic curiosity or a research tool. Nonetheless, we have introduced them in our clinical practice as the most logical approach for VILI prevention.

Some authors advocate the use of other forms of mechanical ventilation in patients with ARDS.[99,100] The rationale of pressure support ventilation in ARDS relies on the possibility of decreasing the need for sedation, while preserving the contribution of spontaneous breathing, and with possible advantages on gas and flow pulmonary distribution.[84] During the full-blown phase of the illness, we prefer to keep the patient well sedated. This approach may help to reduce energy requirement and oxygen consumption and CO_2 production.

The onset of recovery is characterized by the control or reversal, or both, of the cause of ARDS. An increase of systemic oxygenation and respiratory system compliance follows. When a PaO_2 value greater than 80 mm Hg is obtained at FIO_2 of 0.4, we start the weaning from PEEP application, decreasing the PEEP level no more than 1 cm H_2O every 4 to 6 hours, and suspending the process if the oxygenation consistently deteriorates. Subsequently, after an appropriate adjustment of sedation, we shift from pressure-controlled or volume-controlled to pressure support ventilation, initially setting the support at the same inspiratory pressure used during controlled ventilation. According to the patient's response, pressure-support level is progressively decreased, and the final phase of weaning is initiated at pressure support of 5 to 10 cm H_2O, FIO_2 lower than 0.4, and PEEP level equal to 5 cm H_2O.

Possible Adjuncts to Mechanical Ventilation

Prone Position

Prone positioning, first proposed in 1974[101] and first applied in patients with ARDS in 1976,[102] results in improved arterial oxygenation in most patients. After the introduction of CT scanning, showing lung consolidation located in the dependent lung regions and the aerated baby lung in the nondependent lung regions,[12,16] we integrated prone positioning as standard practice in clinical treatment of patients with ARDS to improve systemic oxygenation.[103] The initial hypothesis was that better perfusion of the baby lung, located in the dependent lung regions after prone positioning, would provide advantages in gas exchange. The picture observed was quite different, however. We did observe an improvement in arterial oxygenation, but the mechanism was likely different because CT scans taken in the prone position showed a density redistribution toward the dependent lung areas.[104]

This observation led to our introduction of the "sponge model" as our pathophysiologic understanding of ARDS.[105] Regardless of the patient's position, the increased weight of the nondependent lung tissue squeezes the gas out of the dependent regions of the lung.[46] The mechanisms of improved gas exchange were different from that first hypothesized. It is not the aim of this chapter to discuss the possible physiologic mechanisms of prone positioning, which may be found elsewhere.[106–110] Taken together, all of the studies, including small and large series of patients, consistently showed that in 70% of the patients systemic oxygenation improves in prone positioning compared with supine positioning,[110,111] without any change in the applied airway pressure. There is no doubt that in life-threatening severe hypoxemia a trial in the prone position is indicated.

A different issue is the effectiveness of the prone position in improving ARDS outcome. Is mechanical ventilation in ARDS less harmful in the prone position compared with the supine position? Does mechanical ventilation induce less alveolar stress and strain in the prone position? There is a consistent physiologic rationale to believe that this is the case. In experimental settings[112–115] and in normal subjects and patients affected by ARDS, CT scan shows a more homogeneous distribution of gas throughout the lung parenchyma in the prone position compared with the supine position.[110] This observation strongly suggests that the distribution of alveolar stress and strain is more homogeneous in the prone position. In experimental models of ARDS, there is evidence that prone positioning prevents or significantly delays the development of VILI.[115,116] Two large randomized studies on prone positioning were unable to show a significant benefit on outcome[109,117]; however, prone positioning was applied for only about a quarter of the day, and mechanical ventilation was not controlled. In a more recent trial,[118] in which prone positioning was applied for 20 hours per day and mechanical ventilation was strictly controlled, a positive benefit was found for the patients treated with prone positioning. On these bases the Prone-Supine II study[119] was organized to detect potential survival benefit of prone positioning avoiding the limitations of previous trials. Although the study was not able to show a significant survival benefit in the general population, a favorable trend was detected in the subgroup of patients with severe ARDS. In a meta-analysis including 10 clinical trials on adults and children, Sud et al.[120] found that prone ventilation reduced mortality in severely hypoxemic patients ($PaO_2/FIO_2 \leq 100$ mm Hg, $P = 0.01$; but not in patients with $PaO_2/FIO_2 > 100$ mm Hg, $P = 0.36$). The authors' suggestion was that prone position may provide benefits in severe hypoxemic but it should not be routinely used in all patients affected by acute hypoxemic respiratory failure. In a pooled analysis[119] of the four largest databases[111,117–119] of trials on prone position, the absolute mortality reduction in severe ARDS treated in prone position was approximately 10% (log-rank 0.03). On the contrary, in patients with moderate ARDS prolonged prone position may be useless or possibly harmful. Finally, a recent clinical RCT by Guerin et al. tested the effects of prone positioning on mortality in patients with severe and persistent ARDS.[121] The criteria for the enrollment included $PaO_2/FIO_2 < 150$, FIO_2 60% or higher, PEEP 5 cm H_2O or higher, and the prone position was applied for at least 16 hours/day. The study showed a survival benefit in patients treated with the prone position, with a reduction in mortality of nearly 50%. Therefore the prone position has its definite role in the treatment of patients with severe ARDS.

Extracorporeal Support

Extracorporeal support of ARDS was first applied in 1972.[122] The first randomized trial ever performed in ALI/ARDS showed that patients treated with extracorporeal support or with conventional ventilation had similar mortality, equal to about 90%.[123] In the 1980s, our center introduced extracorporeal CO_2 removal in ARDS, aiming at lung rest with a suggestion of benefit.[124,125] A randomized study performed in 1994 did not show any survival benefit with extracorporeal CO_2 removal support.[126] The results of this trial may have been significantly influenced by bleeding complications

in patients undergoing extracorporeal CO_2 removal. Despite the discouraging results, in Europe few centers continued to use venovenous extracorporeal support as a last resource in selected series of patients.[127] In the United States, Kolla et al.[128] and Bartlett et al.[129] continued to provide extracorporeal support associated with mechanical ventilation with less strict entry criteria and with encouraging results. Interest in extracorporeal membrane oxygenation (ECMO) was renewed after the publication of CESAR (Conventional ventilatory support vs. extracorporeal membrane oxygenation for severe adult respiratory failure) trial in 2009,[130] which showed clear benefits on outcome when severely hypoxemic patients were treated within an expert high–case volume center (with ECMO capability) when compared with nonspecialized hospitals. The rebirth of the technique, however, was due to its use as a rescue therapy during H1N1 flu epidemics in Australia and New Zealand in severely hypoxemic patients untreatable with conventional methods.[131] The approach vas venovenous with high blood flows. This report showed a survival rate higher than 70% and an impressive number of centers in Europe, United States, South America, Canada, and Asia started to use ECMO in severely hypoxemic patients who do not benefit from maximal mechanical ventilation.[132–137] The survival rate ranged between 56% and 79%.

The impressive diffusion of ECMO led to the great improvement of this technology, and there are increasing numbers of reports describing simple forms of extracorporeal support, primarily aiming at CO_2 removal.[138] The actual indications for ECMO depend on the patient's need and the physician's request. The choice of the technique may vary from low-flow bypass with CO_2 removal to high-flow ECMO with total oxygenation support. If the aim is the treatment of life-threatening hypoxemia, the clear-cut indication is high-flow venovenous ECMO. If the patient, however, presents with severe cardiac failure, venoarterial ECMO must be used.

A simplified schema of the possible intervention is shown in Fig. 11.6, which underlines the recent ARDS Berlin definition. As shown, the recent ARDS Berlin definition may be helpful in dictating the sequence of possible intervention when ARDS severity is increasing.

Therapeutic Options According to the Berlin Definition

	ARDS		
	MILD	MODERATE	SEVERE
ALTERNATIVE TREATMENTS			ECMO
		$ECCO_2$-R	
			Neuromuscular Blockade
			Prone Position
Airway Plateau Pressure	≤30 cm H_2O		
Transpulmonary Pressure	≤20 cm H_2O		
PEEP	≈10 cm H_2O		>15 cm H_2O
Tidal Volume	6 mL/kg IBW		
Strain	≤1.5–2		

• **Fig. 11.6** Simplified schema of possible ARDS intervention. *ARDS,* Acute respiratory distress syndrome; *ECMO,* extracorporeal membrane oxygenation; *$ECCO_2$-R,* extracorporeal CO_2 removal; *PEEP,* positive end-expiratory pressure; *IBW,* ideal body weight. (Modified from the Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, Rhodes A, Slutsky AS, Vincent JL, Rubenfeld GD, Thompson BT, Ranieri VM. *Intensive Care Med*. 2012 Oct;38(10):1573–1582. Epub 2012 Aug 25. Erratum in: *Intensive Care Med*. 2012 Oct;38(10):1731–1732.)

Key Points

- The targets of mechanical ventilation in ARDS have shifted from providing normal gas exchange to protecting the lung from VILI.
- Mechanical ventilation replaces the action of the respiratory muscles. The driving force of mechanical ventilation (airway pressure displayed on the ventilator) is spent partly to overcome the resistances to flow, partly to inflate the lung, and partly to inflate the chest wall.
- The distending force of the lung (the trigger of VILI) is the transpulmonary pressure (PL)—the difference between the airway pressure (P_{aw}) and the pleural pressure (Ppl). For the same driving force, in normal conditions, the transpulmonary pressure equals the driving force multiplied by the ratio between the lung elastance and the respiratory system elastance (lung elastance + chest wall elastance): $PL = P_{aw} \times EL/Etot$. In normal subjects, this ratio is approximately 0.5; in patients with ARDS, it may be 0.2 to 0.8. Consequently, the airway pressure alone may be misleading to assess the transpulmonary pressure imposed on the lung by mechanical ventilation (i.e., to assess the stress). We used airway pressure to indicate end-inspiratory pressure.
- The delivered VT increases the lung volume and in the process produces strain on the lung. The ratio of change in lung volume over resting lung volume ($\Delta V/V_0$) is a rough approximation of the strain. Excessive strain causes shape changes of endothelial and epithelial cells, inducing an inflammatory reaction. Because the resting volume (V_0, the baby lung) may vary largely in ARDS, the same VT per ideal body weight may induce largely different strain values.
- Stress and strain, the triggers of VILI, are linked by a constant, specific lung elastance (Espec), accounting for the following relationship: PL (stress) = Espec × $\Delta V/V_0$ (strain). The specific lung elastance is similar in normal subjects and in patients with ARDS.
- Flow may be considered as the rate at which a given strain occurs into the lung, proportional to the energy dissipated into the lung parenchyma.
- VT can be scaled to compliance using the concept of driving pressure (ΔP = Pplat − total PEEP). The lower the driving pressure for a fixed VT, the more compliant is the lung. Physiologic variables are generally poor indicators of the severity of

lung injury, with the alveolar dead space being the only variable associated with outcome. The severity of lung injury may be assessed by CT scan. The fraction of nonaerated lung tissue is strongly associated with mortality risk. The greater the lung injury, the smaller the baby lung, and the greater the stress-strain induced by mechanical ventilation.

- Among outcome studies testing different VTs, only the study comparing the two extreme values tested (6 mL/kg vs. 12 mL/kg) showed a significant benefit of lower VT. Data from clinical studies and rationale from physiologic studies are strongly in favor of using the lowest VT possible, likely associated with lower stress and strain, accepting hypercapnia as a side effect.
- All studies comparing lower versus higher PEEP randomly applied to *unselected* ARDS populations failed to show benefits on survival. In contrast, benefits of higher PEEP were found in more severe *selected* ARDS patients.
- The lung recruitability may vary greatly within the ARDS population (5%–50% of the lung parenchyma) and is correlated with the overall lung injury severity. Higher PEEP possibly should be reserved only for patients with higher recruitability.
- When treating patients with ARDS, individual characteristics (lung injury severity, gas exchange, lung mechanics, abdominal pressure) should be assessed to tailor the least harmful mechanical ventilation setting according to the available evidence and physiologic rationale, providing the lowest stress and strain possible.
- In severe ARDS, in which mechanical ventilation is more harmful, associated therapy such as prone positioning and extracorporeal support must be sought.

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Review Questions

1. A 55-year-old male is admitted to the intensive care unit with respiratory failure. The patient has presumed bacterial pneumonia, chest x-ray shows bilateral diffuse opacities, and an echocardiogram shows normal heart function with no signs suggestive of heart failure. The patient is supported by mechanical ventilation and his partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FIO_2) ratio is less than 200. Given the current clinical scenario, which of the following statements regarding stress and strain on the lungs is most correct for this patient?

a. Stress refers to the injury caused by high airway pressures.
b. Strain is the applied force to the lung and is correlated best with esophageal pressures.
c. Lung-specific elastance is the ratio between alveolar stress and strain.
d. In this patient the lung-specific elastance will be significantly lower than in a normal lung.

Answer: c. The concepts of stress and strain were introduced by Gattinoni et al.[28] and help provide a conceptual framework for better understanding ventilator-induced lung injury in acute respiratory distress syndrome (ARDS). Stress is the applied force, and strain is the linear deformation of material (lung tissue). In the whole lung, the best approximation of stress is the transpulmonary pressure and the best approximation of the average strain is the change in volume relative to the lung resting volume. The lung-specific elastance is defined by the ratio between alveolar stress and strain. The lung-specific elastance is the transpulmonary pressure required to double the lung resting volume. In ARDS, the lung-specific elastance is similar to normal, reinforcing the concept of the baby lung (normal lung is small and not stiff). Furthermore, this concept raises questions regarding normalizing the tidal volume to the ideal body weight. Depending on the severity of ARDS and the size of the residual normal lung (baby lung), a given tidal volume can result in a wide range of levels of strain.

2. Which of the following variables is most strongly associated with a poor outcome in patients with ARDS?

a. Arterial pressure of oxygen (PaO_2)
b. PaO_2/FIO_2 ratio with 100% oxygen
c. PaO_2/FIO_2 ratio with PEEP above 5 cm H_2O
d. Initial amount of dead space

Answer: d. Although most clinicians (and current definitions) equate severity of disease in ARDS with PaO_2/FIO_2, and other oxygenation-related variables, studies have shown poor correlation between these and outcomes in ARDS. Most data suggest that the use of oxygenation variables alone to access lung severity can be misleading. On the other hand, variables derived from carbon dioxide (CO_2) as the total alveolar dead space seem to be of greater value to assess lung severity. Studies have shown that in ARDS dead space at entry is a strong predictor of outcome.

3. Which of the following interventions has been associated with improved mortality in clinical trials of patients with ARDS?

a. Ventilation with low tidal volumes (6 mL/kg of ideal body weight)
b. Ventilation with high PEEP (>10 cm H_2O)
c. Ventilation with inspiratory-to-expiratory ratio (I:E ratio) greater than 2:1
d. High-frequency oscillatory ventilation (HFOV)

Answer: a. Multiple clinical trials have evaluated therapeutic strategies in ARDS. To date the only therapy that has been demonstrated to be associated with a significant improvement in survival in a wide range of patients with ARDs is the use of lower tidal volumes (6 mL/kg of ideal body weight). Other strategies such as higher positive end-expiratory pressure (PEEP) may be of use in selected groups of patients. HFOV has not been demonstrated to improve outcomes. There are no clinical data supporting the use of inverse ratio ventilation (increased I:E ratios) in ARDS.

4. Which of the following patients is most likely to have a mortality benefit from ventilation in the prone position?

a. A 54-year-old female with severe cardiogenic pulmonary edema supported by mechanical ventilation requiring high FIO_2.
b. A 45-year-old male with multifocal pneumonia and ARDS supported by mechanical ventilation (FIO_2 0.7, PEEP 10, PaO_2/FIO_2 90).
c. A 35-year-old female with ARDS postaspiration pneumonia supported by mechanical ventilation (FIO_2 1.0, PEEP 5, PaO_2/FIO_2 250).
d. A 76-year-old male with severe influenza and ARDS supported by mechanical ventilation (FIO_2 0.8, PEEP 12, PaO_2/FIO_2 180).

Answer: b. Prone positioning has been used in ARDS for several decades. Prone positioning has been shown to produce improved oxygenation in up to 70% of patients with ARDS. However, several clinical trials evaluating a wide range of patients with ARDS were unsuccessful in demonstrating improved survival with prone positioning. More recent meta-analyses and clinical trials have shown a mortality benefit with prone position ventilation in patients with severe ARDS. Based on this and considering the most recent definitions for ARDS (see Table 11.1), the patient in option c is most likely to benefit from prone position ventilation.

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Bronchoscopy and Lung Biopsy in Critically Ill Patients

THADDEUS BARTTER, MELVIN R. PRATTER, AND WISSAM ABOUZGHEIB

CHAPTER OUTLINE

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Summary

Bronchoscopy plays an important role in the care of critically ill patients. Since the introduction of the flexible fiberoptic bronchoscope in 1968, flexible bronchoscopy has slowly gained importance as a diagnostic and a therapeutic tool. It has largely replaced rigid bronchoscopy in the intensive care unit (ICU) for several reasons: the lack of need for complete anesthesia, the ease of use, and the fact that flexible bronchoscopy allows one to perform procedures on a critically ill ventilated patient through an endotracheal tube (ETT) or tracheostomy tube.

Lung biopsy is often a procedure of last resort in a critically ill patient with lung disease who is not responding to therapy. Whereas many of these patients are treated with mechanical ventilation, the potential benefits of biopsy need to be carefully weighed against the potential risks.

This chapter reviews bronchoscopy and lung biopsy in critically ill patients. By definition, a critically ill patient has one or more organs that are under stress and has limited functional reserve. Stresses that are usually well tolerated by healthy individuals may have serious or even fatal consequences for a patient in the ICU. This chapter first reviews the physiologic stresses induced by bronchoscopy. It then reviews diagnostic and therapeutic indications for bronchoscopy in the ICU. Finally, we review the potential role of bronchoscopic and nonbronchoscopic approaches to lung biopsy.

Fiberoptic Brochoscopy-Induced Physiologic Changes

General Considerations

The act of cannulation of the airway is not a physiologically neutral event.[1–5] It stimulates both cardiovascular and respiratory responses. In the ICU, there are three common stimuli that provoke these reflexes: intubation, bronchoscopy, and suctioning. Even after the use of sedation and application of topical anesthesia, the passage of a bronchoscope through the larynx typically results in a 30% increase in mean arterial blood pressure and cardiac index, a 40% increase in heart rate, and an 86% increase in pulmonary arterial occlusion pressure.[1] The response seems to represent a reflex to mechanical stimulation of the larynx. A significant hemodynamic response occurs even when patients are anesthetized and paralyzed before the passage of a bronchoscopy through the larynx and into the trachea, with conflicting data as to whether there is a difference in hemodynamic response between the nasal and the oral routes.[3,4] Topical anesthesia of the upper airway with lidocaine attenuates (but does not ablate) the cardiovascular responses.[3,5]

The significance of the cardiovascular changes associated with bronchoscopy is related primarily to their potential impact on the heart and the brain. The increase in rate-pressure product has the potential to cause cardiac ischemia in patients with limited cardiac perfusion. In one small study, 3 of 10 monitored patients undergoing bronchoscopy, all of whom were 55 years of age or older, developed electrocardiographic changes of ischemia.[2] In another study designed specifically for older patients, the incidence of ischemia was 17%.[6] Despite these findings, bronchoscopy has a low rate of ischemic mortality. In studies describing complications from bronchoscopy (ranging from as few as 10 to as many as 48,000 procedures), the rate of death from ischemic events ranged from 0% to approximately 0.01%.[6–11]

A second potential cardiac complication of bronchoscopy is the triggering of arrhythmias. One study looking specifically for arrhythmias during bronchoscopy found an 11% incidence of "major arrhythmias."[12] As with ischemia, however, reported mortality from arrhythmias has been very low; in two large studies of complications of bronchoscopy the mortality from arrhythmias ranged from 0% to 0.04%.[10,11]

With respect to the brain, both bronchoscopy and endotracheal suctioning cause significant increases in intracranial pressure.[2,13] Because mean arterial pressure and intracerebral pressure increase roughly in parallel, there is little overall change in cerebral perfusion pressure.[2,13] This may explain why no adverse intracerebral sequelae have been reported despite the observed increase in intracerebral pressure.[13] Nevertheless, we believe that close attention to intracerebral pressure is warranted whenever possible in brain-injured individuals undergoing bronchoscopy.

Bronchoscopy also affects the work of breathing, respiratory pressures, and lung volumes. Transnasal cannulation of the trachea leads to a decrease in inspiratory and expiratory flow, a decrease in vital capacity, and an increase in functional residual capacity.[14] Bronchoscopy through an ETT in a sedated, but not ventilated, patient leads to significant further decreases in flows and vital capacity and a marked increase in the work of breathing.[14,15]

Special Considerations: Bronchoscopy in Mechanically Ventilated Patients

Before planning a bronchoscopy in the ICU on an intubated patient, it is crucial to know the ETT size while keeping in mind the primary indication of the bronchoscopy. This will avoid patient-related complications as discussed in the following text and bronchoscope-related injuries and damages.

In general, we prefer to use a therapeutic bronchoscope in intubated patients, as we often encounter thick secretions that may hinder the completion of the procedure. However, for patients intubated with an ETT size 7.5 and below, it is advisable to use a diagnostic bronchoscope with an outer diameter (OD) of 5.1 mm. Using a therapeutic bronchoscope with an OD of 6.0 mm requires at least an ETT size 8.0. In addition, the operator needs to ensure the use of a bite block regardless of the level of sedation to avoid accidental biting of the scope and adequate lubrication of the entire length of the scope, which facilitates maneuverability of the bronchoscope through the ETT.

Mechanical ventilation adds additional complexity to the physiologic effects of bronchoscopy. The details were elegantly delineated in a study by Lindholm and colleagues.[15] The first notable change is a dramatic increase in upper airway resistance. Airway narrowing related to ETT insertion by itself increases airway resistance. The subsequent introduction of a bronchoscope through the ETT greatly increases that resistance. The actual degree of increased airway resistance observed is related to the cross-sectional areas of both the ETT and the bronchoscope being inserted.[15] The increased resistance has implications for ventilator gas delivery. The first is a potential decrease in delivered volume. With a volume-cycled mode, pressure increases as needed to deliver the specified volume, but the set volume may not be delivered owing to a pressure pop-off set in the alarm/safety parameters of the ventilator. (Although peak pressures of 60 to 80 cm H_2O can be reached at the airway opening, note that the pressure gradient from the proximal obstruction limits the pressure delivered to the lung parenchyma.)[15] With a pressure-cycled mode of mechanical ventilation, the increase in upper airway resistance caused by bronchoscopic cannulation leads to an immediate decrease in delivered volume, the severity of which again depends on the cross-sectional diameters of both the ETT and the bronchoscope. This effect can be countered by raising the applied pressure and the associated inspiratory airway pressure.

Whereas the driving pressure for inspiratory volumes depends on external force (generated by the ventilator), exhalation is largely dependent on the passive recoil of the lungs. The increase in airway resistance caused by introduction of the bronchoscope into the ETT thus has a disparate and more potentially dramatic effect on expiratory volumes than on inspiratory volumes. Sequential delivered volumes may be incompletely exhaled, causing a gradual buildup of intrathoracic volume and intrinsic positive end-expiratory pressure (auto-PEEP). Lindholm and colleagues[15] documented several cases of auto-PEEP greater than 18 cm H_2O. In one patient undergoing bronchoscopy through an ETT with an internal diameter of 7 mm, auto-PEEP was recorded at 35 cm H_2O.

Suctioning adds another layer of complexity. In addition to the cardiovascular changes stimulated by suctioning mentioned above, suctioning can cause profound changes in intrathoracic pressures and lung volumes. Not only can the auto-PEEP induced during bronchoscopy be eliminated, but with prolonged suctioning negative intrathoracic pressure can be created.[15] This can lead to clinically relevant decreases in functional residual capacity, tidal volume, and minute ventilation, with potential for alveolar collapse, hypercarbia, and hypoxemia.

Special Considerations: Hypoxemia

That bronchoscopy can cause hypoxemia is clear. The degree of hypoxemia ranges from mild to severe, and a variety of potential mechanisms are involved. The administration of benzodiazepines and narcotics can cause hypoxemia and respiratory depression in normal volunteers,[16] and one study showed a 35% incidence of desaturation after sedation even before bronchoscopy was performed.[17] The desaturation may not be completely due to central nervous system depression; Chhajed and coworkers[18] showed that hypoxemia during bronchoscopy could be corrected in most of their lung transplant patients by the insertion of a nasopharyngeal tube, indicating that upper airway collapse was a major cause of hypoxemia in their population. Apart from the effects of sedation on oxygenation, bronchoscopy itself can cause hypoxemia, Changes in airway resistance and the impact of suctioning on functional residual capacity are probably major factors.[19–22] Higher incidences of hypoxemia have been shown to correlate with the degree of prebronchoscopy pulmonary impairment, extent of suctioning, and performing a bronchoalveolar lavage (BAL).[20–25] Furthermore, the hypoxemia induced by bronchoscopy often does not resolve immediately on removal of the bronchoscope; it can persist for more than 2 hours.[17,24,25] Hypoxemia represents another stress in addition to the cardiovascular reflex changes cited early and may have a negative impact on organs at risk. Hypoxemia may play a significant role in cardiac ischemia and arrhythmias associated with bronchoscopy.[1]

Bronchoscopy through the ETT of a patient assisted by a ventilator has been reported to cause an increase in the partial pressure of oxygen (Po_2) with an increase in Pco_2 and a decrease in Po_2 with no change in the partial pressure of carbon dioxide (Pco_2).[14,15] The seemingly contradictory differences in findings probably reflect individual differences in how much patients are suctioned and the degree to which suctioning affects functional residual capacity.

Physiologic Changes With Bronchoscopy Summary

In summary, bronchoscopy and other airway cannulations almost always trigger a reflex response that includes tachycardia and an increase in blood pressure. Bronchoscopy frequently causes hypoxemia, which may be of prolonged duration. For patients supported by ventilators, disparate physiologies can be created based on the mode of ventilation, the size of the ETT, the size of the bronchoscope, the duration of suctioning, and the flow rate that the suction channel of the bronchoscope is able to attain. Bronchoscopy can cause significant physiologic stress, and the critically ill patient may be less able to tolerate such stress than an otherwise healthy individual.

Airway Evaluation and Management

Intubation and Endotracheal Tube Management

Bronchoscopy can be an asset in the insertion and subsequent management of ETTs.[26,27] For patients with difficult airways, an ETT can be placed over a bronchoscope and slid into the trachea after direct visual intubation with the bronchoscope. A similar technique can be used for changing the ETT in a tenuous patient, especially if switching from nasal to oral or oral to nasal route.[27] Bronchoscopy is valuable in the placement of tubes for single-lung ventilation or placement of double-lumen tubes.[27] Bronchoscopy also allows the bronchoscopist to position the tip of an ETT at a point approximately 2.5 cm above the carina under direct visualization or, when there is a process such as tumor compression of the trachea, to place the tube wherever needed for optimal ventilation.[26]

Percutaneous Dilational Tracheostomy

Percutaneous dilational tracheostomy (PDT) has emerged as a primary method of tracheostomy for ICU patients. It has a lower incidence of overall complications than does open surgical tracheostomy, and it can be performed at the bedside, avoiding the risks of transporting a critically ill patient.[28–31] It also is more cost-effective.[29] PDT can be performed not only by surgeons, but also by trained intensivists and pulmonologists[29]; it has become a standard intensivist procedure in many institutions.[32,33] Although its overall safety profile is better than for open surgical tracheostomy, PDT does have a higher risk of posterior tracheal wall injury and false passage.[34] Bronchoscopy can be combined with PDT to allow direct endobronchial guidance for the procedure. Bronchoscopy has been suggested by several authors to be an important safety factor in PDT,[30,31,33a,34–39] although its use is not universally practiced.[32,40,41] Direct visualization is a protection against inadvertent tracheal injury and a means of assessing an injury for intervention should it occur.[34,35,37] The most logical approach to PDT is a team approach[39a] with at least two principal operators—one managing the bronchoscope and ETT and the second working at the neck to insert the tracheostomy tube.[30,31,34,38] The risk of using bronchoscopy for PDT is that of increased hypoventilation because the patient is being ventilated through the ETT during the procedure.[36] This can be obviated with the use of a pediatric bronchoscope for guidance; a large working channel is not needed for this application.

Airway Obstruction and Atelectasis

The upper airway can become obstructed via several mechanisms. Bronchoscopy is valuable in diagnosing all of them. When an ETT is inserted, it becomes part of the airway. Kinking of the ETT or luminal blockage by hardened, inspissated secretions causes the same physiologic problems as a primary tracheal process. Granulation tissue at the proximal end of a tracheostomy tube or at the distal end of a tracheostomy tube or ETT can cause obstruction and difficulty with inflation or deflation of the lungs. (This is much less common with ETTs than with tracheostomy tubes because of Murphy's eye [the distal side port] on ETTs.) Benign or malignant processes can cause strictures or compression of the trachea. Finally, edema of the vocal cords and periglottic structures can lead to upper airway obstruction that is not evident with an ETT in place but which can cause recurrent respiratory failure after extubation; performing extubation over a bronchoscope allows immediate evaluation of the upper airway as the ETT is withdrawn with immediate diagnosis of this problem.[27]

Foreign bodies can cause obstruction at various points in the airways. Traditionally, rigid bronchoscopy was used for management of foreign bodies given its capacity for airway control and the availability of tools larger than those that can be passed through a flexible bronchoscope.[42] Flexible bronchoscopes are the only choice, however, in an intubated patient, and the combination of larger channel scopes (2.8 mm and larger) for the passage of instruments and of different baskets and grasping tools makes flexible fiberoptic bronchoscopy a viable option in many cases.[26,42,43] For nonintubated patients, a flexible bronchoscope through a rigid bronchoscope is sometimes an optimal approach.[42]

Atelectasis is a common ICU problem and has been one of the most common indications for bronchoscopy in ICUs.[44,45] The argument is obvious: if standard "blind" suctioning is effective and useful, why not use suctioning under direct visualization for local airway obstruction caused by secretions? One key study done by Marini and coworkers[46] challenged the assumption that bronchoscopy is an optimal approach to atelectasis. In their study of patients with radiologically evident atelectasis, one group underwent a regimen of initial bronchoscopy followed by regular chest physiotherapy while a second group received regular chest physiotherapy alone followed by delayed bronchoscopy at 48 hours only if atelectasis persisted. The authors showed early bronchoscopy to be the inferior approach; there was no difference in rate or degree of improvement between the two groups, and bronchoscopy led to more significant decreases in oxygenation.[46] The authors also looked at the presence or absence of air bronchograms, postulating that patients with air bronchograms had more distal consolidation (as opposed to proximal obstruction causing atelectasis) and would be more refractory to any attempts to reexpand consolidated lung. Their results strongly supported their postulate.[46]

These data are valuable and should lead to initial trials of chest physiotherapy in most cases of atelectasis, but they do not apply universally in clinical medicine. Some patients with chest trauma or spinal cord injury are not candidates for chest physiotherapy.[47] Some patients have atelectasis and a severe refractory hypoxemia as a result of shunting of blood through the atelectatic lung. In these patients, a 24-hour wait may be inappropriate, and bronchoscopy sometimes leads to marked improvement. Judicious use of bronchoscopy for atelectasis is thus a clinical decision involving the art of medicine.[47] Some patients with atelectasis have severe refractory hypoxemia as a result of shunting of blood through the atelectatic lung. In these patients, trying chest physiotherapy may

be inappropriate because bronchoscopy often can lead to marked improvement almost immediately. Decisions on use of bronchoscopy for atelectasis thus depends on the clinical situation and combining the art and science of pulmonary medicine. For patients who have a bronchoscope inserted for atelectasis, one technique that has been moderately successful is that of isolated segmental inflation; the bronchoscope or a ballooned catheter is wedged into the atelectatic segment, and pressure of at least 30 mm H_2O is applied through the bronchoscope or catheter.[44,47] This focal approach is more rational for focal atelectasis than are recruitment maneuvers applied to the whole chest because recruitment maneuvers are more likely to overdistend compliant alveoli than to open atelectatic alveoli.[44]

Trauma

The value of bronchoscopy for the evaluation of chest trauma was defined in a landmark paper by Hara and Prakash.[48] The authors investigated 53 cases of blunt trauma to the chest, neck, or both in which bronchoscopy was performed within 3 days of injury. Bronchoscopy was believed to be of clinical value in 53% of the 53 cases. They documented injury and tears of the upper and lower airways, contusion or hemorrhage, aspirated material, and plugging or secretions. Only one of eight major tracheal injuries was not completely diagnosed. These data provide compelling evidence for visual bronchoscopic evaluation of the bronchial tree in all cases of significant blunt chest trauma.

Smoke Inhalation

Inhalation injury is a unique form of trauma to the bronchial tree. Most inhalation injuries are due not to heat alone, but to the deposition in the bronchial tree of soot and gases, the products of combustion.[49] Early ventilatory support and aggressive pulmonary toilet probably improve outcomes for inhalation injury,[50,51] but the severity of inhalation injury may not become fully manifest for up to 5 days (usually 3 days).[51] Bronchoscopy has been advocated in the evaluation of patients with possible inhalation injury.[50–52] Some patients have mucosal injuries that are obvious to even an inexperienced bronchoscopist, but sometimes even when there is significant injury, the bronchoscopic appearance of the airways may be minimally abnormal. For patients who have relatively normal-appearing mucosae, biopsy specimens from segmental or subsegmental carinae can yield pathologic information that is predictive of the degree of inhalation injury (or lack thereof) and can be used to guide aggressiveness of management.[50,51] Another tool for evaluation of inhalation injury is the ventilation-perfusion scan,[49,52] but the objectivity and reproducibility of bronchoscopic endobronchial biopsy could lead one to argue that it should be the current standard of care for the diagnosis of possible inhalation injury.

Hemoptysis

Hemoptysis can run the gamut from scant to massive. There are several definitions of massive hemoptysis, with varying quantities of blood specified over different intervals. The best definition of massive hemoptysis is functional: massive hemoptysis is bleeding in quantities that threaten to cause death by asphyxiation from filling of the bronchial tree with blood or by exsanguination.[53,54] Patients with massive hemoptysis should always be admitted to the ICU.

Bronchoscopy plays two roles in massive hemoptysis—diagnostic and therapeutic. Most authors recommend bronchoscopy as soon as possible to localize the site of bleeding.[53–55] Rigid bronchoscopy and flexible bronchoscopy each have their advocates. The argument for rigid bronchoscopy is that it allows better visualization of the major airways, more aggressive suctioning, removal of clots, and local tamponade with packing materials.[55,56] The argument for flexible bronchoscopy is that it does not require the operating room or general anesthesia, it allows more thorough evaluation of the bronchial tree, and it allows directed intubation.[53,55] Intubation may be with a regular ETT in the trachea or in the left lung or with a double-lumen tube. (The right upper lobe takeoff is too proximal in the right bronchial tree to allow selective right main bronchus intubation.) If bleeding is too great, flexible bronchoscopy is of limited value; small amounts of blood can obscure the relatively small lens of a bronchoscope.[53] For massive hemoptysis, the goals of bronchoscopy are to identify the bleeding site and to stabilize the patient enough to allow arterial embolization, surgery, or a sequence of the two; embolization and surgery are usually the two most effective therapies. Several temporizing endobronchial therapies have been advocated: iced saline solution lavage, topical 1 : 20,000 epinephrine, endobronchial tamponade with packing or a Fogarty catheter, and endobronchial laser therapy.[53–55]

Diagnosis of Infection

Bronchoscopy is a valuable tool for the diagnosis of pulmonary infection in a critically ill patient. A variety of organisms, including *Mycobacterium tuberculosis, Pneumocystis jiroveci* (formerly *P. carinii*), fungi, viruses, and bacteria are capable of causing severe pneumonia in critically ill patients. Given the broad differential diagnosis, it is commonly important to try to determine the specific etiology. Bronchoscopy offers access to lower airway secretions, which can lead to accurate diagnosis, focused therapy, and sometimes the withdrawing of unnecessary therapy. BAL is the most useful diagnostic modality and can be performed in a patient who cannot or will not produce expectorated sputum or who is intubated. BAL samples alveoli more reliably than induced sputum. BAL fluid also is helpful for a broader range of diagnoses than induced sputum. In some cases, BAL recovery of organisms is not adequate alone, and biopsy is needed to confirm tissue invasion.

For BAL, the bronchoscope is wedged into a peripheral airway, and aliquots of sterile saline solution totaling at least 120 mL are instilled to ensure that alveolar spaces are reached. Box 12.1 summarizes the recommended method for BAL. Fluid retrieved via suctioning is sent for diagnostic studies. The BAL technique samples about 1 million alveoli, or 1% of the lung.[57] For some infections, the presence of an organism in the lung is pathognomonic for active infection, whereas for others quantitative cultures are needed to distinguish lower respiratory tract infection from upper airway contamination.

M. tuberculosis is a cause of pneumonia that should not be forgotten in critical care medicine. BAL is a sensitive tool for the diagnosis of *M. tuberculosis,* one of the organisms whose presence always means active infection.[58,59] BAL is more sensitive than gastric washings for the diagnosis of tuberculosis.[60] BAL or protected specimen brushings are often positive in patients who have pulmonary tuberculosis but negative sputum smears,[58,61,62] and BAL is also more sensitive than transbronchial biopsies for diagnosis of tuberculous pneumonia.[63] (For miliary tuberculosis, biopsy is of great value.[64]) The addition of molecular techniques such as

• BOX 12.1 Bronchoalveolar Lavage

- Wedge the bronchoscope into a peripheral area of whatever segment is most suspect radiologically. If there is no such segment, wedge into an upper lobe segment if *Pneumocystis* pneumonia is suspected or into a posterior lower lobe segment otherwise.
- Instill 30- to 60-mL aliquots of sterile nonbacteriostatic saline solution through the wedged bronchoscope until some fluid can be retrieved using suction. Discard approximately the first 20 mL of fluid.
- Attach a sterile specimen cup in line with the suction tubing, and instill further aliquots until at least 120 mL have been instilled and at least several milliliters of fluid have been obtained.
- Bilateral lavage has a higher yield than unilateral lavage.
- Have the fluid divided into two aliquots. One is plated using quantitative techniques; the second is centrifuged, stained, and examined for intracellular organisms and other diagnostic findings.
- Time from obtaining bronchoalveolar lavage fluid to plating of quantitative specimen should be <4 hours.

Data from references 57, 98, and 156–158 for this chapter (complete list available online).

polymerase chain reaction (PCR) can further increase the sensitivity of BAL for *M. tuberculosis*.[65]

P. jiroveci is a pathogen in immunocompromised individuals. Its incidence increased dramatically in the 1980s with the emergence of AIDS. In the 1960s and 1970s, only about 100 cases were diagnosed per year in the United States.[66] In the 1980s, thousands of cases were diagnosed.[66] Because the organism cannot be cultured, its detection depends on identification in respiratory secretions. BAL greatly increases the yield for *Pneumocystis* pneumonia over bronchial washings and brushings and is the diagnostic procedure of choice.[63,67,68] As with *M. tuberculosis, P. jiroveci* is an organism that can sometimes be difficult to see on smears, especially in patients with *Pneumocystis* pneumonia who do not have AIDS or who have AIDS but have received inhaled pentamidine.[69,70] PCR can increase the sensitivity of fluid examination with the caveat that some patients can have *Pneumocystis* colonization without infection, and the PCR method is sensitive enough to detect those cases.[71,72] In patients without AIDS or patients with AIDS receiving inhaled pentamidine, transbronchial biopsy increases the diagnostic yield.[69,73]

The diagnosis of fungal pulmonary infection is more problematic; some fungi can colonize the bronchial tree without being a cause of active infection. Fungal infection is a major issue in the immunocompromised host, but it can occur in immunocompetent individuals and can be community-acquired.[74] *Candida* species often colonize the respiratory tract in critically ill patients; their isolation from BAL fluid alone is not diagnostic of tissue invasion.[74,75] *Aspergillus* runs the gamut of possibilities; it can colonize the upper airways without infection, and it can be difficult to detect sometimes when it is the cause of deep tissue infection. In the appropriate clinical and radiologic setting, a BAL positive for *Aspergillus* would be a reasonable criterion for starting therapy, but a BAL negative for *Aspergillus* is inadequate to rule out infection.[76] PCR would seem promising to increase sensitivity for *Aspergillus,* but published results have been variable, and it is not a standard tool.[77–79] Because of the possibility of colonization with *Aspergillus* and *Candida* species, lung biopsy showing tissue invasion is needed to confirm active infection by these fungi.[75,79] In contrast, *Cryptococcus neoformans,* although ubiquitous, does not routinely colonize the respiratory tract; its detection in samples of lung fluid is strong presumptive evidence for an active role in pulmonary infection.[80,81]

The endemic fungi, *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis,* are capable of causing fulminant infection and cannot be ignored as diagnostic possibilities for pneumonia in patients who live in or travel through endemic areas.[80–85] Diagnosis is sometimes difficult, although the organism may be more plentiful and easier to identify in pulmonary secretions of patients who have fulminant disease. BAL fluid has a much higher yield than sputum.[86] If organisms are not seen on smear, fungal cultures can take weeks, an unacceptable interval for seriously ill patients. For *H. capsulatum,* an antigen can be detected in bodily fluids (including BAL) and is of clinical value.[85] The other two endemic fungi are more problematic when not demonstrable on staining of fluids or biopsy material, but promising techniques with antigen detection, DNA probes, and PCR are evolving and should become clinically available soon.[82,84,87,88]

Similar to fungi, viral pneumonias occur more frequently in immunocompromised hosts, but viruses play a role in community-acquired pneumonias as well.[89–91] In a multinational study, viruses alone were identified in 9% of community-acquired pneumonias, and viruses as copathogens were identified in an additional 9% of community-acquired pneumonias.[91] Viral pneumonia is relevant to the critical care setting; in the multinational study, 8% of patients with pure viral pneumonia were admitted to the ICU owing to severity of disease.[91] In another study using the most sensitive available virus detection technique, reverse transcriptase PCR, viruses were present as pathogens or copathogens in 23% of patients hospitalized for community-acquired pneumonia.[89] Analogous to the atypical pneumonias, no clinical characteristics reliably differentiate viral from bacterial pneumonia.[89,91,92]

The virology of viral pneumonia is different for pneumonia in immunocompetent and immunocompromised hosts. In immunocompetent individuals, the most common viruses are influenza A and B, parainfluenza, respiratory syncytial virus, and adenovirus.[92] In immunocompromised patients, the herpesviruses—herpes simplex, varicella zoster, and cytomegalovirus—are most common, with adenovirus, respiratory syncytial virus, and measles also occurring.[92,93] BAL is useful in the diagnosis of viral pneumonia; BAL fluid is an ideal substrate for most studies done to detect viral infection.[94,95] For all but herpes simplex virus and cytomegalovirus, the presence of the virus is diagnostic of infection.[94,96] Cytomegalovirus and herpes simplex virus can be present in BAL fluid in the absence of pneumonia; proof of tissue invasion is far more specific for active infection.[94,96] Viral pneumonias are often difficult to diagnose, and cultures can take days to weeks. Newer diagnostic techniques such as reverse transcriptase PCR offer a far more sensitive diagnostic tool.[97]

BAL is of major utility in the diagnosis of bacterial pneumonias. It has long been recognized that patients in the ICU often have colonization of the upper airways by several potentially pathogenic organisms, and that culture of upper airway secretions cannot be used to diagnose infections of the lower airways and lung parenchyma. Quantitative culture of BAL specimens has been proven to best obviate the issue of upper airway colonization, and BAL has thus emerged as the best currently available diagnostic test for bacterial pneumonia.[57,98] An alternative to BAL is the protected specimen brush (PSB). BAL allows the sampling of a much larger area of lung than does the PSB and logically would be a better diagnostic modality. Although the two modalities are equally accurate in some studies, for several reasons BAL has become the diagnostic procedure of choice for bacterial pneumonia

• BOX 12.2 Reasons to Use Bronchoalveolar Lavage Over Protected Specimen Brush for the Diagnosis of Lung Infiltrates

BAL has a higher sensitivity.
BAL is less expensive.
BAL has a lower complication rate (pneumothorax or bleeding with protected specimen brush).
BAL allows Gram stain of concentrated smear to look for extracellular organisms.
BAL offers the opportunity to evaluate cells for intracellular organisms, additional proof of active infection.
BAL is a tool for the diagnosis of infections other than bacterial infections.
BAL yields specimens that can be used for probe techniques such as polymerase chain reaction.
BAL is a tool for the diagnosis of other infiltrative processes (e.g., alveolar bleeding) that can mimic infection radiologically.

BAL, *Bronchoalveolar.*
Data from references 57, 98, 100 for this chapter (complete list available online).

(Box 12.2).[57,98] A third technique, the blind passage of a protected brush into the airways without bronchoscopic guidance, has been described.[99] This technique has a relatively lower sensitivity than BAL, which probably depends on which lobe is most involved with infection. For example the catheter cannot be passed into the upper lobes.[57,99] For this reason and the reasons cited in Box 12.2, BAL has evolved as the procedure of choice.[98]

Two quantitative methods for bacterial growth of samples obtained by BAL have been described. The first is a simple log count; any bacteria present in greater than or equal to 10^4 colonies by quantitative methods is a pathogen unless proven otherwise.[57] (If PSB is used, a smaller area of lung is sampled and a concentration of $>10^3$ colonies is considered diagnostic of infection.[57]) The second, called the bacterial index, was described by Johanson and colleagues.[100] This method recognizes the fact that in careful studies numerous patients with pneumonia have more than one infecting organism.[23,91,100,101] For the bacterial index, the log numbers of each cultured organism are summed (10^4 *Staphylococcus aureus* + 10^3 *Pseudomonas aeruginosa* = bacterial index of 7). With this system, a bacterial index greater than 6 was a sign of moderate to severe pneumonia.[100] Although the bacterial index system seems more rational, single-organism quantification has become the de facto standard in current clinical practice.

Reinforcing the value of BAL for clinical management of bacterial infection is a study by Rodriguez and associates.[73] The authors performed quantitative cultures on BAL fluid and PSB from 32 ventilated patients not suspected to have pneumonia. There were six "false-positive" results, with quantitative cultures in the pneumonia range. Four of the six patients subsequently developed clinical pneumonia.

If a patient with suspected bacterial pneumonia has already been given antibiotics, the quantitative culture of distal airway secretions loses sensitivity.[102,103] A decrease in recovered organisms becomes significant within 12 hours of initiation of antimicrobial therapy and reaches 50% between 24 and 48 hours.[104] This is not surprising because even quantitative cultures of lung tissue have a dramatic loss of sensitivity and specificity for patients who have received prior antibiotic therapy.[105] Despite this loss in sensitivity, BAL may make sense in the evaluation of critically ill patients with lung infiltrates who are receiving antibiotics as long as these limitations are recognized. BAL can detect organisms not being covered by the current antibiotic regimen, and BAL could help to define nonbacterial infectious agents or other noninfectious processes responsible for the clinical presentation.

When discussing the diagnostic utility of bronchoscopy for the diagnosis of severe lung infection, it is important to mention diagnoses that may be missed by the techniques discussed above. The "atypical pneumonias"—principally *Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* and *C. psittaci*—can be community acquired. The myth that "atypical' and "typical" pneumonias can be distinguished clinically has been refuted. *Legionella* is particularly capable of causing severe disease, and the other organisms can be present as coinfectants in severe disease.[106–108] *Legionella* is not typically visible on Gram stain, does not grow on standard bacterial culture, and requires about 1 week to grow on special media when it is present. BAL material in a patient being evaluated for severe community-acquired pneumonia should be sent for direct fluorescent antibody staining for *Legionella* and for culture.[109] The direct fluorescent antibody staining is reasonably sensitive and very specific for *Legionella,*[106] and direct fluorescent antibody staining of pulmonary secretions and of urine are the most rapid diagnostic tools available. The direct fluorescent antibody of pulmonary secretions remains positive for at least 48 hours after institution of appropriate therapy.[109]

There is an importance to negative BAL for quantitative bacterial culture. A prospective study comparing management based on quantitative cultures from invasive diagnostic techniques (BAL or PSB) with management based on clinical data without quantitative cultures showed that the patients whose therapy was started or withheld based on quantitative bacterial studies had less antibiotic use, lower mortality, and less sepsis-related organ failure.[110] The importance of negative bacterial studies lies not only in the capacity to withhold or discontinue treatment for bacterial pneumonia, but also in the implication that other types of pulmonary infection or injury should be sought, and that, in some cases, extrapulmonary sources of bacterial infection may be present.[57,110] The implications of BAL for a critically ill patient thus extend beyond the lungs.

In summary, bronchoscopic techniques for the diagnosis of pulmonary infection are valuable tools in intensive care medicine. BAL is the most valuable single tool, with diagnostic implications dependent on the organism being evaluated. It is important to remember that a wide spectrum of organisms can cause pneumonia in critically ill patients; the intensivist needs to consider tuberculosis, *Pneumocystis*, viruses, fungi, and atypical organisms in addition to typical bacteria.[111] When BAL fluid has been obtained, the diagnostic techniques of greatest value vary with the infecting organism. For some infecting organisms, detection of a causative organism can be difficult even in the presence of severe infection, and sensitive assays such as PCR can help in the rapid detection of the etiologic agent. In other cases, such as bacterial infection, organisms abound and it can be difficult to separate colonization from infection; in these cases, quantitative cultures are of greatest value. For other organisms, tissue samples are needed for definitive diagnosis. Table 12.1 summarizes diagnostic methods relevant to different lung infections. BAL fluid is the optimal substrate for almost every listed study with the exception of titers and biopsy material.

Lung Biopsy: Surgical, Transbronchial, and Cryobiopsy

The decision of whether or when to perform an open lung biopsy is difficult and a matter of debate. Open lung biopsy is the gold

TABLE 12.1 Diagnostic Techniques for Important Potentially Severe Pulmonary Infections

Important Organism	Presence in BAL Diagnostic?	Culture	Serology	Detection With Antibodies	Gene Amplification	Cytology/Pathology/ Other
M. tuberculosis	Yes	Usually positive—slow			PCR	Necrotizing granulomas
Legionella	Yes	Special media, slow	≥1:256 or 4-fold increase	IF of sputum or BAL	PCR±	DFA of urine or pleural fluid
"Typical" bacteria	No	BAL $>10^4$ PSB $>10^3$ BI >6				DFA—urinary pneumococcal antigen
Influenza (A, B, and C)	Yes	Positive—slow	4-fold increase	IF ELISA (A and B)	PCR	Hemadsorption testing
Herpes simplex	No	Cell culture—cytopathic effects		IF ELISA		Nuclear inclusions (Cowdry A bodies)
Cytomegalovirus	No	Cell culture—cytopathic effects		ELISA		Nuclear inclusions ("owl's eye")
Varicella zoster	Yes	Cell culture—cytopathic effects				Nuclear inclusions (Cowdry A bodies) Typical rash helpful Tzanck preparation
Respiratory syncytial virus (rare)	Yes	Cell culture—cytopathic effects		IF	PCR	Eosinophilic cytoplasmic inclusions
Parainfluenza (1–4)	Yes	Cell culture—cytopathic effects		IF	PCR	Hemadsorption testing Small eosinophilic cytoplasmic inclusions
Adenovirus	Yes	Cell culture—cytopathic effects		IF	PCR	Variable inclusion pattern
Cryptococcus	Yes	Slow				Antigen-serum Tissue invasion
Aspergillus	No					Tissue invasion
Candida	No					Tissue invasion
Coccidioides	Yes		High or increasing			
Histoplasma	Yes		≥1:64 or 4-fold increase	ELISA (cross-reacts with *Blastomyces*)		Can be hard to find even with culture Antigen-urine or serum Tissue invasion
Blastomyces	Yes			ELISA (cross-reacts with *Histoplasma*)		

BAL, Bronchoalveolar lavage; *BI*, bacterial index; *DFA*, direct fluorescent antibody; *ELISA*, enzyme-linked immunosorbent assay; *IF*, immunofluorescence testing (direct or indirect); *PCR*, polymerase chain reaction; *PSB*, protected specimen brush.
Data from references 83, 88, 89, 92, 95, 109, and 111 for this chapter (complete list available online).

standard for the diagnosis of severe cryptogenic lung disease.[112,113] When performed, it has a high diagnostic accuracy although it is not 100%; in one study with 25 patients who had biopsies and subsequent autopsies, the autopsy confirmed the open lung biopsy diagnosis in 76% of cases.[114] Open lung biopsy is useful not only in the diagnosis of infection (particularly infections for which tissue invasion is essential to prove clinical relevance), but also in the diagnosis of primary lung involvement by diseases such as malignancy, nonspecific inflammatory lung disease, and lung-related toxicities of therapeutic interventions. Box 12.3 demonstrates the breadth of possible diagnoses that can be made with open lung biopsy after other diagnostic studies are negative.

Open lung biopsy leads to a change in therapy in 57% to 75% of cases in which it is performed.[112,113,115–117] Open lung biopsy can be performed in patients with respiratory distress and patients supported by ventilators with a reasonable rate of perioperative

• BOX 12.3 Diagnoses With Open Lung Biopsy After Other Study Results Are Negative

- Infection
  - Fungal infection
  - Mycobacterial infection
  - Pyogenic bacteria
  - Cytomegalovirus pneumonia
- Malignancy
  - Leukemia
  - Lymphoma
  - Angiosarcoma
  - Adenocarcinoma
  - Histiocytosis
- Choriocarcinoma
- Cryptogenic organizing pneumonia
- Vasculitis
- Drug toxicity
- Interstitial fibrosis
- Diffuse alveolar damage
- Pulmonary embolism
- Wegener's granulomatosis
- Pulmonary alveolar proteinosis
- Idiopathic pulmonary fibrosis
- Interstitial pneumonitis
- Sarcoidosis
- Diffuse panbronchiolitis

Data from references 112 and 115–117 for this chapter (complete list available online).

complications; death attributed to the biopsy procedure itself is rare, and complications such as persistent air leak usually resolve over time.[113,115,116] Complication rates have been reported to be the same with video-assisted thoracic surgery as with thoracotomy.[117] Several recent studies have reported the frequent use of bedside open lung biopsy, which avoids transport of a critically ill patient and appears to have a morbidity similar to that of doing the biopsy in the operating room.[117–121]

Although the procedure sounds promising, open lung biopsy has several drawbacks. First, authors who separated open lung biopsy results into "specific" (allowing focused therapy thought or known to have some efficacy) and "nonspecific" (a pattern of injury such as diffuse lung damage with no clear cause and no documented effective therapy) found that 38% to 46% of patients had nonspecific injury and no specific therapeutic benefit from the procedure.[113,117] Second, mortality is extremely high in this group despite specific diagnoses and the previously mentioned changes in therapy, particularly if the patients have respiratory compromise; for those patients, the short-term mortality ranges from 52% to 70%.[115–117] (Note that short-term mortality is believed by most authors to be related far more to the underlying disease than to the open lung biopsy procedure.[115–117]) Third, most patients already have received appropriate therapy; in most cases, the change in therapy would be discontinuation of unnecessary drugs or increased dosing of a drug already being given (usually steroids). In some, the benefit of open lung biopsy would be acknowledgment of end-stage disease and withdrawal of all therapy. The most important outcome of open lung biopsy would be a change in therapy that altered outcome from death to survival. Institution of a new potentially lifesaving therapeutic intervention as a result of open lung biopsy is uncommon.[113,115,116] In 1988, Warner and colleagues[116] discussed open lung biopsy in patients with respiratory compromise and said, "any complications of a procedure of unknown benefit is of concern." Some authors hold this opinion to this day. Most patients have received anti-infective drugs, steroids, or both before open lung biopsy is considered, and one could argue that most patients who could respond would have responded before open lung biopsy. Nevertheless, that the controversy is "alive and well" is illustrated by a quote from Chuang and associates[112]: "It is not ethical to avoid open lung biopsy in patients with unclear diagnoses, as open lung biopsy is known to be the most sensitive and specific test available at this time."

Another controversy with respect to open lung biopsy is when to perform it. Two groups have reported open lung biopsy relatively early in the course of respiratory failure with diffuse infiltrates and have withheld therapies until and unless biopsy results demonstrated a specific indication.[120,121] Not unexpectedly, this approach led to a high number of new therapies, usually steroids and/or antivirals. Papazian et al. argued that their approach improved survival.[121] The data provide valuable support for a counterargument—that all patients with idiopathic diffuse lung disease should be treated with both steroids and antiviral drugs. If this had been done in these two series, the added benefit of open lung biopsy would have been very small.

Given the controversies and the available data, a few principles would seem appropriate in considering whether or not open lung biopsy should be performed. First, in most cases, BAL (and perhaps transbronchial biopsy; see later text) should be performed before open lung biopsy is considered. Second, patients who have three or more organs failing (lung plus two more) probably should not undergo biopsy; the prognosis is too poor.[113] Third, decisions about open lung biopsy should be based more on the prior condition of the patient and the potential utility of the study than on the degree of ventilatory distress or compromise of the patient; short-term mortality from the procedure is acceptable. Open lung biopsy in a critically ill patient with undiagnosed pulmonary infiltrates remains a valuable tool that is uncommonly indicated but that will occasionally provide a diagnosis that results in lifesaving therapy.

Bronchoscopic transbronchial lung biopsy may fill the gap between "nontissue" procedures such as BAL and open lung biopsy with its large amount of tissue for pathology and culture. Open lung biopsy by definition requires anesthesia and by definition causes a breach in pleural integrity and requires chest tube placement, with many patients having air leaks after the procedure.[115–117] Transbronchial lung biopsy requires only conscious sedation and would require chest tube placement only if a complication occurred, not as a matter of routine. As noted earlier in the discussion of infection, some diagnoses, such as invasive aspergillosis, *Candida* pneumonia, and cytomegalovirus pneumonia require tissue samples showing tissue invasion. Tissue samples can increase the diagnostic yield for other organisms such as *M. tuberculosis* and *P. jiroveci*.[122]

Diagnoses such as cryptogenic organizing pneumonia and several others listed in Box 12.3 cannot be made without tissue. Transbronchial lung biopsy is reasonable with BAL or after a negative BAL in compromised patients with infiltrates of unknown etiology.[122–125] The available data challenge this concept. It was formerly thought that performing transbronchial lung biopsy in a patient supported by a ventilator carried too high a risk of complications to be warranted. Two early studies[126,127] and several more recent studies[68,124,128,129] have evaluated the yield and complications of transbronchial lung biopsy in ventilated patients. All of these studies showed high yields similar to the yields for open lung biopsy. The pneumothorax rates varied from 0% to 24%. Bleeding

was considered to be significant in 6% to 20%, with all cases self-limited. No fatalities occurred. When transbronchial lung biopsy in ventilated patients is compared with open lung biopsy—for which general anesthesia, incisions, violation of the visceral pleura, and a chest tube are requisites—it is apparent that transbronchial lung biopsy is underused in this population; it has a favorable risk/benefit ratio.

Recently the use of cryoprobes for transbronchial cryobiopsy has gained acceptance, especially in the diagnosis of interstitial lung disease. The cryoprobe concept follows the Joule-Thomson effect, which occurs when a compressed gas is released at a high flow, it expands rapidly and leads to a very low temperature. The cryoprobe is introduced through the bronchoscope channel, extended into the lung parenchyma. The foot pedal is then activated for 3 seconds, leading a "frozen ball" effect around the tip of the probe. Then the specimen, cryoprobe, and bronchoscope are retracted en bloc. Several studies using transbronchial cryobiopsy have documented larger specimens compared with regular transbronchial forceps and with less crush artifacts. Significant bleeding and loss of bronchoscopic visual field are a concern, considering the need to remove the bronchoscope en bloc with the cryoprobe and the frozen specimen to retrieve the specimen. This leaves the airways and potential bleeding "unattended" and may lead to grave consequences.[130–135] Considering that cryobiopsy practice has been often done in patients under general anesthesia, intubation, and mechanical ventilation, the use of transbronchial lung cryobiopsy can be performed in ICU patients with acceptable oxygen requirements. To anticipate and tamponade any potential serious bleeding, a Fogarty balloon is passed to the opening of the targeted bronchus then advanced to occlude the bronchus when the biopsy specimen and bronchoscope are removed.

Placement of Endobronchial Valves

Critically ill patients with bronchopleural fistulae and prolonged air leaks often require longer mechanical ventilation duration, longer ICU length of stay, and are often poor surgical candidates. Bronchoscopic placement of one-way endobronchial valves could be a minimally invasive option. The procedure is easily done in the ICU at bedside. The chest tube drainage system is placed at a bedside table to monitor changes in the degree of air leak. To localize the culprit segment or lobe responsible for the air leak, a sequential bronchoscopic balloon occlusion maneuver is performed while monitoring the air leak. The balloon sequentially occludes the proximal to distal airway to attempt accurate localization of smallest airway possible with either cessation or significant reduction of the air leak. This is followed by bronchoscopic placement of one-way valves (IBV, Spiration Inc., Redmond, WA). Different sized valves are available (5, 6, 7, and 9 mm) and are placed depending on the size of the airways. Several studies have demonstrated the efficacy of those valves in controlling bronchopleural fistulae in critically ill patients supported by mechanical ventilation.[136–138]

Special Situations

Immunocompromised Host

Immunocompromise is a recognized risk factor for respiratory infection. Years of elegant work have helped to define classic types of immunocompromise and patterns of infection that are more typical for the different types.[139–141] Long-recognized diseases causing immunocompromise include solid tumors on chemotherapy, hematologic malignancies, organ transplantation, chronic diseases for which cytotoxic or steroid therapy is given, human immunodeficiency virus infection, and other less common acquired or congenital diseases.[125,141] Although immunocompromise definitely includes the previously mentioned diseases, it has no clear boundaries. Patients with chronic insulin-dependent diabetes, alcoholics, patients with severe malnutrition, and patients using drugs such as infliximab, a tumor necrosis factor antagonist, almost certainly have degrees of immunocompromise that affect their susceptibility to infection.[142–146] The stresses of critical illness and organ dysfunction coupled with the broaching of natural defense systems (skin by central lines, lungs by intubation, urinary tract by catheters) put critically ill patients at increased risk for infection.

Many chronic illnesses probably also carry an increased risk for infection. Shelhamer and colleagues[141] recognized the difficulty with this issue and defined immunocompromise as "any condition, congenital or acquired, temporary or chronic, in which the response of the host to a foreign antigen is subnormal." For patients with classic known forms of immunocompromise, special diagnostic attention must be paid to the possibility of *Pneumocystis* pneumonia, invasive fungal infection, infection with the herpesviruses, and tuberculosis. Three factors make this area gray rather than black-and-white. First, the lack of knowledge that a patient is immunocompromised does not rule out immunocompromise. Second, degrees of immunocompromise exist. And third, most of the pathogens discussed are capable of causing disease in "normal" hosts. For these reasons, some specific issues related to immunocompromise have been mentioned throughout this chapter, but in the clinical approach to a patient with severe respiratory disease, it makes sense to assume that any patient might be immunocompromised; the diagnostic workup should, as mentioned, cast a wide net.

Thrombocytopenia

Thrombocytopenia is an obvious risk factor for bleeding from invasive procedures. BAL has been shown to be safe and clinically useful in thrombocytopenic patients.[147] Bronchoscopic procedures and open lung biopsies have been performed safely in patients with thrombocytopenia.[117,148] Historically, procedures have been limited to BAL, or platelets have been given before bronchoscopic or surgical procedures.[117,148] In our practice, we use platelet count $\geq 50{,}000\ \mu L$ as an absolute cutoff before considering transbronchial bronchoscopic lung biopsy.

Complications and Death

The true incidence of complications of bronchoscopy in the ICU is poorly defined. Most reviews of the topic[27,39,149–152] cite several older studies of bronchoscopy in general,[7–9,11,153] not specifically in critically ill patients. The two largest and most-cited reports are by Credle and colleagues[7] and Suratt and coworkers[11] and reviewed 24,521 (Credle et al.) and "approximately 48,000" (Suratt et al.) procedures. These were retrospective reports based on mailed questionnaires. Death rates were 0.01% and 0.03%, respectively.[7,11]

The next largest study was a retrospective single-institution study of 4273 bronchoscopies, which reported 0% mortality and a 0.5% frequency of major complications (pneumothorax, bleeding, respiratory failure requiring intubation).[9] Three prospective studies reported on 205 to 1146 flexible bronchoscopies and reported mortality rates of 0%,[9] 0.1%,[153] and 0.5%.[8] The highest reported

mortality rate is in a study from a consortium of expert bronchoscopists studying autofluorescence.[154] The study included the requisite of at least two endobronchial biopsies, and in a series of 300 cases the immediate postbronchoscopic mortality was 0.7%. Two retrospective studies[45,155] and one prospective study[68] reviewed bronchoscopies performed specifically in patients in the ICU. No procedure-related mortality was reported. Throughout these studies, only death rates are consistently noted; major and minor complications are variably defined.

Several principles emerge from the previously cited studies. The complication rates depend on the invasiveness of the procedure. The highest incidence of complications occurs with lung biopsy and then, in descending order, with brushings, BAL, and simple observation. For the patients expected to have the highest complication rate—patients supported by ventilators who underwent transbronchial biopsies—there is a pneumothorax rate of 24%, but no fatalities have been reported.[68,124,126–129] None of these studies involved large numbers of patients; it is inevitable that fatalities would occur in this subset of high-risk cases. Nevertheless, many years of experience with flexible fiberoptic bronchoscopy have led to the conclusion that its benefits outweigh its risks. No bronchoscopy should be done in a critically ill patient without a reason, but when a reason is present, bronchoscopy is often the unique or the safest method known of obtaining data that may affect care.

Summary

Since its inception in 1968, flexible fiberoptic bronchoscopy has evolved into a major tool in the evaluation and management of critically ill patients. The bronchoscope allows evaluation of and sometimes management of airway problems. The bronchoscope follows the most natural pathway into the lung—the airway—and allows sampling of secretions and tissues from the alveolar level. The basic techniques have been defined for many years. What has been refined is our understanding of their utility and testing methodologies; increasing sensitivities and specificities over the years have greatly enhanced our capacities, particularly in the diagnosis of lung infections. Some lung infections require lung tissue for definitive diagnosis, as do several diagnoses that can cause diffuse lung disease and can sometimes mimic infection. Open lung biopsy is a time-honored approach with high diagnostic accuracy that may sometimes be an optimal approach. Transbronchial lung biopsy, even in a ventilated patient, has a clinical impact similar to that of open lung biopsy and is probably underused in critically ill patients with diffuse infiltrates in whom empiric therapies fail. It is clear that the more ill the patient, the higher the risk of any invasive procedure, but the literature points the risk/benefit ratio of bronchoscopy in favor of performing bronchoscopy for the indications outlined in this chapter.

Key Points

- Bronchoscopy has become a major tool in the evaluation of the airways and lung parenchyma of critically ill patients.
- Bronchoscopy stimulates a series of reflexes affecting blood pressure, heart rate, and intracerebral pressure, but this is true for any cannulation of the upper airway (e.g., suctioning). Bronchoscopy for the evaluation of lung problems in critically ill patients has a favorable risk/benefit ratio.
- Inserting a bronchoscope through an ETT causes upper airway obstruction and can cause hypoventilation or hyperinflation or both; the physiologic changes caused by the bronchoscope need to be understood and possibly compensated for.
- Bronchoscopy is a valuable tool for the diagnosis and management (especially intubation and percutaneous tracheostomy) of upper airway problems.
- Bronchoscopy with BAL is the most effective and accurate clinical tool currently available for the diagnosis of pulmonary infection in critically ill patients.
- The potential of bronchoscopy for the diagnosis of infection is being advanced at present not by bronchoscopic techniques, but by the development and clinical application of extremely sensitive tools such as PCR assays.
- Critically ill patients with undiagnosed infiltrates occasionally benefit from lung biopsy; the results often affect management but rarely affect outcome. Available data suggest that bronchoscopic transbronchial lung biopsy has yields similar to those for open lung biopsy with a more favorable risk/benefit ratio.

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Review Questions

1. Which of the following is most correct concerning conscious sedation during bronchoscopy:
- **a.** It is not associated with hypoxemia in healthy volunteers.
- **b.** It is associated with hypoxemia in healthy volunteers only after prolonged bronchoscopy >30 minutes.
- **c.** It is associated with hypoxemia even before bronchoscopy starts in healthy volunteers.
- **d.** It is associated with hypoxemia only in patients with underlying lung diseases.

Answer: c. Conscious sedation during bronchoscopy using benzodiazepines and narcotics can lead to hypoxemia in healthy volunteers even before bronchoscopy starts. We recommend the use of supplemental oxygen in all patients undergoing bronchoscopy regardless of whether they have underlying lung diseases or not.

2. You are consulted to perform a therapeutic bronchoscopy in the ICU on a patient with significant right-sided-atelectasis. After reviewing all clinical information, you notice that the patient has not undergone any chest physiotherapy. You inform the consulting physician of the following:
- **a.** You agree to perform the bronchoscopy as it has been shown to be superior to chest physiotherapy in patients with atelectasis in the ICU.
- **b.** Bronchoscopy is equal to chest physiotherapy and associated with the same adverse events.
- **c.** Chest physiotherapy is preferred as initial therapy considering that bronchoscopy could be associated with complications
- **d.** There is no role for bronchoscopy in ICU patients with atelectasis as they are too sick to undergo a bedside bronchoscopy.

Answer: c. Atelectasis is common in the ICU, especially in patients receiving invasive mechanical ventilation. Chest physiotherapy remains first-line therapy for atelectasis as it is proven to be as effective as bronchoscopy as an initial intervention; bronchoscopy is associated with more significant decreases in oxygenation compared with chest physiotherapy. We recommend initiating chest physiotherapy before attempted bronchoscopy. However, some patients have contraindications for chest physiotherapy—such as chest trauma, spinal cord injury, or immediate postthoracotomy—and may require bronchoscopy first.

3. When compared with conventional transbronchial forceps biopsy for interstitial lung disease, cryobiopsy
- **a.** Is associated with increased risks of bleeding
- **b.** Is safer than transbronchial forceps biopsy and provides equal size samples
- **c.** Should be performed only with rigid bronchoscopy
- **d.** Obeys the Pascal law of transmission of fluid-pressure

Answer: a. Cryobiopsy for interstitial lung disease has gained popularity recently as it leads to larger samples compared with transbronchial forceps biopsy during a workup for interstitial lung disease. However, it is associated with increase bleeding complications when retrieving the specimen as the bronchoscope, the cryoprobe, and the specimen need to be retrieved en bloc considering that the "frozen ball" would not fit through the bronchoscope channel. Cryoprobe biopsy can be performed with flexible bronchoscopy and does not require rigid bronchoscopy. It obeys the Joule-Thomson effect.

13

Noninvasive Respiratory Monitoring

AMAL JUBRAN AND MARTIN J. TOBIN

CHAPTER OUTLINE

Gas Exchange
- Pulse Oximetry
- Transcutaneous Blood Gas Monitoring
- Capnography

Respiratory Neuromuscular Function
- Airway Occlusion Pressure
- Maximal Inspiratory Airway Pressure
- Breathing Pattern
- Changes in End-Expiratory Lung Volume

Respiratory Mechanics
- Elastance (Compliance)
- Pressure-Volume Curves
- Resistance
- Intrinsic Positive End-Expiratory Pressure
- Airway Pressure Profile
- Flow-Volume Curves

Various devices are available for effective and noninvasive monitoring of the patient's gas exchange function, respiratory neuromuscular capacity, and respiratory mechanics. Such measurements are helpful in characterizing the pathophysiology of an underlying respiratory disorder, tracking the course of illness and the effects of treatment, minimizing the risk of complications, and determining the patient's readiness for the withdrawal of therapeutic interventions and support devices.

Gas Exchange

The human eye is poor at recognizing hypoxemia.[1,2] With the availability of pulse oximetry, episodic hypoxemia has been found to be more common than was previously suspected, with an incidence ranging from 20% to 82%.[3] Patients experiencing hypoxemia have a threefold higher risk of death compared with patients who do not display desaturations.[4]

Pulse Oximetry

Pulse oximeters determine oxygen (O_2) saturation by measuring light absorption of arterial blood at two specific wavelengths, 660 nm (red) and 940 nm (infrared).[5,6] The ratio of absorbencies at these two wavelengths is calibrated empirically against direct measurements of arterial blood oxygen saturation (SaO_2), and the resulting calibration algorithm is used to generate the pulse oximeter's estimate of arterial saturation (SpO_2) (Fig. 13.1).[3,7]

Accuracy

Compared with the measurement standard (multiwavelength oximeter) for measuring SaO_2, pulse oximeters have a mean difference (bias) of less than 1% and a standard deviation (precision) of less than 2% when SaO_2 is 90% or above.[6,8] Although pulse oximetry is accurate in reflecting 1-point measurements of SaO_2, it does not reliably predict changes in SaO_2.[9] In 1085 simultaneous measurements of SaO_2 and SpO_2 in 41 ICU patients, changes in SaO_2 correlated moderately with changes in SpO_2 ($r = 0.6$), and the pulse oximeter tended to overestimate actual changes in SaO_2.[10]

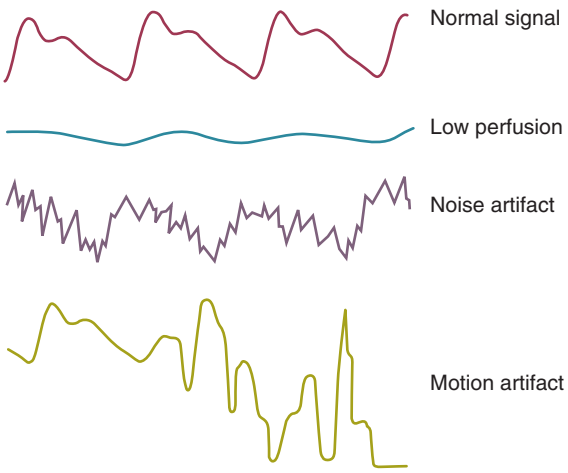
The accuracy of pulse oximeters deteriorates when SaO_2 falls to 80% or less.[9,11] In critically ill patients, poor agreement between the oximeter and a CO-oximeter was observed, with bias ranging from −12% to 18%; and oximetry tended to systematically underestimate SaO_2 when it was less than 80%.[12]

Conventional pulse oximeters use probes that are usually placed on the earlobe, finger, or toe.[13] More recently, reflectance technology has been used to develop probes that can be placed on the forehead.[9] When tested in critically ill patients with low perfusion, the forehead reflectance probe had lower bias and precision than did the finger probe.[14,15] However, the response to change in O_2 saturation was faster for the forehead probe than for the finger probe in patients undergoing anesthesia.[16]

Limitations

Oximeters have several limitations that may lead to inaccurate readings (Box 13.1). Pulse oximeters target measurement of SaO_2, which is physiologically related to arterial oxygen tension (PaO_2) according to the O_2 dissociation curve. Because the dissociation curve has a sigmoid shape, oximetry is relatively insensitive in detecting hypoxemia in patients with high baseline levels of PaO_2.[6,17]

Pulse oximeters use only two wavelengths of light; accordingly, they can discriminate only two substances, oxyhemoglobin and reduced hemoglobin. Elevated carboxyhemoglobin and methemoglobin levels can therefore cause inaccurate oximetry readings.[18–21] Recently multiwavelength oximeters have been developed that can estimate blood levels of carboxyhemoglobin and methemoglobin.[22,23] When tested in patients with suspected carbon monoxide poisoning, the bias between oximetric measurement of carboxyhemoglobin and laboratory measurement of carboxyhemoglobin was less than 3%.[24,25] The limit of agreement between the measurements, however, was large (−11.6% to 14.14%),[25] raising questions as to whether these new oximeters may be a reliable substitute for standard laboratory measurements of carboxyhemoglobin.[9,25,26]



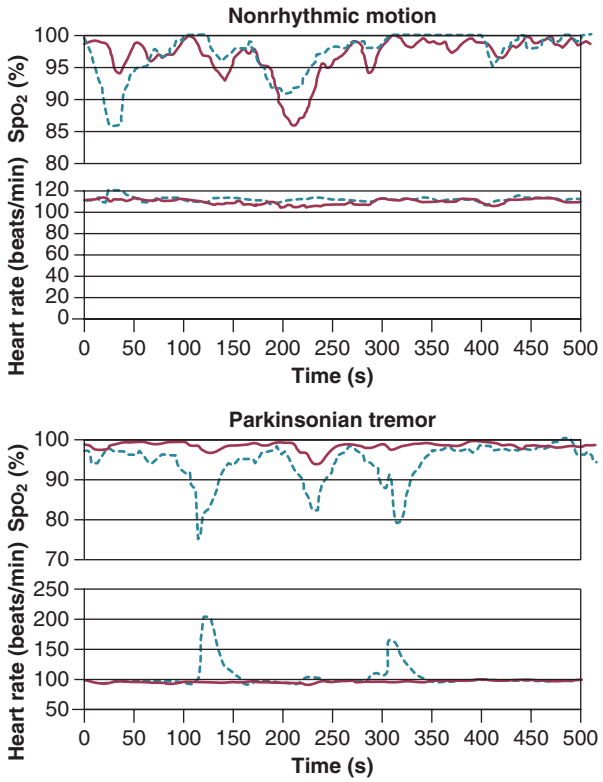
• **Fig. 13.1** Common pulsatile signals on a pulse oximeter. *Top tracing,* Normal signal showing the sharp waveform with a clear dicrotic notch. *Second tracing,* Pulsatile signal during low perfusion showing a typical sine wave. *Third tracing,* Pulsatile signal with superimposed noise artifact giving a jagged appearance. *Bottom tracing,* Pulsatile signal during motion artifact showing an erratic waveform. (From Jubran A: Pulse oximetry. In: Tobin MJ, ed. *Principles and Practice of Intensive Care Monitoring.* New York: McGraw-Hill; 1998:261–287.)

• BOX 13.1 Limitations of Pulse Oximetry

Physiologic limitations
- Shape of oxyhemoglobin dissociation curve

Interference from substances
- Dyshemoglobins: carboxyhemoglobin, methemoglobin
- Dyes
- Nail polish
- Ambient light
- Skin pigmentation

Limitation in signal processing
- Low-perfusion state
- Motion artifact
- False alarms
- Limitation in knowledge of the technique



• **Fig. 13.2** Pulse oximetry signals with motion artifact; *top panel,* recorded during nonrhythmic motion (i.e., gross arm motion); *lower panel,* recorded during parkinsonian tremor. The *red line* denotes Masimo Signal Extraction Technology (SET), aimed at minimizing spurious pulse oximetry readings due to motion artifact; the *blue line* denotes conventional pulse oximetry. Spurious changes in measured oxygen saturation (Spo_2) are less with Masimo SET than with conventional pulse oximetry. (From Dumas C, Wahr JA, Tremper KK. Clinical evaluation of a prototype motion artifact resistant pulse oximeter in the recovery room. *Anesth Analg.* 1996;83:269–272.)

Intravenous dyes can cause falsely low SpO_2 readings.[3,9] In critically ill patients requiring mechanical ventilation, nail polish has been shown not to affect the accuracy of SpO_2 readings.[27] Falsely low and falsely high SpO_2 readings occur with fluorescent and xenon arc surgical lamps.[28]

Skin pigmentation can affect the accuracy of pulse oximetry.[29,30] In critically ill patients,[11] bias plus precision was greater in black patients (3.3% + 2.7%) than in white patients (2.2% + 1.8%); also, a bias greater than 4% occurred more frequently in black patients (27%) than in white patients (11%).

Low-perfusion states, such as low cardiac output, vasoconstriction, and hypothermia, may impair peripheral perfusion, making it difficult for a sensor to distinguish a true signal from background noise. In patients experiencing hypothermia and poor perfusion during cardiac surgery, only 2 of 20 oximeters (Criticare CSI 503 [Criticare Systems, Inc., North Kingstown, RI] and Datex Satlite [Datex Instrumentarium Corp., Helsinki, Finland]) provided measurements within +4% of the CO-oximeter value.[13]

Motion artifact is a frustrating problem, and it results in inaccurate readings and false alarms. An innovative technological approach, termed Masimo Signal Extraction Technology, was introduced to extract the true signal from artifact secondary to noise and low perfusion[31] (Fig. 13.2). When tested in healthy volunteers, the new generation of pulse oximeters that incorporated new technology to filter out artifacts outperformed conventional oximeters in reducing nuisance alarms and ensuring alarm reliability.[8]

Despite their popularity for continuous monitoring of O_2 saturation, pulse oximeters fail to provide valid data in a variety of settings, accounting for almost half of false alarms[32–35]; such alarms were secondary to low perfusion, cardiac arrhythmias, and motion artifacts.[36] An underrecognized and worrisome problem with pulse oximetry is that many users have a limited understanding of how the oximeter functions and the implications of the measurements obtained.[9] One survey revealed that 30% of physicians and 93% of nurses thought that the oximeter measured PaO_2.[37] Some clinicians did not recognize that SpO_2 values in the high 80s represent seriously low values of PaO_2. More recent studies suggest that the knowledge about pulse oximetry is increasing.[9,38] When 551 critical care nurses were interviewed, 86.5% knew that SpO_2 readings are not as accurate when signal quality is poor, and 70% knew that SpO_2 was not a replacement for arterial blood gas analysis in the care of critically ill patients.[39]

Clinical Applications

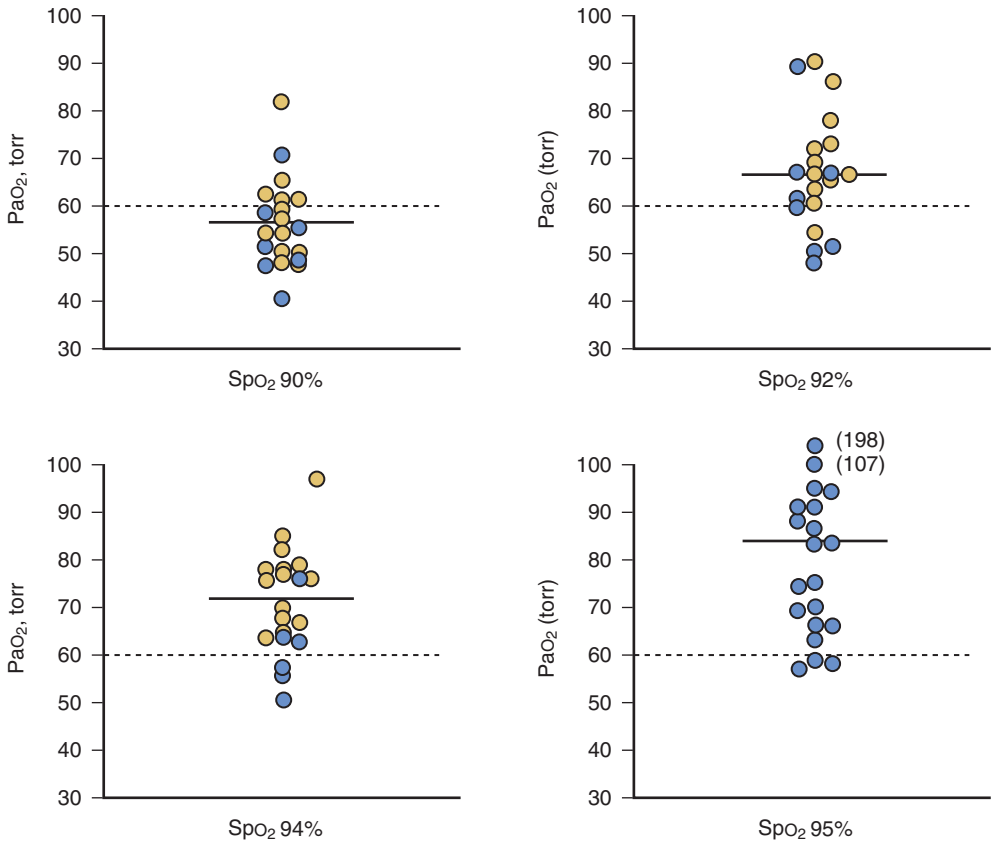
With the introduction of pulse oximetry, hypoxemia (defined as an SpO_2 value <90%) is now detected more often in critically ill patients[40] and in patients undergoing surgery.[41,42] Changes in SpO_2 may not accurately reflect changes in PaO_2. Accordingly, caution is required in clinical decision making in critically ill patients based solely on pulse oximetry. Although pulse oximetry is a suitable way of measuring arterial oxygenation, it does not assess ventilation. Indeed, measurements of SpO_2 have been shown to be inaccurate in assessing abnormal pulmonary gas exchange, defined as an elevated alveolar-arterial O_2 difference.[3]

Pulse oximetry can assist with titration of fractional inspired oxygen concentration (FIO_2) in ventilator-dependent patients, although the appropriate SpO_2 target depends on a patient's pigmentation.[11] The SpO_2 target value that predicts a satisfactory level of oxygenation is 92% in white patients and 95% in black patients (Fig. 13.3).

Pulse oximetry has been evaluated as a means of screening for respiratory failure in patients with severe asthma.[43] Respiratory failure was unlikely in patients with SpO_2 greater than 92%. Of interest, this threshold value of 92% is the same target value that reliably predicted a satisfactory level of oxygenation during titration of FIO_2 in ventilator-dependent patients.[11] Pulse oximetry may be useful in predicting outcome in patients with pulmonary embolus. In patients with documented pulmonary embolism, a room-air SpO_2 less than 95% had an overall diagnostic accuracy of 67% in predicting mortality.[44]

Moller and associates[45] conducted the first prospective, randomized study of pulse oximetry on the outcome of anesthesia care in 20,802 surgical patients. Detection of hypoxemia (defined as an SpO_2 <90%) was 19-fold higher in the oximeter group than in the control group. Myocardial ischemia was more common in the control group than in the oximetry group, occurring in 26 and 12 patients, respectively. Pulse oximetry, however, did not decrease the rate of postoperative complications or mortality.

The lack of proven efficacy of pulse oximetry in the study by Moller and associates[45] was related to the sample size. These investigators concluded that it would take at least 500,000 patients to show a reduction in a rare event such as myocardial infarction, and 1,900,000 patients to show a reduction in anesthesia-related deaths. When anesthesiologists in the study were surveyed, 80% of them reported feeling more secure when they used a pulse oximeter.[46] It is this mindset that has established pulse oximetry as an essential component of the standard of care despite a failure to achieve a level of proven efficacy with a *P* value of less than



• **Fig. 13.3** Arterial oxygen tension *(Pa_{O_2})* values at pulse oximetry oxygen saturation *(Sp_{O_2})* values of 90%, 92%, 94%, and 95%. The inspired oxygen concentration was adjusted to achieve a particular steady-state SpO_2 value in a group of 54 critically ill patients. The *solid horizontal line* represents the mean PaO_2 value obtained at each SpO_2 target. The *orange* and *blue circles* represent values obtained in white and black patients, respectively. In white patients, a SpO_2 target of 92% resulted in a satisfactory level of oxygenation, whereas a higher SpO_2 target, 95%, was required in black patients. (Modified from Jubran A, Tobin MJ. Reliability of pulse oximetry in titrating supplemental oxygen therapy in ventilator-dependent patients. *Chest.* 1990;97:1420–1425.)

0.05. The lack of concurrence between randomized trial proof of efficacy of pulse oximetry and its requirement as part of the standard of care has major ramifications for all monitoring techniques.[47]

Cost-Effectiveness

Studies evaluating the cost-effectiveness of pulse oximetry have reported that fewer arterial blood gas samples were obtained if SpO_2 data were available to the caregivers.[48–50] The effect of implementing pulse oximetry in an ICU without any specific plan for its appropriate use was examined in 148 patients before the implementation of oximetry and 141 patients after its implementation.[51] The number of blood gas samples decreased from 7.2 to 6.4 per patient per day—a reduction of only 10.3%—compared with average reductions of 39% in the previous studies.[3] This suggests that without explicit guidelines, the pulse oximeter was used in addition to, rather than instead of, blood gas sampling.

Transcutaneous Blood Gas Monitoring

Transcutaneous measurements of O_2 tension ($PtcO_2$) are made by placing a heated Clark polarographic electrode directly on the skin and measuring the O_2 that diffuses from the blood to the skin.[52] This technique is used more commonly by neonatologists because neonatal skin is thin.[53] During low-perfusion states, $PtcO_2$ measurements may not reflect changes in PaO_2. In critically ill patients, the $PtcO_2/PaO_2$ ratio decreased from 0.79 ± 0.1 when the cardiac index was greater than 2.2 L/min per m^2 to 0.12 ± 12 when the cardiac index was less than 1.5 L/min per m^2.[54]

Transcutaneous monitoring of the partial pressure of carbon dioxide ($PtcCO_2$) can be performed using a modified Severinghaus electrode. The underlying skin is heated to 44°C to enhance carbon dioxide (CO_2) diffusion through the skin.[54] The correlation of $PtcCO_2$ with the arterial partial pressure of carbon dioxide ($PaCO_2$) usually is good: $r = 0.93$.[53]

The accuracy of $PtcCO_2$ as a surrogate measure for $PaCO_2$ was evaluated in 50 critically ill patients in a medical ICU.[55] Of the available 168 measurements, the mean difference between $PaCO_2$ and $PtcCO_2$ was −0.2 ± 4.6 mm Hg; the correlation between two measurements was 0.92. A strong correlation was observed between changes in $PaCO_2$ and $PtcCO_2$ ($r^2 = 0.78$). These data suggest that transcutaneous PCO_2 may be reliable in monitoring changes in arterial PCO_2, provided that no major vasoconstriction is present.

Capnography

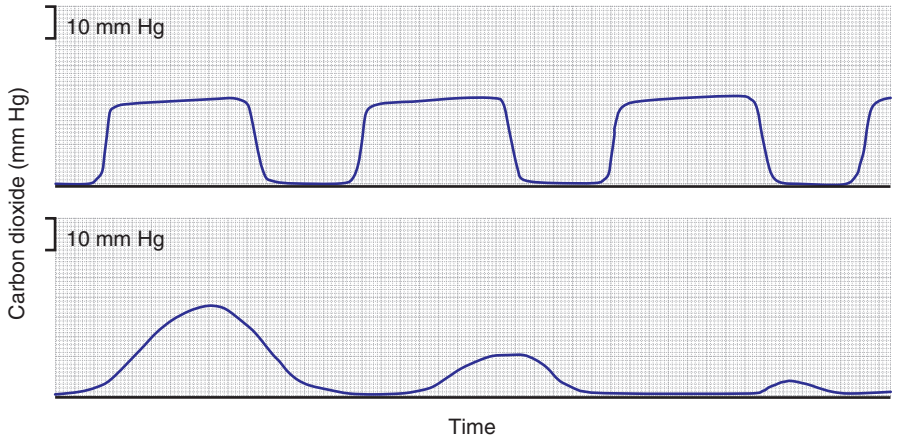
The CO_2 concentration at the end of a tidal breath—end-tidal CO_2—can be used as a continuous, indirect measure of $PaCO_2$. In intubated patients with respiratory failure, correlation between end-tidal CO_2 and $PaCO_2$ was good ($r = 0.78$).[56] The correlation between changes in end-tidal CO_2 and changes in $PaCO_2$ from baseline, however, was considerably weaker ($r = 0.58$). The change in end-tidal CO_2 incorrectly indicated the direction of change in $PaCO_2$ in 43% of patients being weaned from mechanical ventilation after cardiac surgery.[57]

Capnometry commonly is used in detecting esophageal intubation (Fig. 13.4).[58–60] When the trachea of a patient with an intact pulmonary circulation is intubated, end-tidal CO_2 is recorded. When, however, the endotracheal tube is erroneously placed in the esophagus, end-tidal CO_2 will be zero. Other conditions that produce a flat-line waveform on capnometry include obstruction within or distal to an endotracheal tube and prolonged cardiac arrest. Monitoring of end-tidal CO_2 has been compared with three other methods—auscultation, negative-pressure testing using a self-inflating bulb, and transillumination—for verifying tracheal tube placement, and it was found to be the most reliable.[61] During cardiac arrest, capnometry is useful in assessing the adequacy of chest compressions and the return of spontaneous circulation.[62,63]

Respiratory Neuromuscular Function

Airway Occlusion Pressure

Measuring airway pressure 0.1 second after initiation of an inspiratory effort against airway occlusion ($P_{0.1}$) provides a measure of respiratory drive.[64] In ventilator-dependent patients, $P_{0.1}$ has been



• **Fig. 13.4** End-tidal carbon dioxide (CO_2) tracing and esophageal intubation. *Upper panel:* End-tidal CO_2 tracing in a patient in whom an endotracheal tube was inserted correctly in the trachea. During inhalation, end-tidal CO_2 is 0 mm Hg. During exhalation, the CO_2 tracing rises steeply, attains a near plateau, and then quickly returns to the baseline. *Lower panel:* End-tidal CO_2 tracing in a patient in whom an endotracheal tube was erroneously inserted in the esophagus. The expected shape of the CO_2 tracing has been replaced by small transient rises in the CO_2 tracing, which progressively decrease with each squeeze of the Ambu bag.

shown to correlate significantly with work of breathing during pressure-support ventilation ($r = 0.87$).[65] By taking advantage of the decrease in airway pressure (P_{aw}) to open the demand valve during triggering, investigators have demonstrated that commercially available ventilators can measure $P_{0.1}$ accurately.[66] Several studies[66–68] have indicated that an elevated $P_{0.1}$ predicted weaning failure, but the threshold separating success from failure differed among the studies.[69]

Maximal Inspiratory Airway Pressure

Maximum inspiratory pressure (PImax), a global measure of inspiratory muscle strength, is measured using a one-way valve that allows exhalation but prevents inhalation.[70,71] PImax is one of the standard measurements used to determine a need for the continuation of mechanical ventilation. Values that are more negative than −30 cm H_2O are considered predictive of weaning success; values that are less negative than −20 cm H_2O are predictive of weaning failure. These criteria, however, frequently are falsely positive and falsely negative.[72]

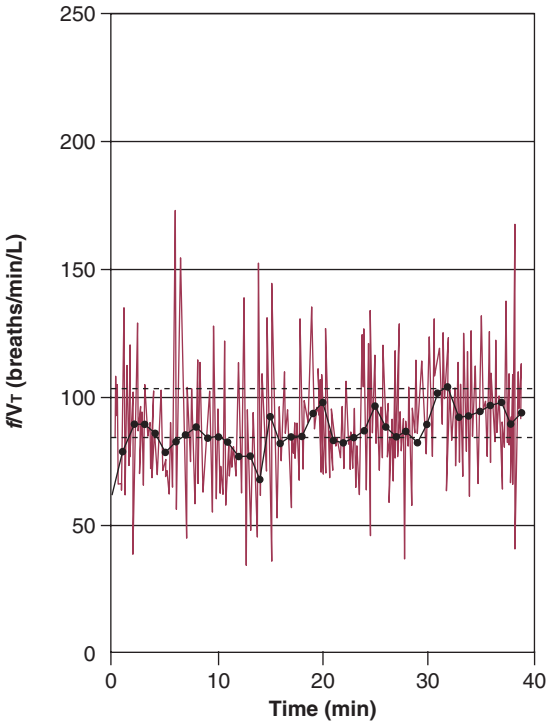
Breathing Pattern

Rapid shallow breathing is a common respiratory pattern in patients in whom a trial of weaning from mechanical ventilation fails,[73] and this can be quantitated in terms of the frequency/tidal volume ratio (f/V_T). An f/V_T above 100 breaths/min per liter suggests that a trial of weaning is unlikely to be successful.[72] When prospectively evaluated, f/V_T was found to be superior to nine other weaning predictors: sensitivity was 0.97, specificity 0.64, positive predictive value 0.78, and negative predictive value 0.95.[69]

The usefulness of f/V_T in predicting weaning outcome was challenged. Using a meta-analysis, an American College of Chest Physicians Task Force concluded that f/V_T was unreliable.[74–77] In their evaluation of published reports on f/V_T, the Task Force ignored the important influence of pretest probability on the interpretation of a test results. The implications of pretest probability are greater for weaning than for many clinical situations because weaning involves a sequence of three diagnostic tests: measurement of predictors, followed by a weaning trial, followed by an extubation trial. The undertaking of three diagnostic tests in a sequential manner poses an enormous risk for the occurrence of test referral and spectrum bias.[78] The introductions of such biases, will, in turn, increase the pretest probability.[79,80] Indeed, the mean pretest probability of weaning success was 75% in the studies included in the meta-analysis. When data from studies included in the Task Force meta-analysis were entered into a Bayesian model with pretest probability as the operating point, the observed posttest probabilities were closely correlated with the values predicted by the original study on f/V_T: $r = 0.86$ for positive predictive value and $r = 0.82$ for negative predictive value.[81]

It has been suggested that measurements of f/V_T at 30 minutes into a weaning trial more accurately predict outcome than measurements in the first minute.[82,83] Although it is true that including data for the first 30 seconds or so may be unrepresentative, this does not mean that it takes 30 minutes to establish a steady state.

Jubran and colleagues[83] studied the time required for f/V_T to reach a point of equilibration in 17 weaning failure and 14 weaning success patients. The median time (plus interquartile range) to reach +10% of the final value of f/V_T was 2 (1 to 2) minutes in both the weaning success and the weaning failure patients (Fig. 13.5). Within 2 minutes of the onset of the T-tube trial, 77% of the weaning failure patients and 73% of the weaning success patients had reached +10% of the final value of f/V_T. As indicated by these data, a reasonable strategy is to commence measurement of f/V_T at 60 seconds after removal of the ventilator and then continue the measurement for another 60 seconds.

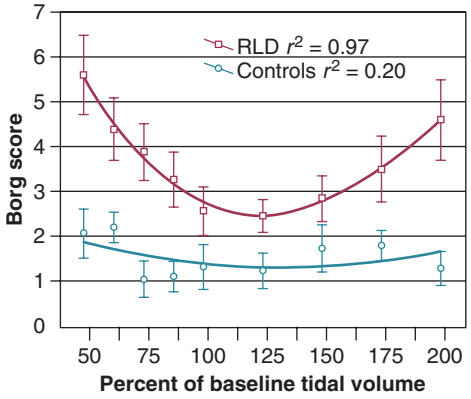


• **Fig. 13.5** Time-series plot of frequency/tidal volume ratio *(f/V_T)* during a T-tube trial of spontaneous breathing in a weaning failure patient. The *black dots* represent 1-minute averages. The *solid line* indicates the average value of f/V_T of the final minute of the trial. The *dashed horizontal lines* indicate +10% of the final minute values of f/V_T. The time taken to reach +10% of the final value of f/V_T was 2 minutes. (From Jubran A, Grant BJ, Laghi F, et al. Weaning prediction: esophageal pressure monitoring complements readiness testing. *Am J Respir Crit Care Med.* 2005;171:1252–1259.)

Continuous recording of breathing pattern provides an important approach for assessing the ability of the respiratory controller to maintain or adjust its response over time.[64] Simple measurements, such as coefficients of variation, indicate that healthy subjects display considerable variation in tidal volume and respiratory cycle time from one breath to the next.[84] Signal analysis techniques reveal that this variability is composed of random and nonrandom fractions.[85–90] The predominantly random character of the variability makes it possible for the respiratory system to engage in tasks other than gas exchange. A smaller fraction of variability is nonrandom; moreover, tidal volume and respiratory cycle time of one breath are significantly related to those of the preceding breath.[85,86,88,89] When healthy subjects are faced with external chemical or mechanical loads, however, the random fraction decreases significantly.[86,88,89] This decrease in random variability may lessen the freedom of the respiratory system to undertake behavioral tasks.[88,89,91]

Using autocorrelation analysis and fast-Fourier transformation, patients with restrictive lung disease display a marked decrease in breath-to-breath variability of breathing.[64,92] The random fraction

of variability was approximately $^1/_{27}$ of that found in healthy subjects, and the nonrandom correlated fraction was as much as three times higher in the patients. Slight variations from the average resting tidal volume caused large increases in dyspnea in the patients, but not in the healthy subjects (Fig. 13.6).[92] In patients undergoing a weaning trial, a higher gross variability of breathing (quantitated in terms of coefficient of variation) was noted in patients who were successfully weaned than in patients in whom the trial failed.[93] These data suggest that an increase in the ability to vary breathing may be associated with a favorable weaning outcome.[94]



• **Fig. 13.6** The relationship between variation in tidal volume and dyspnea *(Borg score)* in patients with restrictive lung disease *(RLD)* and in control subjects. Dyspnea scores were higher in the patients than in the control subjects ($P < 0.01$, analysis of variance [ANOVA]); dyspnea varied with tracked volume in the patients ($P < 0.05$, ANOVA) but not in the control group. The regression between dyspnea and tidal volume was parabolic in the patients ($y = 10.3 - 0.12x + 0.0005x^2$; $P < 0.0001$), but not in the control subjects ($y = 2.76 - 0.02x + 0.00008x^2$; $P = 0.5$). *Bars* represent ± standard error of the mean. (From Brack T, Jubran A, Tobin MJ. Dyspnea and decreased variability of breathing in patients with restrictive lung disease. *Am J Respir Crit Care Med.* 2002;165:1260–1264.)

Changes in End-Expiratory Lung Volume

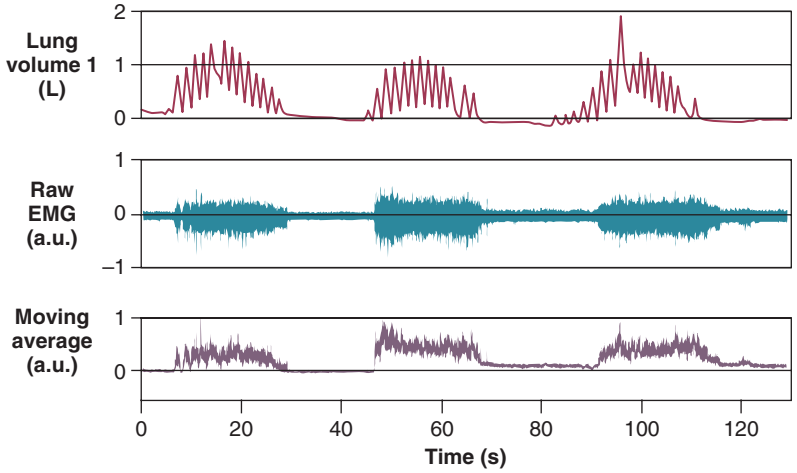
Alterations in the end-expiratory level of signal from an inductive plethysmograph can provide a measurement of the change in functional residual capacity provided that motion artifact is absent (Fig. 13.7).[95,96] Inductive plethysmography has been used to estimate a patient's level of auto-PEEP.[56] By noting the level of external PEEP at which end-expiratory lung volume increased, a close estimate of the patient's original level of auto-PEEP (positive end-expiratory pressure) can be obtained. An attractive feature of this technique is that it does not disturb expiration, unlike the occlusive technique, in which foreshortening of expiratory time is unavoidable.[97]

Respiratory Mechanics

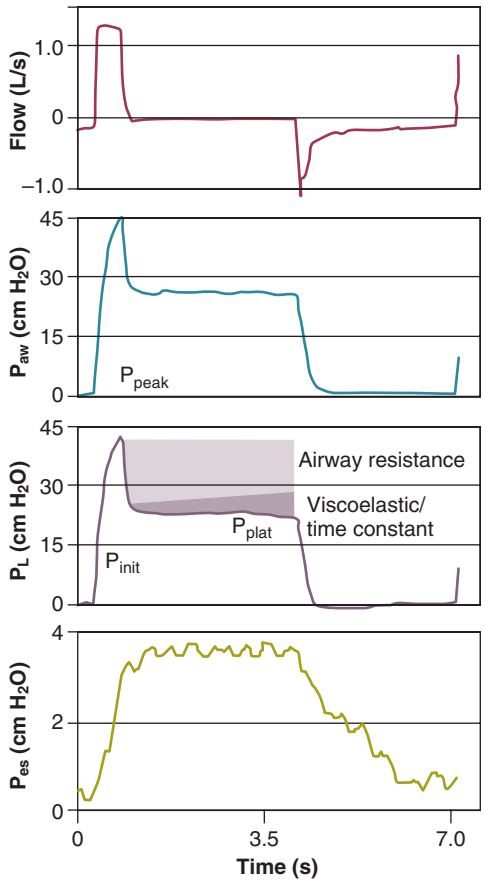
Measurements of respiratory mechanics in a relaxed ventilator-dependent patient can be obtained using the technique of rapid airway occlusion during constant-flow inflation.[84,98] Rapid airway occlusion at the end of a passive inflation produces an immediate drop in both P_{aw} and transpulmonary pressure (P_L) from a peak value (P_{peak}) to a lower initial value (P_{init}), followed by a gradual decrease until a plateau (P_{plat}) is achieved after 3 to 5 seconds (Fig. 13.8).[99,100] P_{plat} on the P_{aw}, P_L, and esophageal pressure tracings represents the static end-inspiratory recoil pressure of the total respiratory system, lung, and chest wall, respectively.

Performing an end-inspiratory occlusion maneuver to measure plateau pressure can help the physician determine immediately the reason a patient is fighting the ventilator (Fig. 13.9).[101] An increase in peak airway pressure without a proportional increase in plateau pressure indicates narrowing of the airway.[101] Narrowing may arise from bronchoconstriction, an increase in secretions, a collection of fluid in the inspiratory limb of the ventilator circuit, kinking of the tubing, a foreign body, or herniation of the cuff of the endotracheal tube over its distal tip.[101]

An increase in peak airway pressure accompanied by a proportional increase in plateau pressure indicates a decrease in thoracic



• **Fig. 13.7** Changes in lung volume measured by inductive plethysmography *(top tracing),* raw electromyographic signal of scalene muscle activity *(EMG) (middle tracing),* and moving time average *(bottom, integrated signal)* during three consecutive cycles of Cheyne-Stokes breathing in a representative patient. Note the repeated increases in end-expiratory lung volume with each hyperpnea. (From Brack T, Jubran A, Laghi F, et al. Fluctuations in end-expiratory lung volume during Cheyne-Stokes respiration. *Am J Respir Crit Care Med.* 2005;17:1408–1413.)



• **Fig. 13.8** Flow (inspiration upward), airway pressure *(P_{aw})*, transpulmonary pressure *(P_L)*, and esophageal pressure (P_{es}) tracings in a representative patient during passive ventilation. An end-inspiratory occlusion produced a rapid decline in both P_{aw} and P_L from a peak value *(P_{peak})* to a lower initial pressure *(P_{init})*, followed by gradual decrease to a plateau pressure *(P_{plat})*. P_{plat} on the P_{aw}, P_L, and P_{es} tracings represents the static end-inspiratory recoil pressures of the total respiratory system, lung, and chest wall, respectively. Using this technique, total resistance can be partitioned into ohmic airway resistance and tissue resistance, which reflects the viscoelastic properties (stress relaxation) and time-constant inhomogeneities within the respiratory tissues. (Modified from Jubran A, Tobin MJ. Passive mechanics of lung and chest wall in patients who failed and succeeded in trials of weaning. *Am J Respir Crit Care Med.* 1997; 155:916–921.)

compliance. A decrease in lung compliance may arise from pulmonary edema, early stages of acute respiratory distress syndrome (ARDS), dynamic hyperinflation associated with intrinsic PEEP, atelectasis, collection of fluid (hemothorax, parapneumonic effusion, or transudative effusion), or a pneumothorax.

Elastance (Compliance)

The end-inspiratory airway occlusion method is used clinically to measure the static compliance, or its reciprocal, elastance, of the respiratory system ($E_{st,rs}$) according to the following equation[102]:

$$E_{st,rs} = P_{plat} - PEEP_{tot}/V_T,$$

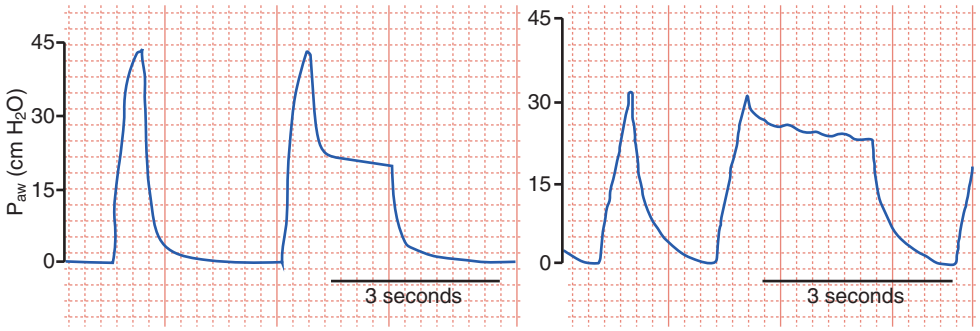
where P_{plat} is plateau pressure obtained after occlusion of the airway, $PEEP_{tot}$ is the sum of external and intrinsic positive end-expiratory pressures if present, and V_T is tidal volume (see Fig. 13.8).

Mechanical ventilation in itself can produce or aggravate lung injury in patients with ARDS.[103–105] Injury may be decreased by minimizing alveolar overdistention. Alveolar volume is reflected by peak alveolar pressure, which can be assessed indirectly by measuring the plateau pressure during an end-inspiratory hold maneuver. It has been recommended that plateau pressure not exceed 32 cm H_2O.[106,107]

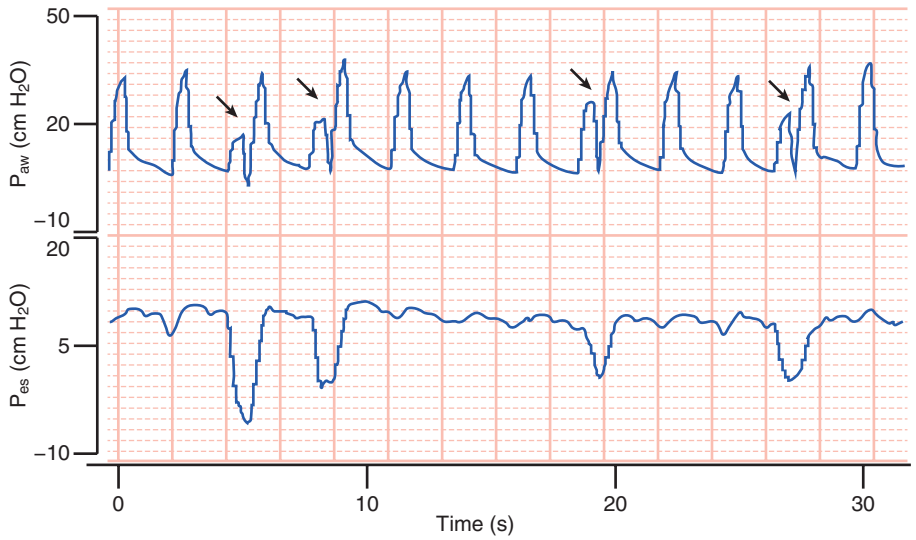
A new era of ventilatory management began in 1990, when a report demonstrated that lowering tidal volume caused a 60% decrease in the expected mortality rate among patients with ARDS.[108] Subsequently, randomized trials were undertaken[109–112] that revealed that use of a high tidal volume (12 mL/kg) is associated with an increased mortality in patients with ARDS.[106,113] To minimize alveolar distension (i.e., limit plateau pressure to 32 cm H_2O or lower), it has become standard practice to lower tidal volume.[106] A low tidal volume is typically accompanied by a short mechanical inspiratory time and thus these patients are especially susceptible to double triggering (Fig. 13.10).[101] Accordingly, conscious attempts to lower tidal volume can paradoxically result in greater alveolar distension than occurs with conventional tidal volume settings.[64,101]

Pressure-Volume Curves

A pressure-volume curve of the respiratory system in a paralyzed patient can be constructed by measuring the airway pressure as



• **Fig. 13.9** End-inspiratory occlusion maneuver during passive ventilation in two patients. In each patient, the second displayed breath was occluded for 2 seconds—a period that was not sufficient to achieve a complete plateau in either patient. *Left panel*: Airway pressure (P_{aw}) drops by 24 cm H_2O during the end-inspiratory occlusion maneuver, indicating the presence of increased airflow resistance. *Right panel*, P_{aw} drops by 5 cm H_2O during the end-inspiratory occlusion maneuver, indicating decreased respiratory compliance consequent to noncardiogenic pulmonary edema secondary to sepsis. (From Tobin MJ, Jubran A, Laghi F. Fighting the ventilator. In: Tobin MJ, ed. *Principles and Practice of Mechanical Ventilation.* 3rd ed. New York: McGraw-Hill; 2012:1237–1258.)



• **Fig. 13.10** Four incidents of double triggering, each indicated by an arrowhead symbol (↑). Airway pressure *(P_{aw})* and esophageal pressure *(P_{es})* during assist-control ventilation at the following settings: tidal volume 600 mL, inspiratory flow 60 L/min, trigger sensitivity −2 cm H_2O, and positive end-expiratory pressure 5 cm H_2O. The duration of neural inhalation of the double-triggered breaths, roughly equivalent to the width of the associated swings in P_{es}, was substantially longer than the neural inhalation of the normally triggered breaths. (From Tobin MJ, Jubran A, Laghi F. Fighting the ventilator. In: Tobin MJ, ed. *Principles and Practice of Mechanical Ventilation*. 3rd ed. New York: McGraw-Hill; 2012:1237–1258.)

the lungs are progressively inflated with a 1.5- to 2-L syringe. A lower inflection point and an upper inflection point may be seen on the pressure-volume curve.[114] The lower inflection point is thought to reflect the point at which small airways or alveoli reopen, corresponding to closing volume. In patients with acute lung injury, investigators have recommended that PEEP be set at a pressure slightly above the lower inflection point.[115]

When an "open-lung approach," consisting of use of a lower tidal volume (<6 mL/kg) with PEEP individually titrated to be consistently above the inflection point on the pressure-volume curve, was compared with a conventional approach, consisting of use of tidal volume of 12 mL/kg and a low PEEP level, the mortality rate was significantly reduced in the group managed with the new approach.[109,116]

A National Institutes of Health–sponsored trial of high versus low PEEP failed to demonstrate a significant survival advantage for patients randomly assigned to the high PEEP group.[117] Methodologic considerations cast doubt on the conclusions of the investigators.[118] First, PEEP-induced recruitment was estimated by improvement in oxygenation. It is well known that changes in oxygenation depend not only on recruitment but also on cardiac output.[119] Thus oxygenation may have improved without any lung recruitment. Second, recruitment potential was not stratified, so that patients who were not likely to benefit were assigned to both groups.[120]

The importance of individualizing PEEP in ventilator management in patients with ARDS was confirmed in a Spanish trial.[121] One patient group was randomly assigned to a treatment group in which PEEP was titrated to 2 cm H_2O above the lower inflection point. The mortality rate was lower in these patients than in control group patients who did not receive customized titration of PEEP.[121]

Two subsequent randomized trials were performed in which PEEP was titrated to oxygenation or plateau pressure, failed to show improved survival with higher PEEP[122,123]; high PEEP, however, decreased the number of patients with severe hypoxemia and was associated with greater ventilator-free days and organ failure–free days.[119]

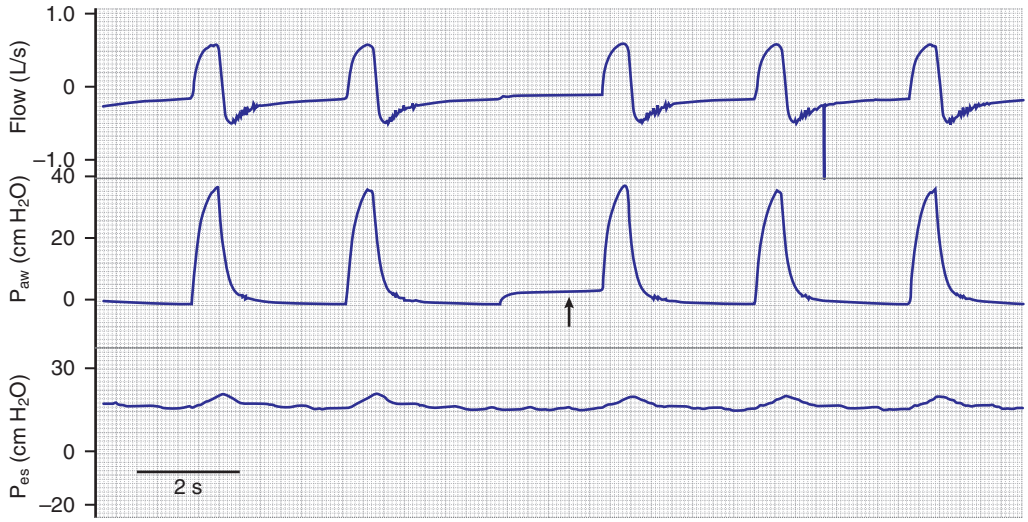
Resistance

Airway resistance can be measured in ventilator-dependent patients using the technique of rapid airway occlusion during constant-flow inflation (see Fig. 13.8).[98,99,102,124] Measurements of airway resistance are helpful in assessing the response of patients to bronchodilator therapy. In a study in ventilator-dependent patients with chronic obstructive pulmonary disease, a significant decrease in airway resistance occurred after giving 4 puffs, with no additional effect after the addition of 8 and 16 puffs (cumulative doses of 12 and 28 puffs).[125,126]

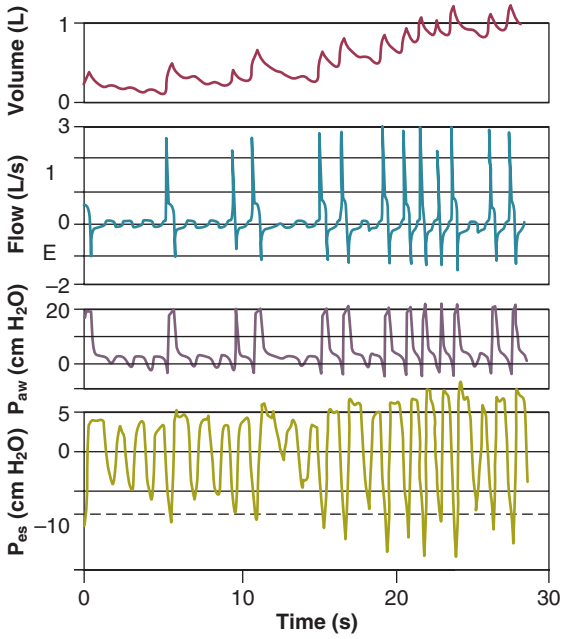
Intrinsic Positive End-Expiratory Pressure

The static recoil pressure of the respiratory system at end-expiration may be elevated in patients receiving mechanical ventilation.[102] This positive recoil pressure, or intrinsic PEEP (static $PEEP_i$), can be quantified in relaxed patients using an end-expiratory hold maneuver on a mechanical ventilator immediately before the onset of the next breath (Fig. 13.11).[47,127]

$PEEP_i$ poses a significant inspiratory threshold load that must be fully counterbalanced by increasing inspiratory muscle effort to generate a negative pressure in the central airway and trigger the ventilator. Thus $PEEP_i$ adds to the triggering pressure such that the total inspiratory effort needed to trigger the ventilator is the set trigger sensitivity plus the level of $PEEP_i$. This is one of the factors that may account for the not infrequent observation of a patient who is unable to trigger a ventilator despite obvious respiratory effort (Fig. 13.12).[128–133]



• **Fig. 13.11** Recordings of flow, airway pressure *(P_{aw}),* and esophageal pressure *(P_{es})* in a patient receiving controlled mechanical ventilation. After the third breath, the airway was occluded at end-expiration using the end-expiratory hold function on the ventilator. During the period of zero flow, pressure in the alveoli and in the ventilator circuit equilibrates, and the plateau pressure reflects auto–positive end-expiratory pressure (PEEP or intrinsic PEEP, indicated by the *arrow*).



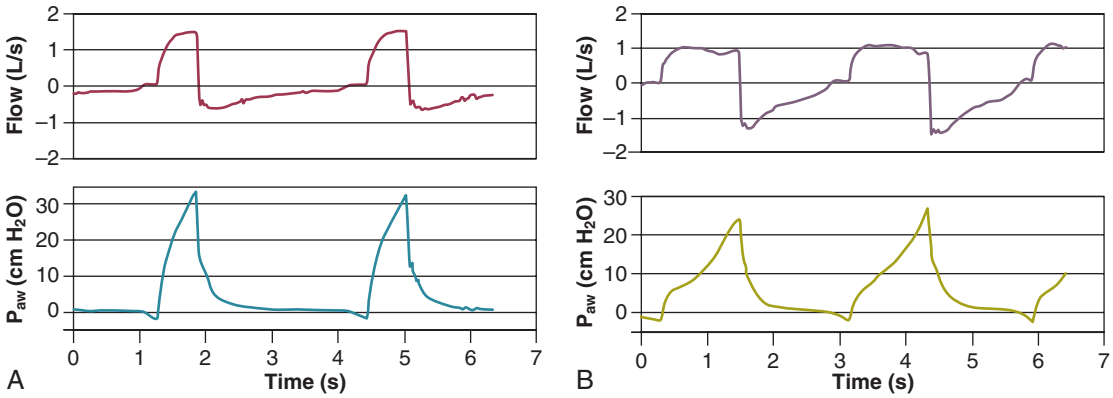
• **Fig. 13.12** Recordings of tidal volume, flow, airway pressure *(P_{aw}),* and esophageal pressure *(P_{es})* in a patient with chronic obstructive pulmonary disease receiving pressure-support ventilation. Approximately half of the patient's inspiratory efforts do not succeed in triggering the ventilator. Triggering occurred only when the patient generated a P_{es} less than 8 cm H_2O (indicated by the *dashed line*), which was equal in magnitude to the opposing elastic recoil pressure. (From Tobin MJ, Jubran A. Pathophysiology of failure to wean from mechanical ventilation. *Schweiz Med Wochenschr.* 1994;124:2139–2145.)

In a study of ventilator-dependent patients, Leung and colleagues[130] reported that ineffective triggering occurred with all assisted modes of mechanical ventilation. The ineffective or wasted efforts were significantly related to resistance ($r = 0.85$), elastance ($r = -0.61$), and static $PEEP_i$ ($r = 0.77$). A decrease in the magnitude of inspiratory effort at a given level of assistance was not the cause—indeed, effort was 38% higher during nontriggering attempts than during the triggering phase of attempts that successfully opened the inspiratory valve. Significant differences, however, were observed in the breaths before the triggering and nontriggering attempts. Breaths before nontriggering attempts were associated with shorter respiratory cycle time and expiratory time and higher static $PEEP_i$ compared with the breaths before triggered attempts. These findings suggest that ineffective triggering resulted not from a decrease in the magnitude of effort but rather from inspiratory efforts that were premature and insufficient to overcome the elevated elastic recoil pressure associated with dynamic hyperinflation.

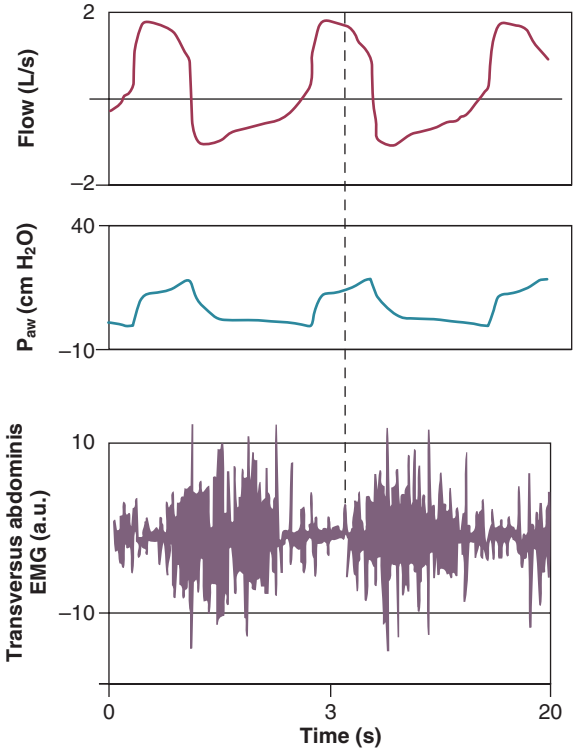
Airway Pressure Profile

A continuous recording of airway pressure provides helpful information about the amount of respiratory work being performed by a patient receiving ventilator assistance. Ideally the waveform should show a smooth rise with a convex appearance during inspiration.[47,134] By contrast, a prolonged negative phase with excessive scalloping of the tracing reflects increased inspiratory effort; this pattern indicates unsatisfactory sensitivity and inappropriate flow settings (Fig. 13.13).[47] A "bump" on the airway pressure tracing observed while the ventilator is still pumping gas in the patient may reflect recruitment of expiratory muscles (Fig. 13.14).[131]

Use of a flow setting that does not meet a patient's ventilatory demands will cause inspiratory effort to increase. Sometimes the flow is increased to shorten the inspiratory time and increase the expiratory time. An increase in flow, however, can cause immediate and persistent tachypnea; if this happens, the resulting decrease in expiratory time may lead to $PEEP_i$.[135,136] In general, however,



• **Fig. 13.13** Flow and airway pressure *(P_{aw})* during assist-control ventilation at different flow rates: 60 L/min (A) and 30 L/min (B). In A, the small negative phase, coupled with the smooth rise and convex appearance of the P_{aw} waveform, indicates that the patient is making a slight inspiratory effort to breathe. In B, the more pronounced negative phase, together with excessive scalloping of the P_{aw} waveform, indicates that the patient is making a strenuous effort to breathe as a result of the inadequate flow setting. (From Jubran A, Tobin MJ. Monitoring during mechanical ventilation. In: Tobin MJ, ed. *Principles and Practice of Mechanical Ventilation.* New York: McGraw-Hill; 2006:1051.)

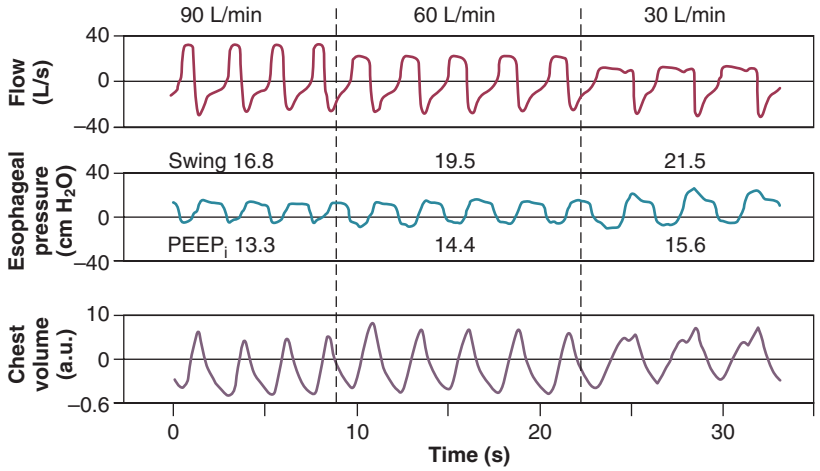


• **Fig. 13.14** Recordings of flow *(top)* and airway pressure *(P_{aw}; middle)* and transversus abdominis electromyogram (*EMG*; *bottom*) in a critically ill patient with chronic obstructive pulmonary disease receiving pressure support of 20 cm H_2O. The onset of expiratory muscle activity *(vertical dashed line)* occurred when mechanical inflation was only partly completed. (From Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. *Am J Respir Crit Care Med.* 1998;58:1471–1478.)

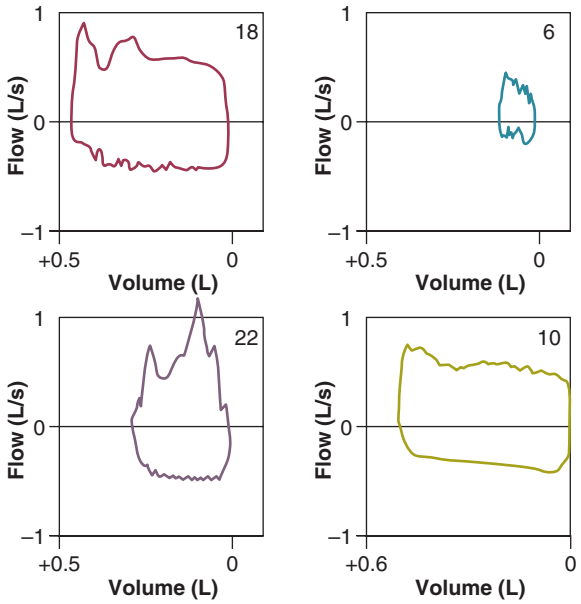
an increase in inspiratory flow does not lead to an increase in $PEEP_i$ (Fig. 13.15).[136]

Flow-Volume Curves

Flow-volume curves may be helpful in indicating a need for endotracheal suctioning. In 50 intubated patients, Jubran and Tobin[137] found that the presence of a sawtooth pattern strongly suggested the presence of secretions (positive predictive value, 94%), and the absence of this pattern suggested that secretions are unlikely to be present (negative predictive value, 77%) (Fig. 13.16). Clinical examination had much higher false-positive and false-negative rates (42% and 43%, respectively) than the flow-volume curves (12% and 14%, respectively). The usefulness of a sawtooth pattern for detecting secretions was confirmed in a study of 62 patients who were receiving pressure-support or assist-control ventilation.[138]



• **Fig. 13.15** Continuous recordings of flow, esophageal pressure (P_{es}), and the sum of rib cage and abdominal motion in a patient with chronic obstructive pulmonary disease receiving assist-control ventilation at a constant tidal volume. As flow increased from 30 L/min to 60 and 90 L/min (from *right* to *left*), frequency increased (from 18 breaths/min to 23 and 26 breaths/min, respectively); intrinsic positive end-expiratory pressure *(PEEP$_i$)* decreased (from 15.6 cm H_2O to 14.4 and 13.3 cm H_2O, respectively); and end-expiratory lung volume also fell. Increases in flow from 30 L/min to 60 and 90 L/min also led to decreases in the swings in P_{es} from 21.5 cm H_2O to 19.5 and 16.8 cm H_2O, respectively. *a.u.,* Arbitrary units. (From Laghi F, Segal J, Choe WK, et al. Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163:1365–1370.)



• **Fig. 13.16** Flow-volume curves obtained in four patients with secretions. Note the presence of a sawtooth pattern on both the inspiratory and expiratory flow-volume curves. (The numbers to the *upper right* in each grid are the original patient numbers.) (From Jubran A, Tobin MJ. Use of flow-volume curves in detecting secretions in ventilator-dependent patients. *Am J Respir Crit Care Med.* 1994;150:766–769.)

Key Points

- Pulse oximetry can accurately measure oxygen saturation at levels of 90% or above; its accuracy deteriorates when the saturation falls to 80% or less.
- Inaccurate readings from pulse oximetry can occur as a result of interference from substances or from problems in signal processing.
- Hypoxemia is detected more frequently in patients monitored with pulse oximetry than in patients in whom this modality is not used.
- Transcutaneous monitoring of P_{CO_2} may be reliable in monitoring changes in arterial P_{CO_2} in the absence of major vasoconstriction.
- Capnometry is reliable in verifying tracheal tube placement after intubation.
- Measuring airway pressure at 0.1 second after initiating an inspiratory effort against an occluded airway is closely associated with increased work of breathing during mechanical ventilation.
- One-time measurements of breathing pattern (frequency and tidal volume) are helpful in predicting weaning outcome; continuous measurements of breathing pattern can provide information about the function of the respiratory controller.
- Measurements of respiratory mechanics in a ventilator-dependent patient can be easily performed at the bedside using the rapid airway occlusion technique.
- Continuous recordings of airway pressure can provide useful information about the respiratory work performed by a patient receiving mechanical ventilation.
- Flow-volume curves may be helpful in indicating a need for endotracheal suctioning.

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Review Questions

1. A 56 year-old man with a history of drug abuse is being managed in the intensive care unit for respiratory failure and bacteremia. The patient continues to be febrile despite broad-spectrum antibiotics. On the fifth day, transesophageal echocardiography was done to rule out vegetation on the valves. The patient received midazalom, fentanyl, and benzocaine spray for the procedure. An hour later, you are called to his bedside because the pulse oximeter is reading a saturation of 86% with a good pulse waveform. On examination, the patient is breathing comfortably at a rate of 18 breaths/min on the following ventilator settings: assist-control mode, tidal volume 500 mL, backup rate 12 breaths/min, and positive end-expiratory pressure 5 cm H_2O. Vital signs are stable. Bilateral breath sounds are present. Arterial blood gas values show a pH 7.34, partial pressure of carbon dioxide 46 mm Hg, partial pressure of oxygen 72 mm Hg, and oxygen saturation is 94%. What should you do next?

a. Increase the backup rate on the ventilator to 16 breaths/min.
b. Measure oxygen saturation with a multiple-wavelength co-oximetry.
c. Increase the fraction of inspired oxygen to 100%. Obtain arterial blood gas samples 1 hour later.
d. Perform a computed tomography pulmonary angiogram.
e. Administer naloxone.

Answer: b. Methemoglobinemia should be suspected when the pulse oximeter estimate of arterial saturation is significantly less than the calculated arterial oxygen saturation as seen in this patient. The patient had a transesophageal echocardiogram in which benzocaine, a common cause of methemoglobinemia, was used. Multiwavelength oximetry will confirm methemoglobinemia as the cause of erroneous pulse oximetry readings.

2. When using capnometry to confirm the position of an endotracheal tube, a flat waveform on capnometry in an intubated patient indicates all of the following *except:*

a. Prolonged cardiac arrest
b. Foreign body obstruction
c. Bronchospasm
d. Esophageal intubation

Answer: c. A flat-line waveform on capnometry indicates that the endotracheal tube is in the esophagus. Other situations that produce flat-line waveforms include obstruction within or distal to an endotracheal tube, prolonged cardiac arrest, or technical malfunction of the monitoring device. Bronchospasm will produce detectable levels of end-tidal carbon dioxide.

3. A 76-year-old man has been improving on assist-control ventilation for adult respiratory distress syndrome associated with sepsis. Ventilator settings are fraction of inspired oxygen of 0.40, tidal volume of 0.6 L, inspiratory flow rate 60 L/min, respiratory rate 20 beats/min, and positive end-expiratory pressure of 8 cm H_2O. Arterial blood gas measurements are pH 7.42, arterial partial pressure of carbon dioxide 37 mm Hg, and arterial partial pressure of oxygen 70 mm Hg. Peak pressure is 35 cm H_2O and plateau pressure is 32 cm H_2O. Suddenly, the ventilator alarm goes off, indicating high peak airway pressures. Peak pressure is now 65 cm H_2O and plateau pressure is 34 cm H_2O. Breath sounds are decreased slightly on the right. The patient remains hemodynamically stable. An immediate chest x-ray is obtained. What is the most likely cause of patient distress?

a. Kinking of the endotracheal tube
b. Right mainstem intubation
c. Pneumothorax
d. Auto–positive end-expiratory pressure as a result of dynamic hyperinflation

Answer: a. This patient developed an increase in peak airway pressure without a proportional increase in plateau pressure, indicating narrowing of the airway. The narrowing of the airway occurred because of kinking of the endotracheal tube. The other options listed will occur because of a decrease in thoracic compliance; accordingly, the increase in peak airway pressure should be accompanied by a proportional increase in plateau pressure.

14

Bedside Tracheostomy in the Intensive Care Unit

WISSAM ABOUZGHEIB AND STEVEN E. ROSS

CHAPTER OUTLINE

Definition

History

Epidemiology

Indications

Contraindications
- Tracheal Anatomy
- Timing
- Organization of Care and Safety During Bedside Tracheostomy

Techniques
- Percutaneous
- Surgical
- Posttracheostomy Care

Summary

Definition

Tracheostomy is the creation of an opening in the anterior neck into the trachea with insertion of an indwelling tube to facilitate airflow or evacuation of secretions. The procedure is most often an elective measure, rarely an emergency, and should be well planned. Although rare, serious complications can result in severe consequences. Tracheostomy placement in critically ill patients is best performed at the bedside to avoid the logistical challenges and added costs associated with using the operating room. Two major techniques, percutaneous and surgical, have been widely used at bedside and are discussed in detail in this chapter.

History

The first description of tracheostomy goes back nearly 6000 years. The word "trachea" is derived from the Greek term *trakheia arteria* (rough artery), or "windpipe," as the ancient Greeks thought the arteries were filled with air.[1,2] Tracheostomy refers to a permanent opening, whereas tracheotomy refers specifically to an incision in the trachea. These terms are often used interchangeably in reference to the procedure of tracheostomy, but tracheostomy is the correct term for an artificial airway established in this manner and is in more common use. Two Egyptian tablets from Abydos and Saqqara dating to about 3600 BCE have been interpreted as depicting tracheostomy.[3] Alexander the Great used the point of his sword to open the trachea of one of his soldiers who was choking, according to a description by Homerus of Byzantium.[4] Tracheostomy was successfully performed to relieve airway obstruction in the second century but remained controversial. Paul of Aegina described the technique of tracheostomy in the seventh century and recommended its use for airway obstruction.[5] The technique was also described in the Arabic surgical literature of the period. During the Dark Ages in Europe, the technique of tracheostomy was abandoned.[6,7] During the Renaissance, European surgeons applied tracheostomy in cases of injury or obstruction caused by a foreign body, drowning, or Ludwig angina.

The clinical importance of tracheostomy became evident during sporadic diphtheria epidemics.[7] Fear of tracheostomy was quite prevalent in America, as evidenced in the death of George Washington in 1799, when bloodletting won over tracheostomy to relieve an epiglottitis-related upper airway obstruction.[6,8]

The development of the modern intensive care unit (ICU) and the frequent need for prolonged mechanical ventilation have resulted in the acceptance of tracheostomy as a standard procedure in the ICU. Tracheostomy has become one of the most frequently performed procedures in critically ill patients. The need to perform this procedure at the bedside in the ICU has led to the development of new methods of percutaneous dilational tracheostomy (PDT) using the Seldinger technique, most notably by Ciaglia and colleagues in 1985.[9] Several modifications of those techniques have improved the efficiency and safety over the past 30 years. Bedside tracheostomy by surgeons and intensivists has become the norm for ICU care, rather than the exception.

Epidemiology

Tracheostomy is a common procedure in the ICU. About 800,000 patients require mechanical ventilation for acute respiratory failure in the United States annually.[10] More than 100,000 tracheostomies are performed in the United States every year,[11] and it is estimated that 10% of patients receiving mechanical ventilation for at least 3 days eventually need tracheostomy.[12]

• BOX 14.1 Indications for Tracheostomy

1. Prolonged mechanical ventilation
2. Failure of extubation
3. Inability to clear secretions/pulmonary toiletry
4. Severe traumatic brain or cervical spine injury
5. Upper airway obstruction

• BOX 14.2 Contraindications for Tracheostomy

Absolute

1. Inexperienced operator
2. Infected insertion site
3. Uncorrected coagulopathy
4. No informed consent

Relative Contraindications (Favoring Surgical Tracheostomy)

5. Difficult anatomy
6. Unstable cervical spine
7. Presence of pulsatile vessels at the insertion site
8. High PEEP or F_{IO_2} requirements
9. Enlarged thyroid gland

F_{IO_2}, Fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure.

Indications

With advances in critical care, more patients are supported by mechanical ventilation for a longer duration. Most of these patients require prolonged intubation and will eventually be considered for tracheostomy.[13] Although the decision for, and the timing of, tracheostomy must be adapted to each patient, the general indications are listed in Box 14.1. The primary indication remains prolonged mechanical ventilation and failure of extubation, followed by traumatic brain injury and inability to clear airway secretions. Upper airway obstruction is not a common indication in the ICU setting. Many factors are involved in the decision-making process: balanced consideration of the projected recovery course, risks and contraindications, and the patient's and family wishes relative to overall outcomes.

Over the years the guideline recommendations have progressively changed. In 1989 the American College of Chest Physicians indicated that tracheostomy is preferred over endotracheal tube (ETT) placement if the need for an artificial airway is expected to be longer than 21 days.[14] The European consensus in 1998 recommended that when intubation is anticipated to last between 10 and 21 days, daily assessment should occur regarding the need for continued intubation.[15] More recent guidelines from the American College of Chest Physicians suggest that tracheostomy should be considered within 3 to 7 days when it becomes apparent that prolonged mechanical ventilation is likely.[16]

Contraindications (Box 14.2)

Bedside percutaneous or surgical tracheostomies are elective procedures involving a vital organ system where errors can be deadly. The most important contraindications in this setting are operator inexperience, followed by difficult anatomy, active site infection, and uncorrected coagulopathy. When planning the procedure, appropriate history, including a history of previous tracheostomy, coagulation factors review, and physical examination—particularly of the neck anatomy—are crucial. More importantly, discussion with the patient or family members and answering their questions regarding risks and benefits need to occur before obtaining an informed consent. If the patient is unable to consent and has an advance directive or physician order for life-sustaining treatment, this should also be reviewed to ensure that the patient's wishes are known.

Neck anatomy should be carefully examined when deciding on technique—percutaneous versus surgical. Patients with cervical spine injury require extra attention to spine immobilization during the procedure. In the past this was considered a relative contraindication for percutaneous tracheostomy,[17] although one recent study demonstrated feasibility and safety. The examination needs to include identification of midline neck masses, such as goiter and crossing vessels around the surgical site. If needed, preoperative ultrasound examination may lead to fewer complications by delineating vascular anatomy.[18]

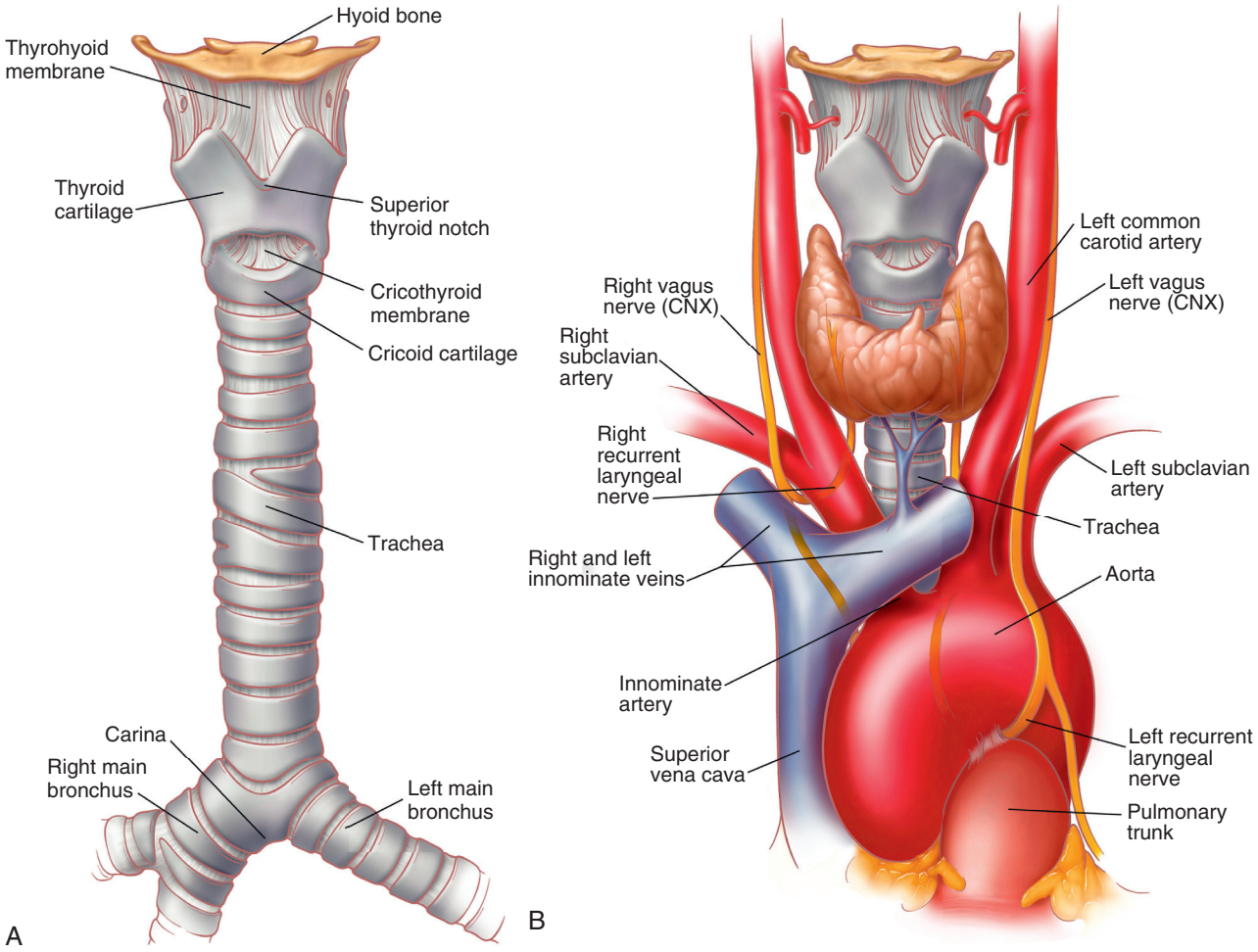
Common concerns in ICUs that affect the timing of tracheostomy are oxygen requirements and high levels of positive end-expiratory pressure (PEEP) during mechanical ventilation. Breaking the circuit and pulling the ETT to the subglottic area during the procedure may lead to worsening oxygen saturation levels. One must exercise caution in approaching tracheostomy in patients requiring a high fraction of inspired oxygen (F_{IO_2}) or advanced ventilator modes such as airway pressure release ventilation. One study documented the safety of performing bronchoscopy-guided percutaneous tracheostomy in patients with high PEEP (average of 16 cm H_2O) with no significant change in oxygenation at 1 hour and 24 hours after the procedure; however, most apply lower thresholds in practice.[19]

Tracheal Anatomy

Knowledge of the patient's anatomy is crucial before any surgical procedure. In the case of tracheotomy, there are two main factors to consider: (1) the site of the procedure, which is surrounded by major vessels and vital organs, and (2) the critical role of the trachea itself.[20] The trachea begins at the lower edge of the cricoid cartilage and extends to the level of the carina. It consists of 18 to 22 anterior C-shaped tracheal rings lined by a posterior membranous wall. It starts anterior and midline in the neck below the cricoid cartilage and then it dives posterior in the mediastinum. The esophagus starts at the same level and lies at the left posterior border of the trachea. The thyroid gland is found anterior and lateral to the proximal trachea with the isthmus projecting apically at the level of the second or third tracheal ring. The structure associated with this procedure's deadliest complications is the innominate artery. It crosses the anterior aspect of the trachea in an oblique fashion inferior to the third or fourth tracheal ring[20] (Fig. 14.1).

Timing

The advantages of tracheostomy in the setting of prolonged mechanical ventilation are well established. However, the timing of replacing a temporary artificial airway (ETT) with a tracheostomy has been controversial[14] because of two main challenges. One is the inability of clinicians to predict the need for prolonged mechanical ventilation accurately within several days of initiation. There is also ongoing debate regarding early versus late tracheostomy. Early timing has been generally defined as within 3 to 10 days,



• **Fig. 14.1** A, Principal features of the larynx and trachea. Anterior view. Tracheobronchial angles vary widely. (B) Relationships of trachea to surrounding structures. Anterior view. *CNX,* Cranial nerve X. (From Minnich DJ, Mathisen DJ. Anatomy of the trachea, carina, and bronchi. *Thorac Surg Clin.* 200717:571–578.)

whereas late is beyond that period. Although numerous studies have evaluated this subject, the majority were observational or retrospective, and only a few recent ones were well-designed prospective randomized trials. The most positive study on early tracheostomy was a prospective randomized trial involving several centers by Rumbak et al.[21] In this study, early tracheostomy was associated with significantly lower mortality, nosocomial pneumonia rate, and shorter duration of ICU stay and mechanical ventilation. Several other studies have demonstrated no difference in mortality but decreased duration of mechanical ventilation.[22,23] Systematic reviews and meta-analysis of randomized trials have also shown no difference in rates of mortality[24,25] but were variable relative to mechanical ventilation duration and ICU length of stay. More recently, a large prospective randomized trial (TracMan trial) compared early tracheostomy (within 4 days of intubation) to late tracheostomy (after 10 days if still indicated).[26] This trial was one of the largest to date exploring the timing of tracheostomy and found no advantage to early tracheostomy with regard to 30-day mortality or other secondary outcomes such as duration of mechanical ventilation, ICU length of stay, or hospital length of stay. Furthermore, this study showed that more than half of patients in the late group did not require tracheostomy by day 10.

Patients with severe head trauma often require tracheostomy for airway protection because of poor cough and clearance of secretions, rather than the need for mechanical ventilation. This group has been the subject of studies of the timing of tracheostomy.[23] One well-designed, prospective randomized trial comparing early tracheostomy to prolonged intubation found no difference in frequency of pneumonia or mortality between the two groups. However, early tracheostomy decreased total days of mechanical ventilation and specifically the duration of mechanical ventilation after development of nosocomial pneumonia in this group of patients.

The biggest challenge in designing trials regarding the timing of tracheostomy is the ability of treating physicians to predict duration of mechanical ventilation. In several randomized trials comparing early versus late tracheostomy, about 20% of patients randomly assigned to the late group did not ultimately require tracheostomy in the late group; this reflects the difficulty in predicting need for prolonged mechanical ventilation.

Organization of Care and Safety During Bedside Tracheostomy

Tracheostomy is one of the most hazardous procedures performed in the ICU. Although intraprocedural complications are rare, vascular injury resulting in hemorrhage, loss of airway control, or airway injury is catastrophic and may rapidly result in death, with

rates as high as 75%[27,28] for loss of airway control. It is prudent to take appropriate precautions to avoid these problems or manage them when they arise. A number of measures have been demonstrated to reduce complication rates, and some commonsense steps that can prepare the team for safer practice and handling of emergencies.[29]

The first step is appropriate patient selection. There are few absolute contraindications and a small number of relative contraindications (described elsewhere in this chapter).[30] The practitioner evaluating the patient for possible bedside tracheostomy must exercise judgment regarding the risks of location and technique to eliminate preventable complications.

The development of a team approach and a safety checklist for bedside tracheostomy has been demonstrated to decrease complications.[31] This should include a well-trained lead physician and assistant; an airway management practitioner who is capable of reintubation if necessary and will manage the ventilator; a nurse or other provider to administer sedation and pain medication and monitor the patient's clinical status; and a circulator who can run for supplies. If bronchoscopic support is planned, a skilled bronchoscopist should be included. Some practitioners consider that such bronchoscopic assistance is required for PDT, but the literature does not support improved complication rates.[32] The bronchoscope should be available immediately for emergencies, even if not used routinely. Ultrasound has also been used as an adjunct to avoid vascular injury but it has not yet been demonstrated to be of benefit in this setting.[33] If the primary proceduralist is not a surgeon, it is appropriate to have surgical "backup" in the hospital. It is therefore wise to plan elective bedside tracheostomy during daytime hours to ensure the availability of maximum personnel support in an emergency.

The equipment for the procedure should be in the room before starting, as well as any equipment that may be needed to deal with unplanned events. An assortment of tracheostomy tube sizes should be available as well as endotracheal tubes and laryngoscopes for reintubation. Electrocautery may be necessary and should be in the ICU, at least with grounding pads applied to the patient before the procedure. If PDT is planned, a surgical tracheostomy tray should be in the unit, as well as equipment for cricothyrotomy should the need arise. Good lighting is essential and headlamps may be of benefit.

The team should prepare for bedside percutaneous or surgical tracheostomy as they would for any operation. This includes discussion of the plan for sedation, the procedure itself, the roles of the team members, and any particular concerns regarding the individual patient. Structuring this practice with the use of a World Health Organization style checklist has been demonstrated to reduce complication rates significantly for bedside tracheostomy.[34]

Techniques

Percutaneous (Box 14.3)

PDT, also known bedside tracheostomy, is the placement of a tracheostomy tube. This technique uses a small skin incision and dilation of the subcutaneous tissue into the tracheal lumen without direct surgical visualization of the trachea. It is considered minimally invasive and is often done at the bedside in the ICU, avoiding the risks of transporting a critically ill patient and the costs of the operating room. PDT is done with continuous monitoring of the patient's vital signs and often is performed under direct bronchoscopic visualization.

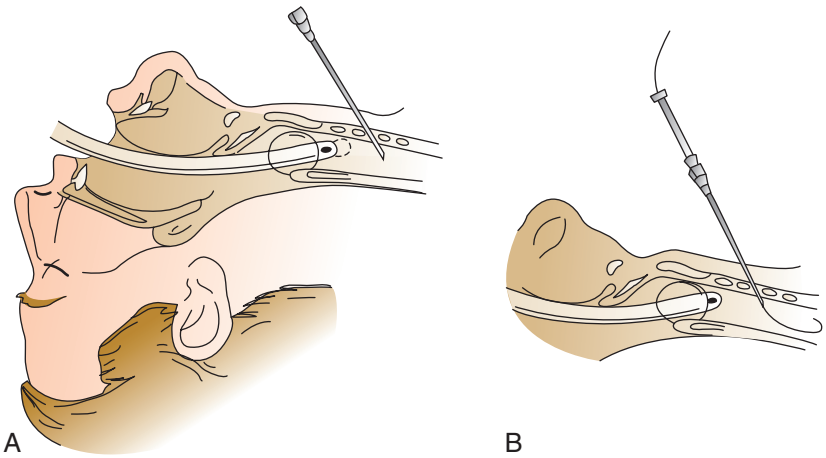
• BOX 14.3 Steps for Percutaneous Dilatational Tracheostomy

1. Hold tube feeding at least 4–6 hours prior to procedure
2. Hold anticoagulation appropriately to agent used
3. Keep patient on 100% FiO_2
4. Properly position the patient with maximum neck extension
5. Ensure adequate sedation and paralysis of the patient
6. Place bite block to avoid injury to teeth or bronchoscope
7. Deflate the ET cuff and withdraw ET under laryngoscopic vision until cuff is visualized just below cords, then reinflate the cuff
8. Clean, drape the patient as per protocol
9. Identify the site of insertion
10. Infiltrate the skin with local anesthetic containing a vasoconstrictor
11. Make a 2–2.5 cm transverse incision at the proposed insertion site
12. Advance a sheathed introducer needle into trachea stabilizing the trachea during the process
13. Tracheal placement of needle is confirmed by aspirating air bubbles into the saline solution–filled syringe attached to the needle, and by direct visualization through the bronchoscope
14. Withdraw the needle and insert Seldinger guidewire through the plastic sheath which is withdrawn out
15. Dilate the insertion site with the help of a small tracheal dilator
16. Single graduated dilator is moisturized with saline and then loaded over the guiding catheter
17. The whole assembly is then loaded over the guidewire and advanced as a unit into trachea in a sweeping action
18. After adequate dilatation, dilator is removed and tracheostomy tube with appropriate adapter is inserted into trachea over the guiding catheter
19. Placement of tracheostomy tube is confirmed by direct visualization of carina through the bronchoscope or by $EtCO_2$ graph
20. Connect tracheostomy tube to ventilator and ensure volume return
21. Suture tracheostomy to the skin and secure using a trach tie

ET, Endotracheal tube; $ETCO_2$, end-tidal carbon dioxide; FiO_2, fraction of inspired oxygen.

Classically the ability to hyperextend the neck is important in preoperative planning, but recent literature suggests that PDT is applicable in patients with spine injury whose necks cannot be hyperextended. There must be sufficient space between the cricoid cartilage and the suprasternal notch to allow tracheostomy tube placement.

Several different systems and approaches for PDT are available. The most common technique used is the Ciaglia technique (Video 14-1). With this technique, there is no sharp dissection involved beyond the skin incision. The patient is positioned and prepared in the same way as for the standard operative tracheostomy. Deep sedation is administered and all steps are done under bronchoscopic vision. The endotracheal tube is withdrawn under bronchoscopic guidance about 1 to 2 cm below the vocal cords to expose the space below the first tracheal ring by using digital pressure at 2 cm above the sternal notch while looking at the bronchoscopic view. The incision site is selected to correspond to the space between the second and third tracheal rings. Lidocaine 2% with epinephrine is used for local anesthesia and then a 2-cm incision is made. The pretracheal tissue is then cleared with blunt dissection. The operator enters the tracheal lumen below the second tracheal ring with an introducer needle through the incision (Fig. 14.2). The tract between the skin and the tracheal lumen is then serially dilated over a guidewire and stylet. A tracheostomy tube is placed under direct bronchoscopic vision over a dilator. Placement of the tube is also confirmed by visualizing the tracheobronchial tree through the



• **Fig. 14.2** A, Insertion of a 15-gauge needle into the trachea. B, The guidewire is inserted through the needle into the trachea. (From Friedman Y, Franklin C. The technique of percutaneous tracheostomy. Using serial dilation to secure an airway with minimal risk. *J Crit Illn.* 1993;8:289–297. Copyright Margulies Medical Art, Miami, FL.)

tracheostomy. The tracheostomy tube is then secured to the skin with sutures and a tie or device encircling the neck.

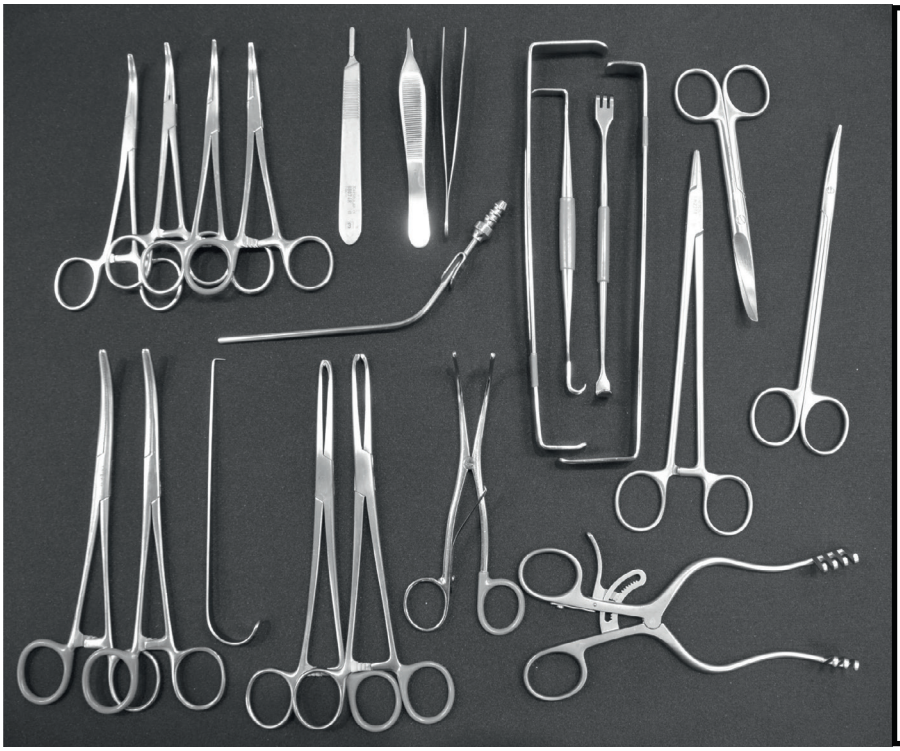
Although there is a learning curve to the technique, there are several advantages of PDT. The time required for bedside PDT is considerably shorter than that for an open tracheostomy. The elimination of operating room scheduling issues and costs, as well as the risks of transport, provide benefit to the patient and critical care team. In fact, the cost of performing PDT at the bedside is roughly half that of performing open surgical tracheostomy in the operating room.[35]

Surgical

Elective open surgical tracheostomy has been performed at the bedside in ICUs since the 1960s.[36] The performance of these procedures at the bedside remained controversial,[37] but as intensive care improved and more and sicker patients required tracheostomy for ongoing mechanical ventilation, the practice became more common. Concern for transport of critically ill patients from the ICU to the operating room,[38] as well as logistic concerns, prompted evaluation of this practice. Reported technical and long-term complications were not found to be different than those performed in the operating room.[39,40] Although early studies since the acceptance of percutaneous tracheostomy suggested that the surgical technique offered safety and cost advantages,[41] meta-analysis has suggested that they are equivalent from the standpoint of mortality and operative complications.[42] Open tracheostomy at bedside may be an alternative to open tracheostomy in the operating room for patients with normal neck anatomy; however, potential difficulty in reintubation via the oral route—such in those with oral pathology or with cervical spine fractures—could be the deciding factor to move the patient to the operating room. The ability to directly visualize the withdrawal of the endotracheal tube via the tracheotomy site itself reduces (but does not eliminate) the risk of accidental extubation during the procedure. The surgeon must be experienced and comfortable with the procedure at the bedside; otherwise, the procedure should be performed in the operating suite. Patients with neck pathology—such as those with head and neck masses or goiter or those in halo devices—should not be considered candidates for bedside tracheostomy.

The technique of open tracheostomy is generally the same as in the operating room. The general requirements for patient management during the procedure do not differ from those of the percutaneous method. The patient should be supported by a controlled method of ventilation and receiving 100% oxygen concentration while receiving monitored sedation with appropriate analgesia. A nurse should be available at bedside at all times for ongoing monitoring and sedation management. Continuous pulse oximetry and end-tidal carbon dioxide monitoring should be in place. The decision for paralysis during the procedure is the proceduralist's choice. Some practitioners recommend nonparalysis as a safety measure to maintain spontaneous ventilator effort if there is difficulty with the procedure, but many use paralytic agents. Local anesthetic should be used liberally for the area of incision and dissection, even with sedation and paralysis. Good lighting is critical, and the use of headlamps is advisable. Electrocautery should be available, but caution should be exercised to not use it to open the trachea or while the tracheotomy is open. Use of electrocautery in the presence of 100% oxygen is a fire risk.

It is best to perform the procedure with a surgeon and assistant, as well as an experienced airway management practitioner (respiratory therapist or a member of the anesthesia team). The minimum instrumentation for the procedure is listed and shown in Fig. 14.3. A variety of sizes of tracheostomy tubes and airway rescue equipment should be immediately available. In the absence of cervical spine injury or pathology precluding extension, a roll should be placed behind the patient's shoulders to hyperextend the neck, allowing better exposure of the trachea. An incision midway between the cricoid and the sternal notch is made. A vertical incision is advisable to reduce the risk of division of branches of the anterior jugular veins and the attendant bleeding. Bleeding vessels may be controlled with suture ligature or electrocautery as needed. The dissection is carried out by blunt and sharp dissection to expose the trachea. The thyroid isthmus, if it is in the way, may need to be divided and controlled with suture ligatures. The third tracheal ring is identified and elevated into the wound with a Jackson Tracheal Hook (Skflar Surgical Instruments, West Chester, PA). The third ring is incised with a variety of techniques, based on the training and experience of the surgeon. Complex techniques, such as suturing a tracheal flap to the skin, should be avoided in bedside



• **Fig. 14.3** Instruments for bedside surgical tracheostomy tray.

tracheostomy. The tracheotomy is dilated with the tracheal dilator, the endotracheal tube withdrawn to just above the tracheotomy under direct visualization of the operator, and the tracheostomy tube inserted and the cuff inflated. The patient is then ventilated via the tracheostomy and once correct placement is confirmed by end-tidal carbon dioxide and breath sound auscultation, the endotracheal tube can be removed. The tube is secured with a tracheostomy tie encircling the neck, and the tracheostomy tube is sutured to the skin, and if necessary the skin wound is approximated. Some practitioners will obtain a postprocedural chest x-ray, but in the absence of clinical suspicion of new pathology this is unnecessary.[43]

Complications of Tracheostomy (Table 14.1)

Elective tracheostomy, whether surgical or percutaneous, is relatively safe and well tolerated.[44] This procedure involves maneuvering the ETT and pulling it to just below the vocal cords with the risk of accidental extubation. It also involves performing incision and deep dilation or dissection in a location surrounded by major vessels and vital organs. The reported mortality is less than 1%, and morbidity ranges between 4% and 10%.[44,45] Complications may be intraprocedural (during insertion procedure), early postprocedural (<7 days or before stoma maturation), or late procedural (>7 days).

Several of these complications are serious and warrant extra attention. Two immediate intraprocedural complications are critical and require swift intervention. One is surgical site bleeding, which can be significant. It is typically caused by soft tissue dissection and small vessel injury. It is often self-limited and managed by applying pressure to the site until the bleeding stops. We have also used 2% lidocaine with epinephrine injection around the site, which works almost immediately. Electrocautery may be useful for small branches of the anterior jugular veins, and occasionally these will require ligation during either PDT or surgical tracheostomy. Occasionally it is due to major vessel injury, in which case it can be massive and lethal, requiring immediate surgical intervention.

The second potentially lethal complication is loss of airway control during the procedure. This may be due to premature extubation, in which case rapid recognition and either reintubation or immediate completion of the tracheostomy is effective treatment. This may also be a result of the technical misadventure of false

TABLE 14.1 Complications of Tracheostomy

Intraoperative	Early	Late
Bleeding	Bleeding	Subglottic stenosis
Accidental extubation	Accidental decannulation	Accidental decannulation
False tract	Infection	Infection
Pneumothorax/ pneumomediastinum		Tracheo-innominate fistula
Posterior wall puncture/ esophageal injury		
Hypoxia		

cannulation,[46] which occurs in fewer than 1% of patients and is linked to wire kinking. This complication is often associated with a poor visual bronchoscopic field while attempting to apply too much pressure trying to advance the tracheostomy tube through the fresh stoma over a kinked wire.[46] Once again, rapid recognition and ensuring a controlled airway are critical in this setting. Then the procedure can be completed.

Another immediate serious, yet preventable, complication is puncture of the posterior tracheal wall. This complication may occur during percutaneous tracheostomy but is easily preventable when bronchoscopy is guiding intraluminal insertion of the wire, dilation, and placement of the tracheostomy tube.[47]

The most dramatic and life-threatening late complication—tracheo-innominate artery fistula—is delayed (within 3 weeks) and very uncommon. It can occur with either open or percutaneous tracheostomy and its incidence varies between 0.3% and 0.8%.[48] The risk factors include a low insertion site (below the third tracheal ring), the tracheostomy tube tip abutting against the anterior tracheal wall and eroding through the airway, or an overinflated cuff at the level of the artery. This complication is an absolute surgical emergency and is associated with a high mortality rate.

Posttracheostomy Care

After tracheostomy, weaning from mechanical ventilation and the tracheostomy begins. As in other mechanically ventilated patients, frequent assessment for liberation is conducted. The decrease in sedation requirements frequently leads to a rapid weaning process. Trials of tracheostomy collars may be initiated as tolerated as soon as the patient's oxygen requirements allow. Once mechanical ventilation is no longer needed, tracheostomy tube downsizing/capping and decannulation should be undertaken. In patients with neurologic compromise (e.g., stroke, traumatic brain injury) the assessment for initiating this process must include the patient's cough and swallowing function. Inability to maintain a safe airway may preclude decannulation. The rationale behind downsizing/capping a tracheostomy tube is to allow airflow around the tube through the vocal cord and detect any potential upper airway stenosis caused by the presence of an artificial airway—whether the ETT or tracheostomy tube.[45] Strategies and specifics of a weaning/decannulation protocol are usually institution dependent. Our decannulation protocol includes bedside evaluation with "digital occlusion" of the initial tracheostomy tube while observing any signs of respiratory distress or upper airway obstruction. If well tolerated, initial cuffed tracheostomy tube is downsized to a smaller uncuffed tube. If well tolerated, 24 hours later the tracheostomy tube is then capped for another 24 to 48 hours followed by decannulation.[49] The need for frequent suctioning or poor clearance of oral secretions should be assessed during the capping trial as these factors need to be considered in the decision to decannulate. Any signs of respiratory distress during any stage of tracheostomy tube occlusion should be followed by bronchoscopic evaluation of upper and lower airways.

During the first week after initial tracheostomy, an inadvertent decannulation should be treated as an emergency. The immature stoma can close rapidly, and blind reinsertion attempts can easily lead to a false tract and severe respiratory consequences. When inadvertent decannulation occurs, this should be treated by immediate orotracheal intubation unless a practitioner experienced in performing tracheostomy is present at the bedside. The practitioner may choose to attempt reinsertion of the tracheostomy tube with or without using a guide wire or modified Seldinger technique.[45]

Summary

Bedside tracheostomy is frequently performed in the ICU for patients requiring prolonged ventilation or an artificial airway for secretion or aspiration control. Both percutaneous and open surgical techniques have been used at the bedside in critical care units and have been demonstrated to be safe and effective with no difference in outcomes and the rate of complications. The timing of tracheostomy has been explored in a number of studies with marginal advantages to early compared with late (2–3 weeks). Bedside tracheostomy is associated with a low rate of complications if performed by an experienced operator, regardless of specialty, and a dedicated team.

Key Points

- Tracheostomy is a common procedure in the ICU and often done at the bedside whether it is percutaneous or open.
- Both techniques have similar safety profiles and are associated with a low complication rate.
- Timing of tracheostomy placement has been studied extensively; early tracheostomy has fewer minor advantages with no effect on major outcomes such as mortality or ventilator associated–pneumonia.
- A team approach and preset checklists are crucial when performing bedside tracheostomy.
- In case of accidental decannulation within the first week, preparation for orotracheal intubation should be initiated and tracheostomy reinsertion should be attempted only by an experienced operator.
- After weaning from mechanical ventilation, downsizing and capping should be initiated before decannulation. If not tolerated, bronchoscopic airway evaluation should be performed.

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Review Questions

1. You are supervising your senior fellow who is performing a bedside percutaneous tracheostomy using the Ciaglia technique while another trainee is performing the bronchoscopy. The fellow performing the tracheostomy informs you that he is only able to push the tracheostomy tube partially over the tapered dilator into the tracheal lumen and is meeting resistance. He had already ensured that the guidewire was inside the tracheal lumen and this was confirmed by the bronchoscopist. What is the next best step?

a. Order a smaller tracheostomy tube immediately.
b. Abort the procedure and close the wound.
c. Ask your fellow to apply more pressure to get the tracheostomy tube inside the tracheal lumen.
d. Pull back the tracheostomy tube, tapered dilator, and guidewire en bloc as the guidewire may have kinked and caused a false channel anterior to the trachea.

Answer: d. The most common reason for creation of a false passage is failure to use a true Seldinger technique. Just as in placement of a central venous line, if the device is advanced with the wire, rather than keeping the wire stationary and advancing over it, the wire frequently kinks, resulting in the clinical situation as outlined. The solution is to withdraw the device, pull the kinked wire back into the introducer, and advance the device and introducer over the wire. Applying more pressure will only worsen the condition. If this complication results in desaturation or hemodynamic instability, it may be appropriate to convert to an open approach or abandon the procedure with replacement of the orotracheal tube. The wound should not be closed. A smaller tube will still result in the same outcome unless the technique is corrected.

2. You are reconsulted to evaluate a patient for decannulation after a tracheostomy for prolonged mechanical ventilation (about 4 weeks with orotracheal intubation). The critical care team has already downsized the tracheostomy to a cuffless Shiley No. 6, and the patient has not required mechanical ventilation for more than 10 days. You perform a digital occlusion maneuver and notice significant respiratory discomfort after only 10 to 15 seconds. What is the next step?

a. Continue with decannulation.
b. Downsize the tracheostomy one more time to a cuffless Shiley and then reassess.
c. Perform a diagnostic bronchoscopy through the tracheostomy and through vocal cords to assess for upper airway stenosis likely caused by the prolonged orotracheal intubation.
d. Order a one-way valve.

Answer: c. Respiratory embarrassment caused by airway obstruction (complete or partial) is an absolute contraindication to decannulation in this setting. After prolonged endotracheal intubation, the most frequent cause is likely to be related to laryngeal edema and/or scarring, but vocal cord paralysis or granuloma may be present at that level. Subglottic stenosis caused by prolonged intubation with high cuff pressures is less likely but should be evaluated by endoscopy.

3. You are asked to evaluate a 34-year-old female with severe acute respiratory distress syndrome (ARDS) secondary to pneumonia for an "early tracheostomy." She has been intubated for only 4 days. The intensivist informs you that the patient is expected to require long-term mechanical ventilation considering the severity of her illness and would like the patient to have a tracheostomy. She has had a recent drop in positive end-expiratory pressure (PEEP) (12 cm H_2O) and oxygen (a fraction of inspired oxygen of 50%) requirements; the intensivist wants to take the opportunity to place the tracheostomy as the patient's condition might worsen, precluding the procedure. What are the factors to consider when making a decision about tracheostomy in this patient?

a. It is imperative to wait and not perform a tracheostomy in patients with ARDS requiring high PEEP as it may lead to loss of recruited alveoli and severe oxygen desaturation.
b. Tracheostomy with bronchoscopic guidance is contraindicated in patients with more than 10 cm H_2O of PEEP as inserting the scope through the endotracheal tube may lead to excessive airway pressures.
c. The ability of practitioners to predict long-term mechanical ventilation is not very high; this patient may eventually get extubated without the need for a long-term artificial airway.
d. Proceed with tracheostomy as requested as the advantages of tracheostomy have been very well established and may decrease the risk of mortality in this patient.

Answer c. Many studies have been conducted in an attempt to help identify clinical factors that predict the duration of mechanical ventilation in the critically ill patient. None have provided sufficiently accurate prognosis to be applied to the individual patient. The benefits of early tracheostomy are restricted to a few specific populations but they do not include those with ARDS.

15

Chest Tube Thoracostomy

ZIAD BOUJAOUDE AND DAVID SHERSHER

CHAPTER OUTLINE

Historical Perspective

Anatomy and Physiology of the Pleural Space

Physiologic Changes With Pleural Effusions and Pneumothorax

Indications for Tube Thoracostomy
- Pneumothorax
- Noninfectious Pleural Effusions
- Hemothorax
- Complicated Parapneumonic Effusions and Empyema
- Malignant Pleural Effusions

Contraindication to Tube Thoracostomy

Drainage Systems

Optimal Chest Tube Size for Drainage

Technique of Chest Tube Insertion
- Small-Bore Tube Thoracostomy
- Large-Bore Tube Thoracostomy

Management of the Chest Tube and Troubleshooting

Complications

Chest tube thoracostomy consists of a percutaneous insertion of a small- or large-bore tube into the pleural cavity. The procedure is primarily used to drain fluid or air from the pleural space and can be lifesaving in certain conditions. Patients requiring chest tubes are often acutely ill with multiple comorbidities and the procedure could be associated with serious complications. It should be performed only by experienced or adequately supervised operators who are familiar with the indications and the potential risks of the procedure. In this chapter we review the historic development of chest tubes, discuss the indications, contraindications and complications of chest tube insertion, outline the technique of insertion, and review the evidence-based management of chest tubes after insertion.

Historical Perspective

Hippocrates was the first to drain an empyema of the pleural space with a metal tube 2400 years ago.[1] Playfair described an underwater seal in 1872, and in 1876 Hewitt designed the first closed tube drainage system with a rubber catheter that drained into a glass jar filled with a weakly antiseptic solution.[2,3] Because of technical problems, this procedure was not widely accepted until 1917, when chest tubes were extensively used for the treatment of pleural empyema associated with the influenza pandemic.[4] Emergency tube thoracostomy became an extremely frequent procedure in treating hemothorax and tension pneumothorax during both the Second World War and the Korean War, and the drain was connected for the first time to a two-bottle water seal system.[5] Thereafter synthetic and more flexible and easier to place tubes replaced metal tubes, and modern three-chamber drains have been used since 1952.[6]

Anatomy and Physiology of the Pleural Space

The pleural cavity is the space formed between the visceral and parietal pleurae, which is crucial for efficient pulmonary and chest wall function. Each pleura is formed from a single layer of mesothelial cells.[7] The parietal pleura covers the inner surface of the thoracic cage including the mediastinal surface and the diaphragm. The visceral pleura covers the outer surface of the lung including the interlobular fissures. The parietal pleura is richly supplied with arterial blood derived from systemic arteries (intercostal, internal mammary, subclavian, and mediastinal arteries), whereas the blood supply of the visceral pleura is divided between the bronchial (mediastinal and interlobular surface) and the pulmonary circulation (costal and diaphragmatic surface). The majority of the venous drainage of the parietal pleura is through the azygos vein and eventually the superior vena cava, whereas the greater part of the visceral pleura is drained through the pulmonary veins. The lymphatic circulation of the visceral pleura is divided into a superficial plexus and a deep plexus composed of a network of lymphatic capillaries and collecting vessels that drains to the hilum. The lymphatic system of the parietal pleura is more extensive and complex with a flow directed to the intercostal and mediastinal nodes. This system plays a key role in the formation and removal of pleural fluid in normal and pathologic states. The effective removal of fluid, cells, and debris relies on the presence of pleural-lymphatic communications including pleural stomata and lymphatic channels.[8]

The parietal pleura is innervated by somatic intercostal nerves and phrenic nerve, whereas the visceral pleura is innervated by the vagus nerve and sympathetic trunk. The pain resulting from irritation of parietal pleura is felt at the adjacent chest wall and may be referred to shoulder. The visceral pleura contains no pain fibers.

In a normal physiologic state, pleural fluid is produced mostly by the parietal pleura according to the net hydrostatic-oncotic pressure gradient, at an approximate rate of 0.5 mL/h in adults.[9]

Drainage of fluid and proteins occurs almost exclusively via the parietal pleural stomata and the pleural lymphatics. Pleural effusion occurs when these homeostatic mechanisms are disrupted, affecting transit of pleural fluid across the pleural space. Movement of fluid between the pleural space and the alveolar or pulmonary interstitium is restricted by tight junctions between visceral mesothelial cells. This barrier can be damaged in disease states such as congestive heart failure or acute respiratory distress syndrome.[10] Additionally, intercostal and diaphragmatic muscle activity influences the rate of lymphatic flow, and hypoventilation and anesthesia can reduce lymphatic flow and the rate of absorption of protein, altering the physiology of the pleural space.

Physiologic Changes With Pleural Effusions and Pneumothorax

The effects of a pleural effusion on pulmonary function are difficult to determine. Generally speaking, it imposes a restrictive ventilatory defect on the patient. One study showed a 20-mL increase in forced vital capacity for every 100 mL of pleural fluid withdrawn, but there was large interindividual variability.[11] For patients supported by mechanical ventilation, one study showed immediate improvement of compliance and the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FIO_2) ratio, but another study showed no effect.[12,13] The presence of a large pleural effusion can lead to diaphragmatic inversion and marked dyspnea and can compress the heart and lead to a compromised cardiac output.

A pneumothorax occurs when air enters the pleural space through a communication between the alveoli or the ambient air and the pleural space. Information on the effect of pneumothorax on pulmonary function is limited as most patients are symptomatic. However, it has been shown to adversely affect blood gases in humans. In one study of 12 patients with pneumothorax, the PaO_2 was below 80 mm Hg in 9 patients and below 55 mm Hg in 2 patients.[14] The PaO_2 was lower in patients with pneumothoraces. The effect of a small pneumothorax on diaphragm and cardiac output is minimal; however, the effect exponentially increases when a tension pneumothorax develops. Tension pneumothorax occurs when air enters the chest with each mechanical or spontaneous breath, with no route for escape. Initially, the affected lung simply collapses, but as tension increases, the diaphragm flattens, and the mediastinum shifts toward the contralateral side. The contralateral lung is compressed, further decreasing effective ventilation. Most importantly with respect to acute hemodynamics, the great vessels also are compressed and venous return is reduced. This reduction in venous return results in rapid and disastrous cardiopulmonary collapse.[15]

Indications for Tube Thoracostomy

Chest tubes are primarily used to remove liquid or air from the pleural space, but they can also be used to instill sclerosing agents to induce pleurodesis. In the critically ill patients, they are frequently used to treat pneumothoraces, pleural effusions, parapneumonic effusions and empyema, hemothoraces, and malignant pleural effusions.

Pneumothorax

A pneumothorax can be spontaneous (primary or secondary), iatrogenic, or traumatic (non-iatrogenic). A secondary spontaneous pneumothorax is defined as a pneumothorax that occurs as a complication of underlying lung disease. In contrast, primary spontaneous pneumothorax occurs without a precipitating event in the absence of clinical lung disease. Patients with primary spontaneous pneumothorax who are symptomatic or who have a distance greater than 2 cm from the surface of the lung to the inside of the chest wall should undergo drainage.[16] Simple aspiration with a 14- to 16-gauge catheter is as effective as a large-bore chest drain and may be associated with fewer days of hospitalization.[17,18] The patient may be observed for a few hours and then discharged home if the pneumothorax does not recur. Small-bore chest tubes have been shown to be as effective as large-bore catheters if a tube is indicated.[19] Most spontaneous secondary pneumothoraces are related to chronic obstructive pulmonary disease. In these patients, needle aspiration is usually not sufficient, and most require drainage with a small-bore chest tube.[16] One nonrandomized study demonstrating equivalence of size of tube thoracostomy compared the results in 61 patients treated with pigtail catheters (10F–14F) and 22 patients receiving large-bore chest tubes (22F–28F), reported that the success rate was 72.5% with the pigtail catheters and 72.7% with the large-bore catheters.[20] In our practice and consistent with these data, we prefer to use small-bore chest tubes for simple pneumothoraces.

Traumatic (non-iatrogenic) pneumothorax can result from either penetrating or nonpenetrating chest trauma. Tube thoracostomy may not be necessary for patients with occult or small pneumothoraces. Knottenbelt and van der Spuy observed 333 patients with small (<1.5 cm from lung to chest wall) pneumothoraces and reported that only 33 required subsequent drainage for an enlarging pneumothorax.[21] An occult pneumothorax is a pneumothorax that is not visible on the chest radiograph but is visible on the computed tomography CT scan. This accounts for 40% of all traumatic pneumothoraces and does not require treatment with a chest tube unless patients require positive-pressure ventilation while using mechanical ventilation (to avoid the risk of development of tension pneumothorax). Although there are no controlled studies, small-bore rather than large-bore chest tubes are recommended for traumatic pneumothoraces that are not associated with pleural effusion that may be a hematoma related to the mechanism of injury. After placing a small-bore chest tube, if the lung does not expand a large-bore chest tube should be inserted. If the pneumothorax is not resolved after this, consideration should be given to performing video-assisted thoracic surgery to control air leak and/or prevent development of a trapped lung.[22,23]

The most common causes of iatrogenic pneumothoraces are transthoracic needle aspiration, subclavian vessel puncture, thoracentesis, pleural biopsy, and mechanical ventilation.[24] Asymptomatic iatrogenic pneumothorax may be treated with supplemental oxygen. If symptomatic, needle aspiration is effective in more than 90% of patients.[25] A small-bore tube is indicated if the lung does not expand and a large-bore chest tube should be inserted if no resolution occurs.[22] One special situation with iatrogenic pneumothorax is in patients supported by mechanical ventilation. In general, all such patients should receive a chest tube because of the possibility of the development of a tension pneumothorax.[26] The decision to place a large-bore or small-bore chest tube in this situation is largely determined by training paradigm and institutional preference. Lin and associates reported their experience with 70 patients supported by mechanical ventilation who developed a pneumothorax. When the pneumothorax was due to thoracentesis, central line insertion, or central venous access stick, pigtail catheters were successful in 35 of 40 (87.5%) patients. However, when the

pneumothorax was due to barotrauma, pigtail catheters were successful in only 13 of 30 (43.3%) patients.[27] The results of this study suggest that if a pneumothorax is due to barotrauma in mechanically ventilated patients, it is probably better to insert large-bore chest tubes.

Tension pneumothorax is a life-threatening emergency that requires immediate decompression. In the absence of hemodynamic compromise, the diagnosis should be confirmed on chest radiograph before drainage, but often the diagnosis is made clinically without radiographic support. Unstable patients should be treated immediately with needle decompression of the second intercostal space at the mid-clavicular line using a 14- or 16-gauge long angiocatheter, followed by formal insertion of chest tube. A 14F to 16F chest tube is successful in our experience.

Noninfectious Pleural Effusions

Transudative and exudative pleural effusions are common in the intensive care unit (ICU). The incidence varies with screening methods, from approximately 8% for physical examination to more than 60% for routine ultrasound.[28] Several factors contribute to the occurrence of pleural effusions in ICU patients. Large amounts of intravenous fluid are often administered during the first few days to patients admitted for shock. Heart failure, atelectasis, hypoalbuminemia, and liver disease are present in many ICU patients. Cardiac or abdominal surgery is often complicated by pleural effusion; the majority of effusions are small and if clinical suspicion for infection is low, observation of these effusions is warranted initially. Most effusions are caused by noninfectious processes that should resolve with treatment of the underlying disease.[29] However, drainage with a small-bore chest tube may be indicated when an effusion is large and symptomatic. Drainage of large pleural effusions may result in a significant improvement in oxygenation for mechanically ventilated patients in acute respiratory failure who are poorly responsive to treatment with mechanical ventilation and positive end-expiratory pressure.[13]

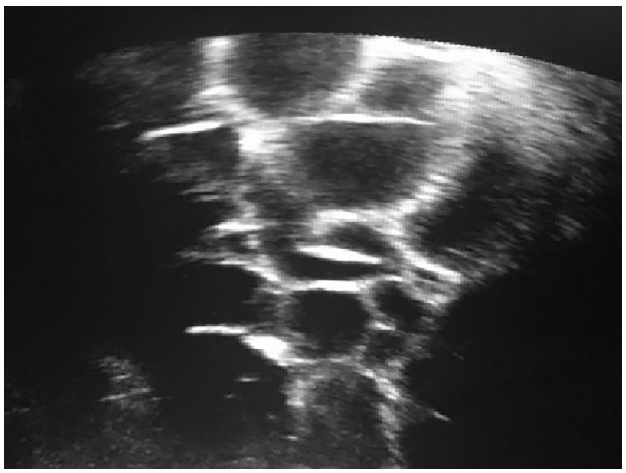
Hemothorax

A hemothorax is defined by a hematocrit of the pleural fluid of at least 50% of the peripheral hematocrit. Most hemothoraces are due to trauma, and some are due to malignancy, anticoagulation, or other conditions.[22] The presence of a hemothorax requires immediate insertion of a chest tube. Insertion of the tube allows complete evacuation of blood and quantification of the amount of bleeding. It helps to stop the bleeding if caused by pleural laceration as the two pleural surfaces come into apposition and decrease the incidence of subsequent infection, empyema, and fibrothorax.[30] In general, a large-bore tube is recommended. Massive hemorrhage (>1500 mL) or drainage of more than 250 mL/h is an indication for surgical exploration.[31]

Complicated Parapneumonic Effusions and Empyema

Empyema is defined by the presence of frankly purulent pleural fluid. Conversely, the criteria for a complicated parapneumonic effusion are broader and include the presence of pus, gram stain–positive or culture-positive pleural fluid, pleural fluid pH less than 7.20, and pleural fluid lactate dehydrogenase level greater than three times the upper limit of normal of serum lactate dehydrogenase. The British Thoracic Society guidelines recommend that patients with frankly purulent or turbid/cloudy pleural fluid on thoracentesis sampling should receive prompt pleural space chest tube drainage. In addition, the presence of organisms identified by Gram stain and/or culture from a nonpurulent pleural fluid sample indicates that pleural fluid is infected and should lead to prompt chest tube drainage. The guidelines also state that patients with parapneumonic effusion and pleural fluid pH less than 7.20 or patients with loculated parapneumonic effusions should also receive early chest tube drainage.[32] Loculation is defined by the presence of one or more pockets of fluid in the pleural space. A loculated effusion tends to have a lower pH and glucose level and the fluid analysis in the majority of patients with loculations indicates that tube thoracostomy should be performed (Fig. 15.1). There is no consensus on the optimal size of the chest tube, and it is reasonable to start with a smaller size and proceed to surgical tube placement if the effusion does not improve. Masket et al. collected data on the size and the complications of chest tubes on 405 patients who participated in the Multicenter Intrapleural Streptokinase Trial that was designed to assess the efficacy and safety of streptokinase in patients with complicated parapneumonic effusions.[33] The group reported that there was no significant difference in the frequency with which patients either died or proceeded to surgery for source control when comparing chest tubes of varying sizes.[34] Another study reviewed the results of tube thoracostomy in 103 patients who were treated with 8F to 12F pigtail catheters or 10F to 14F Malecot catheters (Cook Medical, Bloomington, IN) placed with the Seldinger technique. This study reported that the small catheters served as the definitive treatment in 78% of the patients.[35]

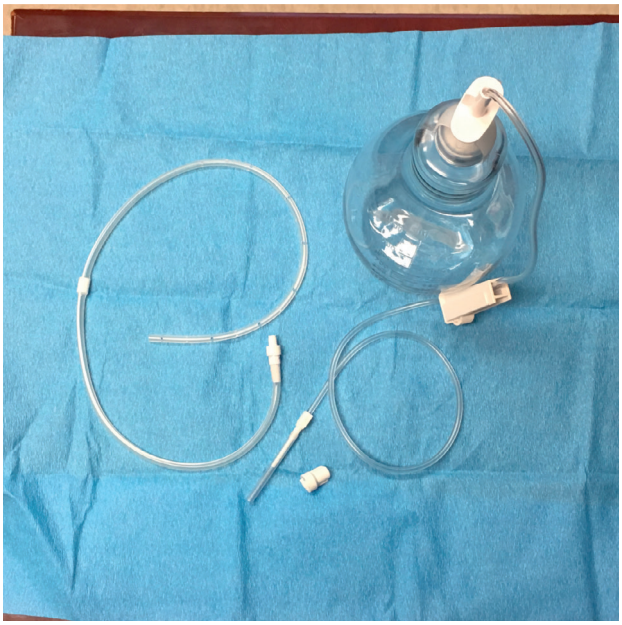
The British Thoracic Society guidelines state that a small-bore catheter (10F–14F) is adequate for most cases of complicated parapneumonic pleural infection. The guidelines recommend regular flushing of small-bore flexible catheters to prevent clotting with debris, using 20 to 30 mL of saline solution every 6 hours via a three-way stopcock. It should be noted that flushing larger-bore drains is technically more difficult as these do not routinely have three-way stopcock, and disconnection for irrigation might encourage the introduction of secondary infection.



• **Fig. 15.1** Ultrasound examination of a multiloculated pleural effusion. Pleural fluid with a pH of less than 7.20 in such patients with multiple loculations should be treated with early chest tube drainage.

Malignant Pleural Effusions

Chest tubes are often used in the management of malignant pleural effusions to perform pleurodesis or to drain the pleural fluid on a long-term basis. The available evidence suggests that small-bore catheters are as efficacious as large-bore catheters to effect pleurodesis.[36–38] Indwelling, tunneled catheters are used for long-term home drainage and are extremely comfortable and effective. The most commonly used is the Pleurx catheter (CareFusion, San Diego, CA) (Fig. 15.2). The PleurX catheter is a 15.5-F silicone rubber catheter that is 66 cm long. It has a one-way valve on the external part of the catheter that allows drainage of the pleural fluid when an adaptor attached to a vacuum bottle is inserted into the valve. Tunneled pleural catheters allow symptomatic improvement in 95% of the patients, reduce the length of hospitalization, and can induce spontaneous pleurodesis. They are associated with low obstruction and infection rates.[39] They can be combined with pleuroscopic talc pleurodesis to reduce the duration of hospitalization and to provide a backup mechanism in case of pleurodesis failure.[40]



• **Fig. 15.2** PleurX catheter (CareFusion, San Diego, CA) indwelling device that is inserted with a subcutaneous cuff for outpatient drainage of pleural effusion.

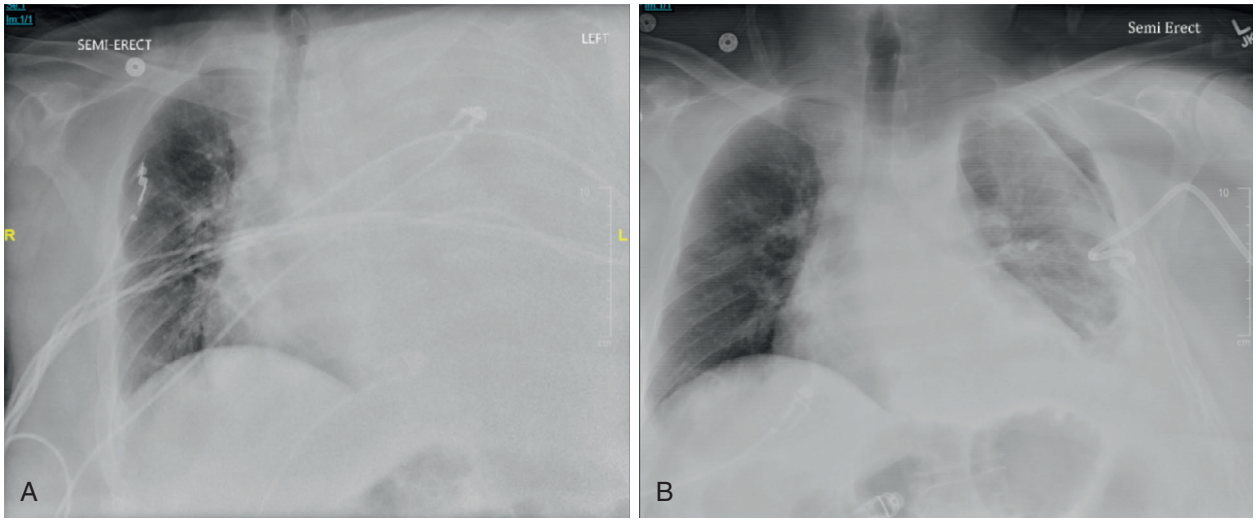
Contraindication to Tube Thoracostomy

With appropriate operator experience or experienced supervision, there are few technical contraindications to performing bedside tube thoracotomy. Relative contraindications are thrombocytopenia (platelet count <50,000/μL and international normalized ratio >1.5 IU), but these are more applicable to percutaneously placed tubes owing to inability to manually control periprocedural bleeding leading to hemothorax. In our institution's practice, we have safely placed chest tubes with a bedside cut-down approach in coagulopathic patients using appropriate hemostatic surgical principles and transfusion of blood products.

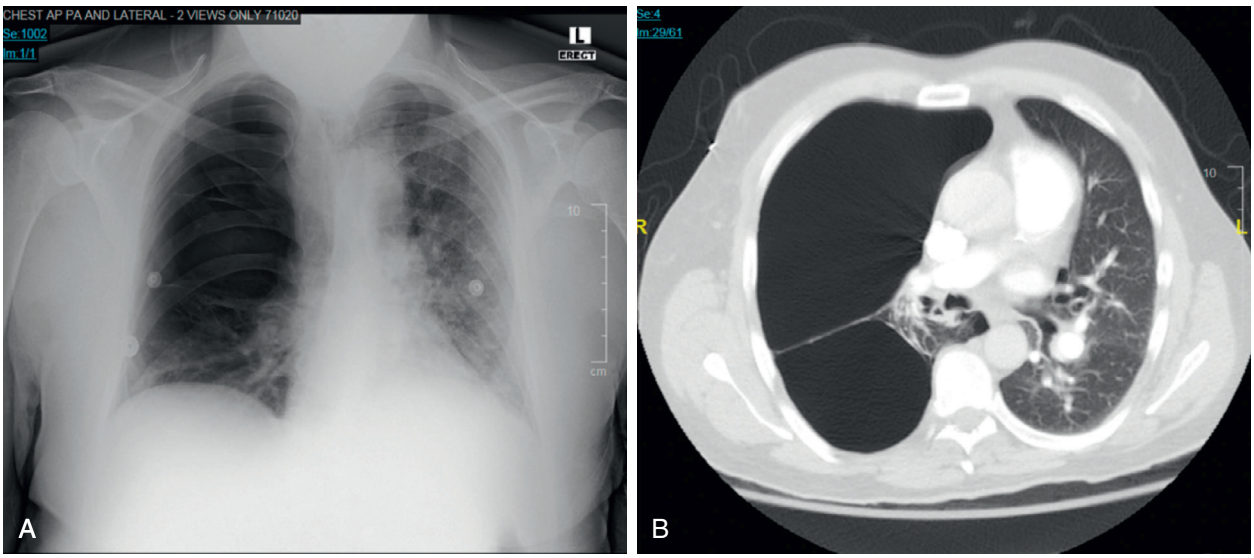
There are two specific contraindications to tube thoracostomy that are most often missed in the haste of radiology imaging review and procedural treatment of a sick patient: trapped lung and bullous disease mistaken for a pneumothorax. The former condition is often associated with a thickened pleural rind that can be seen on chest enterography and better demarcated on CT. Whether the trapped lung is due to chronic empyema, metastatic disease, or fibrothorax, placement of a chest tube will likely not expand the lung to create pleural apposition. The appropriate treatment is surgical decortication. Fig. 15.3 demonstrates a prefilm (part A) and postfilm (part B) image after incomplete pulmonary reexpansion in a patient with trapped lung. The latter condition, bullous disease, may be mistaken for a large pneumothorax on rapid radiographic evaluation of a hypoxic patient. The result of this "misread" can be dangerous, as placement of chest tube into a large bullae will result in a large bronchoatmospheric fistula that will likely need surgical control to seal. Fig. 15.4 demonstrates a chest radiograph and subsequent CT example of bullous disease.

Drainage Systems

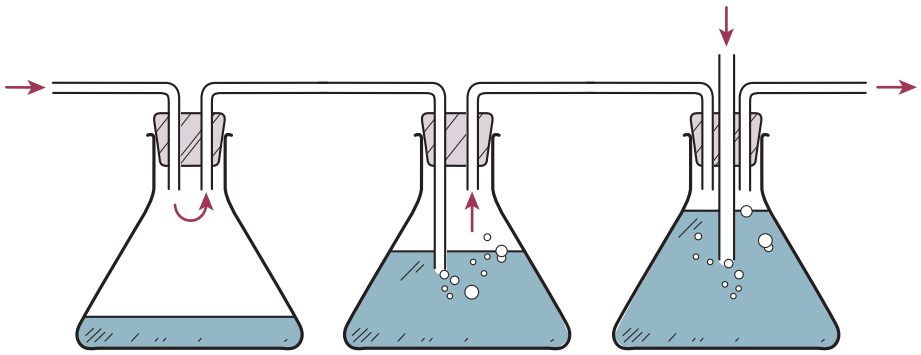
The original drainage system was a single-bottle system consisting of a water seal and drainage bottle. This was ultimately advanced



• **Fig. 15.3** Demonstration of a trapped lung: (A) shows appearance of chest radiograph before drainage of pleural fluid with tube thoracostomy and (B) afterward, now demonstrating trapped lung.



• **Fig. 15.4** Chest radiograph (A) and computed tomography scan (B) demonstrating giant bullae in the right lung. As demonstrated, chest radiography alone can confuse clinicians as to a potential diagnosis of pneumothorax with ensuing complication of large bronchopleural fistula if a chest tube is mistakenly inserted in the belief that the bullae is a pneumothorax.



• **Fig. 15.5** Historically the three-bottle collection system was used; the system consisted of (from *left* to *right*) trap bottle, water-seal bottle, and manometer bottle. These are now all integrated into a single self-contained collection system.

to a three-bottle system (Fig. 15.5), which allowed a separate chamber for fluid collection, air expulsion, and ultimately external suction connection to hasten evacuation of air and fluid from the pleural space (rather than relying solely on water seal pressure as a function of height differential between the chest tube tip and the water column). The modernization of this three-chamber system is found in single compartmentalized boxes such as those made by Atrium (Atrium Medical Corp., Hudson, NH) or Sahara (Teleflex Inc., Morrisville, NC) (Figs. 15.6A and B, respectively). Both allow connection to various degrees of suction that can be manipulated on the side of the device. The factory setting is −20 mm Hg, which corresponds to a negative pressure generated with a 20-cm column of water in the original three-bottle system. Advanced digital systems such as the Medela (Medela Healthcare, McHenry, IL) system are based on the same design principle but objectify air leak and quantity of drainage better than conventional analog systems (Fig. 15.7). Proponents argue that these devices lead to earlier chest tube removal and decreased hospitalization.[41] This was recently corroborated in a multicenter randomized trial with subjective improvement in patient satisfaction scores, especially considering that these portable devices could be used at home.[42] Opponents cite benefit/cost issues as a barrier to use.

Finally, water seal–equivalent options exist for patients with prolonged air leak, defined as leak persisting longer than 5 days after intervention, who can be discharged home with adequate control of the pleural space.[43] The two most common devices are demonstrated in Fig. 15.8, with the former device (part A) permitting efflux of air and the latter device (part B) also allowing capture of pleural fluid into a closed sterile chamber.

Optimal Chest Tube Size for Drainage

Chest drains are usually divided into two size categories: large-bore (>20F) or small-bore (≤20F). French refers to the outer diameter and (1F) is equivalent to 0.333 mm. Like all cylindrical tubes, pleural drains obey Poiseuille's law and the Fanning equation. The Fanning equation ($\nu = \pi^2 r^5 P/fl$, were ν is the flow, r is the radius, l is the length, P is the pressure, and f is the friction factor) determines the flow of the moist gas (such as in a pneumothorax) or liquid with turbulent flow through the tube.[44] Poiseuille's law

• **Fig. 15.6** Common modern self-contained pleural drainage systems are made by Atrium (A) or Teleflex (B). These function similarly and utilize the principles of the three bottle collection system.

• **Fig. 15.7** Modern digital drainage system (Medela; Medela Healthcare, McHenry, IL) can objectify air leak and quantity of drainage better than conventional analog systems.

• **Fig. 15.8** A, The Heimlich valve (Becton, Dickinson and Company, Franklin Lakes, NJ) and (B) Atrium Pneumostat devices are two ambulatory systems designed to allow one-way drainage of small air leaks and permit short-term outpatient management of patients. (B, Copyright [2004] Atrium Medical Corporation. All rights reserved.)

($\nu = \pi r^4 \Delta P / 8 \dot{\eta} L$, where ν is the flow, r the radius, $\dot{\eta}$ the liquid's viscosity, L the tube's length, and ΔP the difference between the tube's ends) determines the flow of corporeal fluids. If the diameter of the tube is doubled, flow increases by a factor of 16, implying that a small increase in the size of the drainage tubes would result in substantial improvements in the flow rates. The internal diameters (bore) and the length of the tube, which may vary according to the manufacturer, are obviously key determinants for the successful drainage of pleural collections. However, equally important are the characteristic of the drained material, its formation rate, the ability of the tube to remain patent, and for all or the majority of the collection being drained to be in communication with the tube. Patient safety and comfort should also be considered. A large-bore catheter would appear to fulfill most of the criteria, and traditionally large tubes are used whenever a high risk of drain

obstruction is expected as in cases of active bleeding or empyema. However, review of the published literature suggests that small-bore tubes are at least as effective as large tubes for most indications.[19,20,34–38] An experimental study compared the drainage capacity of a 19F and 28F tube in vivo and in vitro, showing that the larger tube had an in vitro capacity 9 times higher than the other, whereas in vivo both tubes had the same drainage capability over time.[45] Similar results were also found by Park and colleagues, who compared the catheters' drainage times according to their size, taking into account the characteristics of fluid including viscosity.[46] The authors observed that the tube's size was significantly different only for catheters smaller than 8F, whereas it was not so for the larger ones. Furthermore, small-bore tubes are easier to insert, they cause less pain for the patient both during insertion and while in place, and they appear to have a lower risk of complications.[31]

In our institution, small-bore tubes are routinely used for most indications, including initial drainage for complicated effusions and empyema, tension pneumothorax, and nontraumatic hemothorax with high success. Small-bore catheters may also complement larger tubes that have drained most of the chest but have left small residual pockets, which would be difficult to access blindly with large, less flexible tubes.

Technique of Chest Tube Insertion

Small-Bore Tube Thoracostomy

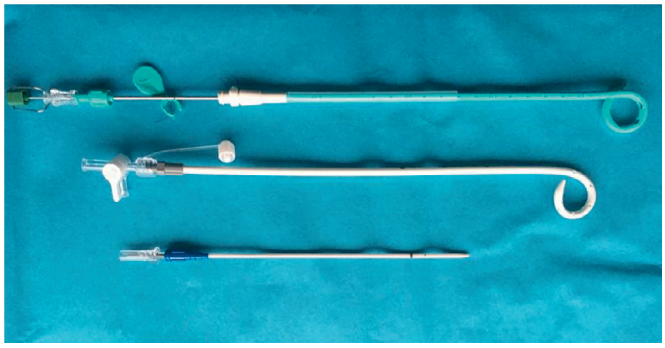
Small-bore chest tubes (<20F) are inserted using a catheter system such as the catheter-over-needle and the catheter-over-guidewire (Seldinger) technique. The procedure begins with patient positioning after explaining the procedure and obtaining informed consent.

Several positions are used; the most important issue is accommodating overall comfort of patient and operator. Patients could be positioned to sit on the bed with their back straight and upright with arms resting on a pillow placed on a table in front of them. For mechanically ventilated patients or those too ill to sit upright, the procedure could be performed with the patient in the supine or lateral decubitus position with arm raised overhead or reaching contralateral side (Fig. 15.9).

Physical examination allows safe selection of the insertion area in most cases. The general teaching approach is that insertion should be attempted one interspace below the spot where tactile fremitus is lost and the percussion note becomes dull. One must recognize, however, that the position of the diaphragm in the supine and lateral decubitus positions can be as high as the fourth intercostal space. In case of a pneumothorax, the catheter is inserted in the second anterior intercostal space, mid-clavicular line. Pleural ultrasonography is a safe and simple noninvasive technique for determining the presence of pleural fluid and identifying the insertion site. It can be performed at the bedside and can provide information about the quantity and the quality of pleural fluid, including the presence of loculations and the precise location of loculated pockets. Studies have shown that complications are decreased with ultrasound guidance, including in patients receiving antiplatelet agents.[47–49] As ultrasound is becoming more available in most ICU, we recommend its routine use to guide the insertion of small-bore tubes.

The selected site is cleaned thoroughly with antiseptic solution and sterile draping is applied. It is essential to anesthetize the skin, intercostal space, and the parietal pleura with a satisfactory amount of local anesthetic. A short 25-gauge needle is used to raise a small wheal with 1% lidocaine at the selected site. Then a long 22-gauge needle is advanced through the wheal directly over the rib with gentle aspiration. Lidocaine is injected every 2 to 4 mm as the needle is advanced until a small amount of fluid or air comes up into the syringe, at which point the needle is then removed. When

• **Fig. 15.9** Patient positioning for bedside thoracostomy is critical to adequately expose the axillary angle and permit safe insertion of a chest tube. Depicted are two common positions: (A) with arm across body and (B) with arm in abduction.



• **Fig. 15.10** Examples of commonly used small-bore chest tubes manufactured by *(top)* Skater (Argon Medical Devices, Frisco, TX); (*middle*) Wayne (Cook Medical, Bloomington, IN), and (*bottom*) Arrow (Arrow International, Reading, PA). Clinicians must be familiar with the type of tube and deployment system used to allow for safe tube thoracostomy.

the catheter-over-needle technique is used, the catheter sheath and needle are advanced until fluid or air is obtained and then the catheter is advanced while holding the needle in place. In case of a pneumothorax, the catheter is directed toward the apex, whereas in case of pleural effusion, it is directed inferiorly and posteriorly into the costal diaphragmatic recess. When the Seldinger technique is used, an 18-gauge hollow needle is advanced until fluid is obtained and then a guidewire is passed through the needle into the space. After removal of the needle, a small incision is made and then a dilating catheter is threaded over the guidewire and advanced using a twisting movement. The tube is next advanced over guidewire. A third technique for insertion uses a chest tube mounted on a sharp-tipped trocar. The whole unit is advanced until parietal pleurae are reached and then the catheter is advanced while the trocar is held in place. The distance to the pleura is premeasured with a 22-gauge needle. Examples of small-bore tubes that are inserted with the above techniques are Skater catheter (Argon Medical Devices, Frisco, TX), Wayne pneumothorax catheter (Cook Medical), and Arrow pneumothorax catheter (Arrow International, Reading, PA) (Fig. 15.10).

Large-Bore Tube Thoracostomy

All critical care proceduralists and surgeons must be familiar with large-bore tube thoracostomy, as this is the mainstay to initial and sometimes penultimate control of the pleural space in a critically ill patient. The procedure should be performed with an experienced proceduralist or supervisor after reviewing appropriate chest imaging, attaining consent, marking the appropriate site, and performing a timeout with nursing staff and equipment in the room. Patient positioning is important and can be performed in one of two ways as described earlier in Fig. 15.9.

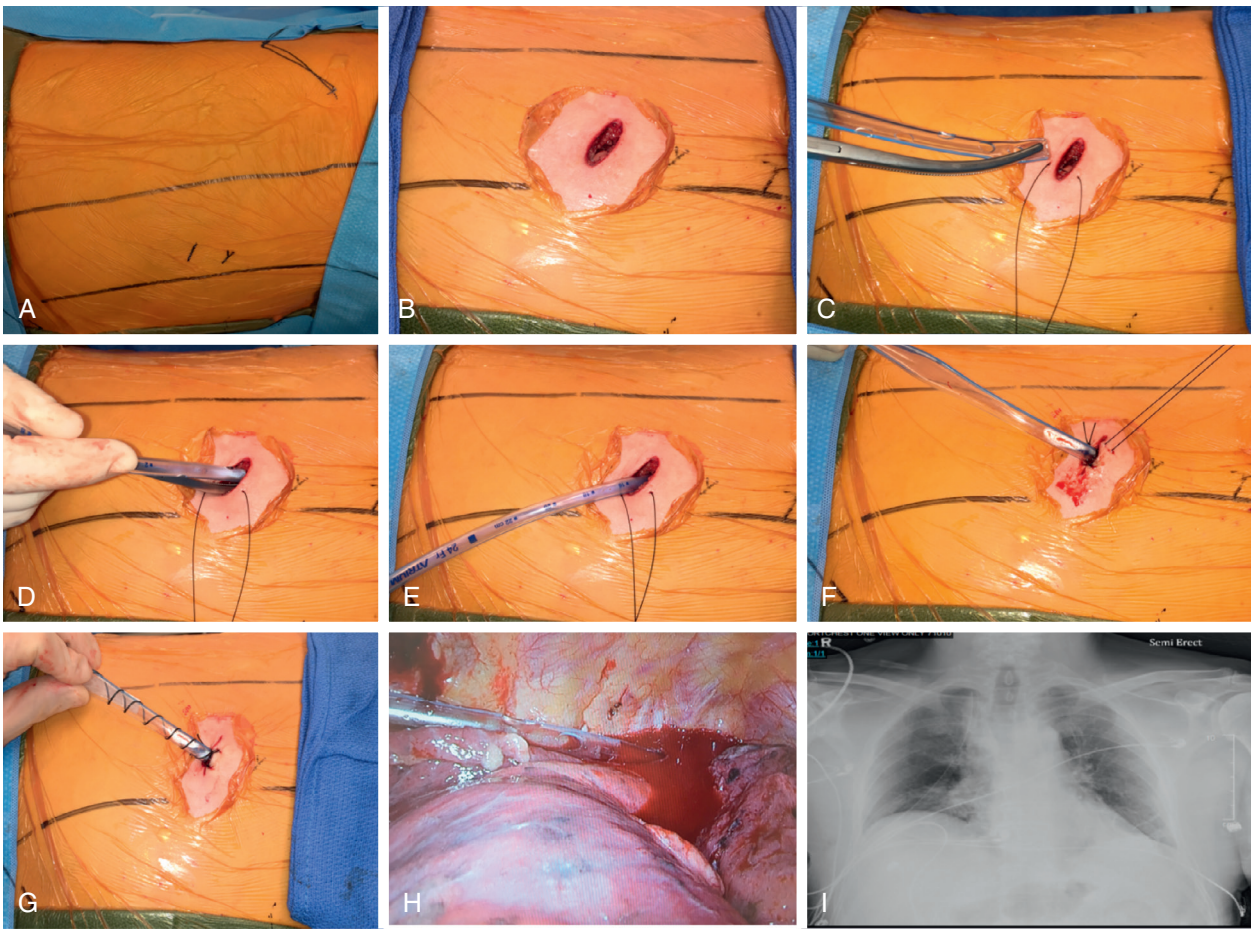
Each chest tube kit should contain the following components:

1. Lidocaine
2. Antiseptic solution
3. Sterile drape
4. Syringes (10 mL)
5. 21-gauge or smaller gauge needles
6. Scalpel
7. Size 0 silk sutures
8. Heavy scissors
9. Curved hemostat clamp
10. Larger Kelly hemostat clamp
11. Chest tube (24F for pneumothorax, 32F or larger for hemothorax or empyema)
12. Drain sponges, tape
13. Pneumovac canister

After obtaining consents and prepping and draping the patient, we routinely identify and mark the fifth intercostal space at the mid to anterior axillary line. This corresponds well to the inframammary crease demarcated by the Y (Fig. 15.11). The scapula is shown at the top of the screen, as are the posterior and anterior axillary lines along with the sixth intercostal space (which was used for this particular chest tube insertion). Occasionally, the fourth or sixth intercostal spaces may be used dependent on patient anatomy. We use local analgesia with 20 mL of 1% lidocaine (10 mL infiltration into incision and 10 mL as an intercostal nerve block) and intravenous sedation and analgesia if needed. We perform an intercostal nerve block of the site of interest using a long 21- or smaller gauge needle and marching up the bottom of the rib while infiltrating the parietal pleura. This avoids injury to the intercostal bundle. After making a 1-cm skin incision in the direction of the rib at the lower edge of the intercostal space, this incision is carried down to the intercostal muscle. A combination of controlled pressure and dissection using a curved hemostat just above the top border of the underlying rib permits safe entry into the pleural space. Using finger palpation, intrapleural loculations are gently disrupted and the pleural space is freed. Next, the chest tube (which should have been already prepared with a Kelly clamp at the tip and another hemostat at the end to prevent spillage of fluid around the sheets) is positioned posteroapically or in the direction of maximal pathology. The chest tube is secured to the skin with an anterior simple anchor stitch using size 0 silk suture. Additionally, to prevent accidental dislodging, the amount of chest tube leakage is decreased after the procedure and uncomplicated removal of the chest tube is facilitated; either a simple vertical stitch or a U-stitch is performed, tied down to the skin, and wrapped around the chest tube. The chest tube is then attached in a sterile manner to the pneumovac and dressed appropriately with gauze and tape. Fig. 15.9 demonstrates this sequence and also shows both an intrathoracic view of appropriate posteroapical placement and its radiographic postprocedure correlation.

Management of the Chest Tube and Troubleshooting

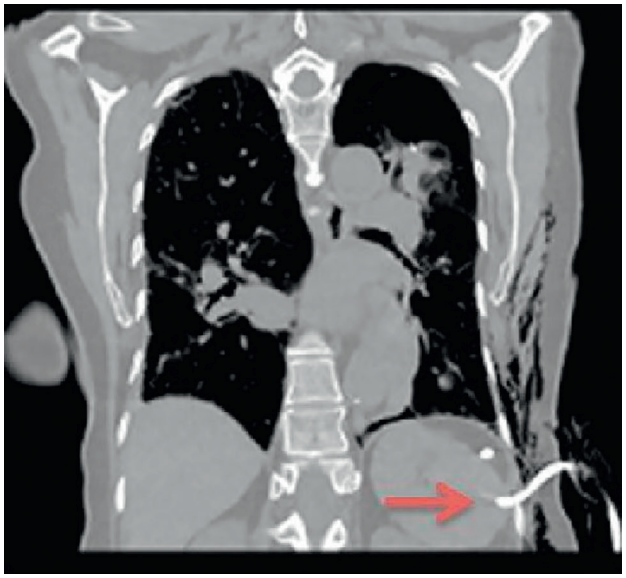
After chest tube insertion, our institution's practice is to immediately order a postinsertion chest radiograph with the chest tube to −20 mm Hg suction to confirm placement and either drainage of effusion and/or reexpansion of the lung. The appropriate use of pleural drainage systems as previously described is reported by the American College of Chest Physicians and does not discriminate between use of suction and water seal when effective.[50] However, the debate of water seal or suction is age-old; two recent meta-analyses published in 2010 and 2012 found no difference in terms of prolonged air leaks, duration of air leak, length of hospital stay, or length of indwelling tube thoracostomy when comparing suction to water seal.[51,52] Suction may hasten resolution of pleural effusion or pneumothorax in certain cases, but at the expense of increased risk of reexpansion pulmonary edema and possibly potentiating prolonged air leaks, without a decrease in duration of chest drain placement and hospital stay.[52,53]



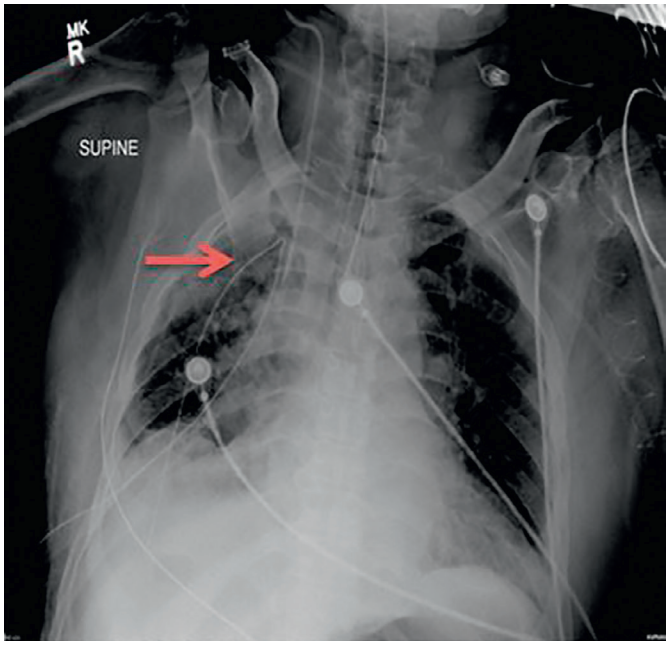
• **Fig. 15.11** Sequence of insertion of surgical tube thoracostomy (from A to G) with confirmation of placement intrathoracically (H) and radiographically (I) after the procedure. It is critical to identify patient landmarks between the anterior and posterior axillary lines. Obtaining a follow-up chest radiograph is a mandatory step to confirm position after tube placement.

Predictive tools have been created to best triage and treat prolonged air leaks, although these tools have not been adopted on a multiinstitutional scale.[53] In clinical practice, determination of the removal of the chest tube is made by the absence of worsening pneumothorax or subcutaneous emphysema (a prognosticator of pneumothorax) as well as absence of air leak with chest tube on water seal. In our practice, if pleural fluid drainage is less than 300 mL/day, the tube may be removed. Some other groups even recommend a threshold of drainage at less than 450 mL/day, demonstrating variability in clinical practice.[43] If the previous factors exist and the air leak is small and controlled on water seal, the clinician should ensure that there is no break in the tubing, and a provocative clamp trial can mimic removal of the tube. If pneumothorax worsens, then the chest tube is not ready to be removed. One must be aware of development of tension pneumothorax during the clamp trial and prepare the nursing staff and patient, with close monitoring during the duration of the trial. In our practice, we rarely perform provocative clamp trial (owing to patient safety), and subscribe to use of portable chest drainage systems such as a Heimlich valve (Becton, Dickinson and Company, Franklin Lakes, NJ) or Pneumostat chest drain valve (Maquet, Wayne, NJ), which allow resolution of air leak at home. Other groups use digital portable systems to monitor air leaks and send patients home without discontinuing the chest tube, although this is not commonplace across practice and quite expensive.[41,54] Finally, if air leak does not resolve, patients may require procedural interventions, including video-assisted thoracoscopy, thoracotomy, or endobronchial interventions, which are beyond the scope of this chapter.

Should a chest tube be removed at end-inspiration or end-expiration? At the end of expiration, the pleural and atmospheric pressure difference is minimized, decreasing the potential for "sucking air" into the pleural space. However, at end-inspiration, the lung is fully expanded, which may aid in pleural apposition and reduction of pneumothorax after the tube is removed. French and colleagues and others determined that there is no difference between the two strategies, as long as the patient maintains Valsalva maneuver throughout chest tube removal[55,56]; as such we recommend removing the chest tube at end-expiration. We do not obtain a radiograph after the chest tube is removed provided the removal was uncomplicated, because up to 25% to 30% of patients may have a clinically insignificant pneumothorax.



• **Fig. 15.12** A percutaneously placed chest tube entering the spleen *(arrow).* This complication can be avoided by choosing a higher intercostal space for insertion.



• **Fig. 15.13** Tubes can be malpositioned as seen on this postprocedure film. The nonfunctional kinked tube *(arrow)* should repositioned by pulling the tube back or replacing it.

Complications

Complications from tube thoracostomy insertion are avoidable in most cases. Described injuries include placement of the chest tube into bullae resulting in persistent air leak, placement in lung parenchyma with resultant bleeding, intercostal bundle trauma with bleeding, hemothorax, and insertion of chest tube into other organs (heart, liver, spleen, and so on) (Fig. 15.12). The most common complication is tube malpositioning (Fig. 15.13). With experience and proper technique and review of preprocedural imaging, these complications should be minimized.

Another unique complication is reexpansion pulmonary edema, which is related to the presence of mechanical injury to the alveolar-capillary membrane, resulting in reperfusion injury with reexpansion.[57] This may be related to the duration of the pneumothorax.[58] In the case of large, suspected long-standing pleural effusion or pneumothorax, some recommend slow reexpansion using lower suction or water seal, although it is likely the rate of reexpansion is more significant in creating lung injury than the amount of negative suction.

Key Points

1. Tube thoracostomy can be lifesaving but may be associated with serious complications. It should be performed only by experienced or adequately supervised operators.
2. The choice of the chest tube, including the size, the shape, and the insertion site, depends on the indication, the nature of the fluid to be drained, and its rate of formation.
3. Small-bore tubes are sufficient for the initial management of spontaneous and iatrogenic pneumothoraces, malignant and nonmalignant pleural effusions, parapneumonic effusions, and empyema.
4. Large-bore tubes are preferred for patients at risk for large air leak (e.g., mechanical ventilation, anastomosis dehiscence) or patients at high risk for tube obstruction (e.g., traumatic hemothorax).
5. Thoracic ultrasound should be routinely used to guide insertions of small-bore tubes.
6. In the hemodynamically unstable patient, the suspicion for tension pneumothorax should lead to immediate needle decompression followed by tube thoracostomy.
7. Blind insertion of chest tubes in patients with pleural adhesions, trapped lung, or suspected bullous disease can be dangerous. Imaging guidance with CT scan is recommended.
8. The most common complication of chest tube insertion is tube malpositioning.
9. Reexpansion pulmonary edema is a rare but serious complication, related to rapid drainage of air and fluid. Initial pleural fluid drainage should be limited to 1.5 L. Placement of the chest tube to water seal should be performed as soon as possible after tube insertion.

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Review Questions

1. In a patient with a spontaneous primary pneumothorax, which of the following is incorrect?
   - **a.** A small stable pneumothorax can be treated with either needle aspiration or small-bore chest tube insertion.
   - **b.** The first intervention for tension pneumothorax with instability is tube thoracostomy.
   - **c.** Large-bore chest tubes are equivalent to small-bore chest tubes with respect to resolution of pneumothorax.
   - **d.** It is appropriate to manage some primary spontaneous pneumothoraces with supportive care and serial radiographic observation.

   Answer: b. See the "Indications for Tube Thoracostomy" section.
2. Which of the following steps is *not* involved for surgical tube thoracostomy?
   - **a.** Consent, review of imaging before the procedure, and timeout
   - **b.** Infiltration of the intercostal space as well as incision with lidocaine
   - **c.** Pleural entry into the seventh intercostal space
   - **d.** Positioning of patient's arm across body
   - **e.** Position of patient's arm with arm stretched to open the axillary angle

   Answer: c. See the "Technique of Chest Tube Insertion" section.
3. Which of the following is not a possible complication associated with tube thoracostomy insertion?
   - **a.** Splenic or hepatic laceration
   - **b.** Parenchymal injury and hemothorax
   - **c.** Reexpansion pulmonary edema
   - **d.** Inadequate drainage of fluid collection
   - **e.** Plural fluid embolus

   Answer: e. See the "Complications" section.
4. Which of the following is incorrect when choosing chest tube size?
   - **a.** If the diameter of the tube is doubled, flow increases by a factor of 16.
   - **b.** Important issues are the quality of the drained material, its formation rate, the ability of the tube to remain patent, and for all or the majority of the collection being drained to be in communication with the tube.
   - **c.** Patient safety and comfort should also be considered.
   - **d.** Small-bore tubes are not as effective as large-bore tubes for most indications.

   Answer: d. See the "Optimal Chest Tube Size for Drainage" section.
5. Which of the following statements is false with respect to removal of chest tubes?
   - **a.** At the end of expiration, the pleural and atmospheric pressure difference is minimized, decreasing the potential for "sucking air" into the pleural space.
   - **b.** At end-inspiration, the lung is fully expanded, which may aid in pleural apposition and reduction of pneumothorax after the tube is removed.
   - **c.** Chest tubes should not be removed at the end of expiration.
   - **d.** Occlusive dressings should remain in place for at least 24 hours after chest tube removal.

   Answer: c. See the "Management of the Chest Tube and Troubleshooting" section.

16

Multimodality Intracranial Monitoring

ALAN R. TURTZ AND HAYAN DAYOUB

CHAPTER OUTLINE

Intracranial Pressure Monitoring
- Ventricular Catheter
- Fiberoptic Intracranial Pressure Monitors
- Catheter Tip Strain Gauge

Cerebral Blood Flow Monitoring

Brain Tissue Oxygenation Monitoring

Cerebral Microdialysis

Summary

Advancements in neuromonitoring techniques and improved understanding of the pathophysiology of brain injury have led to new developments in the field of neuro-critical care. This chapter reviews the fundamental tools of neuromonitoring: intracranial pressure (ICP), cerebral blood flow (CBF), brain tissue oxygenation, and cerebral microdialysis. These tools supplement the clinical neurologic examination and brain imaging in guiding patient care. Given that each tool has advantages and limitations, the choice of a single or combination monitoring strategies should be part of a rational management plan individualized for each patient.

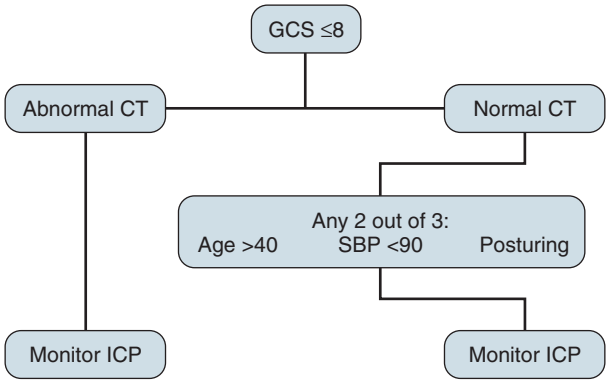
Intracranial Pressure Monitoring

The history of ICP monitoring dates to 1891, when Quincke measured the cerebrospinal fluid (CSF) pressure via a lumbar puncture.[1] Soon afterward, Cushing showed that as ICP increases and approaches systemic arterial pressure in an animal model, hypertension, bradycardia, and respiratory changes become evident.[2] The use of continuous ICP monitoring was first described by Guillaume and Janny[3] using an intraventricular catheter in 1951. Nine years later, Lundberg[4] published the first systematic observations of ICP and its response to medical and physiologic interventions. Using ventricular catheters, he showed the clinical value of direct ICP monitoring and described pressure waveforms, of which the Lundberg A wave has the most practical importance in the intensive care unit (ICU). These A, or plateau, waves were originally characterized by a steep increase in ICP to 60 to 80 mm Hg lasting 2 to 5 minutes or longer, followed by a rapid decrease to near-initial baseline pressures. This represents a pathologic response to decompensation of pressure controlling mechanisms.[4–6] Since these early investigations, CSF pressure and ICP measurement have been developed and refined further.

An ICP monitor is an invaluable research and clinical tool, contributing to the understanding of intracranial pathologic conditions and the assessment of therapeutic interventions. ICP monitoring can be used for patients with intracerebral hemorrhage, Reye syndrome, hepatic encephalopathy, encephalitis, stroke, hydrocephalus, near-drowning, and subarachnoid hemorrhage, but most of the clinical experience with ICP monitoring involves traumatic brain injury (TBI). In severe TBI, it is important to know if ICP is elevated. Early signs and symptoms of increased ICP include headache, lethargy, nausea, and vomiting. In critically ill patients, these clinical signs may be nonspecific and unreliable.[6] In addition, the positive trend toward early intubation and sedation, if not pharmacologic paralysis, eliminates the neurologic assessment of a patient with the exception of pupils. Even papilledema, a hard physical sign of increased ICP, is rarely seen acutely in patients with TBI.[7] Computed tomography (CT) is arguably the most useful diagnostic tool in patients with TBI, but may not reliably determine the ICP.

ICP monitoring in severe TBI has become routine because it facilitates rational management and provides prognostic information.[8–11] ICP monitoring can provide crucial information relative to cerebral perfusion pressure (CPP); detect the development or enlargement of a mass lesion, such as contusion or hematoma; facilitate the estimation of intracranial compliance; and be the only parameter to follow in a pharmacologically paralyzed patient, apart from the pupillary examination. It is rarely justifiable to treat a patient for intracranial hypertension empirically without a mechanism for measuring the effect of treatment, such as a clinical examination or ICP. The importance of clinical examination is highlighted by the findings of a study conducted in Bolivia and Ecuador that did not support the superiority of treatment based on ICP monitoring over treatment guided by neurologic testing and serial CT imaging in improving recovery in patients with severe TBI.[12] This study, referred to as the BEST:TRIP trial (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure), has been criticized; however, it does demonstrate the value of serial clinical examinations.[13]

There are well-defined guidelines from the Brain Trauma Foundation (BTF) for the use of ICP monitoring in TBI, which include patients with an abnormal CT scan and a Glasgow Coma Scale score of 8 or less after cardiopulmonary resuscitation. An abnormal CT scan is defined as one that reveals hematomas, contusion, edema, or compressed cisterns. It also is recommended to consider monitoring patients with severe head injuries with a Glasgow Coma Scale score of 8 or less even if the head CT scan



• **Fig. 16.1** Indications for intracranial pressure *(ICP)* monitoring. *CT,* Computed tomography; *GCS,* Glasgow Coma Scale score; *SBP,* systolic blood pressure. (From Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Management and prognosis of severe traumatic brain injury: Part I. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma.* 2000;17:47–69.)

is negative if two of the following three criteria are met on admission: age older than 40 years, systolic blood pressure less than 90 mm Hg, or signs of posturing (Fig. 16.1).[14] The BTF guidelines for ICP monitoring were modified in 2016 based on the limited studies with relatively high levels of scientific evidence.[15] This approach resulted in focused conclusions limited by study design and are, therefore, carefully worded to reflect the specific methodology of the study used to support specific a recommendation, hence the level IIB recommendation for patients with TBI: ICP monitoring is recommended to reduce in-hospital and 2-week postinjury mortality. Likewise, the BTF 2016 update for monitoring CPP, important information obtained from an ICP monitor, is equally limited to a specific Level IIB recommendation for CPP monitoring to decrease 2-week mortality.[15] These limited recommendations have not changed clinical practice based on previous BTF recommendations to monitor ICP and CPP for severe TBI patients. Although ICP monitoring can be a useful tool in the ICU, this technology has limitations. It is crucial not to assign undue weight to a normal ICP if other clinical information suggests otherwise. ICP does not always increase in the presence of midline shift.[16,17] More specifically, a temporal lobe mass can herniate over the tentorial edge and cause brainstem compression without a concomitant increase in ICP.[18,19] Likewise, there is not good correlation between supratentorial and infratentorial pressures,[20] so it is imperative to remember that the condition of patients with a posterior fossa mass can deteriorate rapidly without a significant increase in ICP measured in the supratentorial compartment.[6]

ICP waveform analysis includes systolic and diastolic pressures with superimposed respiratory variation; however, the mean pressure is of practical importance. A normal adult mean ICP is 10 mm Hg or less with transient physiologic elevations above this value seen in a head-down position or during a Valsalva maneuver (see Chapter 63).[6] The Association for the Advancement of Medical Instrumentation developed standards for ICP monitoring devices that require a pressure range from 0 to 100 mm Hg, an accuracy of ±2 mm Hg in the range of 0 to 20 mm Hg, and a maximal error of 10% between 20 mm Hg and 100 mm Hg.[21] There are three basic types of contemporary, clinically useful monitoring systems: ventricular catheter, fiberoptic device, and catheter tip strain gauge.

Ventricular Catheter

A ventriculostomy is the gold standard for ICP monitoring. It can be inserted through a twist drill craniostomy at the bedside and can also be used to drain CSF or for the estimation of intracranial compliance. The catheter is connected to a fluid-filled system, which is connected to an external transducer. The transducer converts the measured pressure to an electrical signal, which provides a waveform and numerical value displayed on a monitor through a signal processor. A three-way stopcock is used to divert CSF from the monitor to a drainage bag if needed. This setup allows the catheter to be zeroed as frequently as necessary with the transducer positioned at the level of the center of the brain, which generally corresponds to the external auditory meatus. The BTF has a specific Level III recommendation stating continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use. However, it is important to recognize that ICP cannot be accurately monitored when a standard ventricular catheter is open to drain.

This system has the potential to be contaminated and infected. The most significant risk of a ventriculostomy is infection; rates of 27% have been cited,[10,22–25] although most reported rates are in the 1% to 10% range.[24,26–29] Infection rates are similar regardless of procedure location (ICU or the operating room).[23,24,30] Tunneling the catheter subcutaneously to a distant skin exit site seems to reduce the infection risk. Other risk factors for infection include irrigation of the catheter or drainage system and the presence of intraventricular blood.[23,24,31] Duration of monitoring also may be a risk factor for infection. Some studies have found an increase in infection rates when ventriculostomies were left in place for longer than 5 days,[23,24,28] but more recent data reveal no significant reduction in infection rates when catheters were replaced before the fifth day.[32] Likewise, other investigators have found no significant relationship between duration of monitoring and rate of daily infection for 2 weeks.[33] The literature on the role of prophylactic antibiotics during external CSF drainage is also variable.[23,29,31,34] A BTF Level III recommendation discourages routine ventricular catheter exchange as well as prophylactic antibiotics for ventricular catheter placement.[35] Antibiotic-impregnated catheters have been shown to reduce infection rates[36] and are being used routinely in some centers.

Hemorrhage at the time of placement occurs about 1% to 2% of the time and only rarely needs to be surgically evacuated.[6,28,37] A more common problem with placement is difficulty in accessing small, compressed, or shifted ventricles, resulting in malposition and a poor waveform. Although a ventriculostomy is generally considered the most precise and accurate method of measuring ICP,[38] malfunction occurs if the ventriculostomy becomes clogged with air, blood, or debris, or if the ventricles are collapsed around the fenestrations in the catheter tip.

In addition to its primary use as an ICP monitor, a ventriculostomy is commonly used in the ICU as a drain for patients with TBI or hydrocephalus. Common causes of acute hydrocephalus in an adult ICU include cerebellar stroke or hemorrhage, intraventricular hemorrhage, and aneurysmal subarachnoid hemorrhage. A common and often debated concern regarding CSF drainage with a ventriculostomy is that it can cause subfalcine herniation in the presence of a hemispheric mass or upward herniation of the cerebellum in the presence of an infratentorial lesion.[39] Under these circumstances, we believe that surgical decompression of the primary mass also should be considered. Another potential risk of ventricular catheter insertion is aneurysmal rebleeding[40] after an

acute subarachnoid hemorrhage. Our group's opinion is that the benefit of treating hydrocephalus with high ICP outweighs the small, potential risk of aneurysmal rebleeding, and we have a low threshold for placing a ventriculostomy in these patients and carefully drain CSF.

If a ventriculostomy is primarily used for drainage of CSF, adequate spontaneous CSF resorption must be restored before the catheter can be safely removed. CSF resorptive capacity must be gauged according to the CSF drainage rate. Adjusting the height of the drainage system drip chamber controls the rate of external CSF drainage and the ICP that must be exceeded before drainage occurs. It can be assumed that 1 cm of CSF equals 1 cm H_2O. The height of the drip chamber is measured from the same external anatomic landmark as the ICP transducer, ranging from 0 to 20 cm (approximately 15 mm Hg) above the external auditory meatus in usual circumstances.

To reduce the amount of external CSF drainage, the drip chamber is usually raised by incremental amounts every 12 to 24 hours. As this is done, CSF resorptive mechanisms are gradually challenged. If CSF resorption is insufficient, most of the CSF continues to drain through the ventriculostomy, but if CSF resorption is sufficient, little CSF drains externally. When CSF resorption seems to be sufficient, CSF drainage is stopped, and ICP is monitored for 24 hours or more to confirm that spontaneous CSF resorption is adequate and ICP will not increase to dangerous levels. A confirmatory CT scan may also be useful.

We generally manage ventriculostomies for hydrocephalus by leaving the reservoir open to drain at a specific height above the ear and close it every hour for an ICP reading. In hydrocephalus, the ICP should never be significantly higher than the gradient the patient is draining against (i.e., the height of the drip chamber). We also specify our drainage gradient in millimeters of mercury to correlate the drip chamber to the monitor, and manually correlate the height of the CSF column in the drainage system with the monitor as a system check at least daily. A typical order may read: "leave ventriculostomy open to drain at 15 mm Hg (20 cm CSF) above the ear and monitor ICP every hour." ICP readings with the drain open are inaccurate as stated earlier, and the drainage port needs to be temporarily clamped when measuring an ICP. Likewise, the drain should be clamped and placed to monitor when changing position or during transport to avoid overdrainage, which may cause ventricular collapse and possibly subdural bleeding.

Fiberoptic Intracranial Pressure Monitors

Fiberoptic ICP monitors use miniature transducers that are coupled via fiberoptic cables to an external instrument. These monitors can be placed at the bedside through a standard twist drill craniostomy or through a smaller opening made with a 2.71-mm bit. The transducer is incorporated into the end of a tube and can be used alone or in combination with a ventriculostomy. Fiberoptic systems operate by projecting light through an optic fiber to a miniature, displaceable mirror in the catheter tip.[41] The amount of light reflected to a collecting optic fiber depends on the mechanical displacement of the mirror, which is a function of ICP. Fiberoptic devices can be inserted into the lateral ventricle, the brain parenchyma, or the subdural space. The greatest advantage of fiberoptic catheters is that they do not require fluid coupling for pressure transduction, which avoids the problems of waveform dampening and artifacts from poor coupling. Because they do not require fluid coupling, there also is less opportunity for contamination. The mechanism that does the actual pressure transduction is what is inserted into the patient; the system functions independent of head position and the monitor is zeroed once before it is placed. This feature also is a disadvantage because the transducer cannot be recalibrated to zero after insertion, although newer designs do not require zeroing. System accuracy compared with a ventriculostomy has been shown in the subdural space, brain parenchyma, and ventricles, although the parenchymal fiberoptic pressures may consistently exceed ventriculostomy pressures by nearly 10 mm Hg.[42–44] The fiberoptic device has an average daily drift of ±0.6 mm Hg. Over a 5-day period, there is an average drift of 2.1 mm Hg with a maximal drift of ±6 mm Hg. This drift over time may be enough to necessitate replacement if ICP monitoring is required for more than 5 days.[6,44,45]

Complications with the use of fiberoptic catheters relating to hemorrhage[46,47] and infection[46] have been reported, but our experience is that clinically relevant problems are unusual, particularly with intraparenchymal monitors. We do exercise caution, however, in patients with coagulopathy.

Catheter Tip Strain Gauge

The catheter tip strain gauge consists of a miniaturized solid-state pressure sensor mounted in a titanium case at the tip of a long, thin, flexible nylon tube. The transducer tip contains a silicon microchip with diffuse piezoresistive strain gauges that connect to tiny wires that travel the length of the tube. This is a small wire with a diameter of 1.2 mm that can be placed at the bedside. It can be incorporated into a ventricular catheter and used in any intracranial space. This device is accurate with a low daily drift range between −0.125 mm Hg and ±0.110 mm Hg. It shares many of the advantages and disadvantages of fiberoptic devices.[6,48,49]

Cerebral Blood Flow Monitoring

The primary objective concerning the ICU management of patients with brain injuries is the prevention and management of secondary injury in an effort to prevent ischemia. We typically monitor ICP and mean arterial blood pressure continuously, which allows us to calculate CPP; CPP = MAP − ICP, where MAP is mean arterial pressure. Under normal circumstances, knowing the CPP allows a good estimation of CBF, which is a more direct measure of blood supply to the brain. In head injury, the relationship between CPP and CBF is less predictable owing to local injury or to disruption of natural mechanisms of autoregulation. An ideal intracranial monitor would provide direct, continuous measurements of regional and global CBF at the bedside.

Measuring CBF outside the ICU began with Kety and Schmidt in 1948 and more recently has been done with xenon-enhanced CT,[50,51] but these methods provide only snapshots of CBF and do not allow for continuous monitoring at the bedside.[52] Continuous monitoring techniques in the ICU are classified as direct or indirect. Direct and continuous monitoring of CBF at the bedside includes laser Doppler flowmetry and thermal diffusion.

The laser Doppler flow sensor (1.5-mm diameter), which emits a monochromatic light, is placed into the white matter through a burr hole. The sensor measures the volume or concentration of red blood cells and their velocity and generates a flow signal. Although laser Doppler flow does allow continuous measurements of perfusion, the sample volume is small (1 mm^3) and only relative changes can be determined. Laser Doppler flow provides a qualitative estimate of regional CBF displayed in arbitrary units.[53] A

quantitative estimate of regional CBF can be acquired with the thermal diffusion method.[54] With this technique, a probe with two small thermistors is inserted into the brain to measure the tissue's ability to dissipate heat, and a microprocessor converts this into CBF displayed in the standard units of mL/100 g per minute.[52]

An indirect method for measuring blood flow at the bedside is transcranial Doppler ultrasound, which measures mean blood flow velocity in the basal cerebral vessels.[55] Although not equivalent to volume flow, changes in CBF can be inferred from changes in blood flow velocity.[56] Continuous transcranial Doppler monitoring is still cumbersome, however, because of problems of probe fixation to the head and computer interfacing.[52] Another indirect way of continuously monitoring CBF at the bedside is by measuring jugular venous bulb oxygenation.

Normal mean CBF is approximately 55 mL/100 g per minute with higher flow in the gray matter and lower flow in the white matter. When hemoglobin is fully saturated with oxygen, arterial blood carries approximately 20 mL of oxygen per deciliter to the brain. The oxygen content of venous blood draining the brain varies and depends primarily on how much oxygen the brain extracts. Normal internal jugular hemoglobin oxygen saturation ranges from 55% to 69%, and the normal difference between the arterial and jugular venous oxygen content (arteriojugular difference [$AJDO_2$]) is 6.3 ± 2.4 mL/dL. Stated differently, under normal circumstances, the brain extracts 6.3 ± 2.4 mL/dL of oxygen from the arterial blood to meet the metabolic needs of the brain.

Normally, the cerebral metabolic rate of oxygen ($CMRO_2$) is coupled to CBF; as demand increases, supply increases, and vice versa. In head injury, there may be a problem with supply (i.e., CBF may be compromised). If there is inadequate CBF to meet the metabolic demands of the brain, more oxygen is extracted from the available blood. Under this circumstance, the difference between blood going into the brain and blood coming out of the brain increases; $AJDO_2$ increases as the oxygen saturation in the jugular vein decreases.

$AJDO_2$ is proportional to $CMRO_2$ or inversely proportional to CBF or both.[57–60] Assuming that the $CMRO_2$ is constant, an increase in the amount of oxygen extraction—as reflected by a decrease in jugular oxygen saturation (increased $AJDO_2$)—implies that CBF has been compromised. Conversely, if $AJDO_2$ decreases and metabolism remains constant, we can infer an increase in CBF (i.e., hyperemia). Measuring jugular bulb oxygen can be a useful way to monitor a patient who requires hyperventilation for ICP control (see Chapter 63). Hyperventilation is a powerful tool for reducing ICP and enhancing CPP, but at the expense of increasing cerebrovascular resistance, with the consequent reduction of blood in the brain. The goal of treatment is to prevent ischemia, the ultimate and proximate cause of secondary injury. There is an obvious conflict when attempting to prevent ischemia by reducing the amount of blood delivered to the brain. $AJDO_2$ is sensitive to changes in cerebrovascular resistance; jugular vein monitoring may reveal inappropriate reductions of CBF as a result of hyperventilation.[57]

Most of the data concerning jugular bulb monitoring come from the trauma literature. In a prospective study of 353 patients with severe TBI, Cruz[61] found that outcome at 6 months was significantly better in the patients who had monitoring and management of cerebral extraction of oxygen along with CPP compared with the patients undergoing monitoring and management of CPP alone.

Increased $AJDO_2$ also can be detected during the early phases of head injury when CBF is pathologically reduced. Typically, the patient is being rescued at the scene, transported, and has triage during this early phase of injury, when CBF is low and ventilation is not carefully titrated. Hyperventilation is frequently used during this vulnerable period, often empirically and sometimes inadvertently.[57,62] Complicating this scenario is superimposed hypotension and hypoxia, which can occur during the early phases of resuscitation and later in the ICU.[63–65] Despite its usefulness, there are significant limitations to this monitoring technique. Measurements can be done by intermittent sampling, which is accurate but is limited by intermittent information, or continuous monitoring of oxygen saturation using fiberoptic catheters, which require careful maintenance and have reliability issues.[58,66]

It is easier to use the oxygen saturation of the venous blood in the jugular, rather than direct measurements of oxygen content, but because the percentage of oxygen saturation in the jugular bulb depends on hemoglobin concentration, it cannot be used independently for estimating the relationship between $CMRO_2$ and CBF. If the patient is anemic, more oxygen may be extracted from the available blood, even under conditions of normal CBF. When measuring oxygen saturation, $AJDO_2$ needs to be calculated, taking the hemoglobin concentration into consideration. Also, $AJDO_2$ is an overall estimate of the global relationship between CBF and $CMRO_2$ and cannot differentiate focal abnormalities. In addition, there is a limit to how much oxygen can be extracted from the available blood. If maximal extraction is reached and CBF continues to deteriorate, the $AJDO_2$ does not continue to increase. Under this circumstance, $AJDO_2$ appears stable despite a progressively worsening situation. Other pitfalls in monitoring $AJDO_2$ are observed under conditions in which oxygen extraction itself is impaired, such as in cases of mitochondrial dysfunction or a large stroke in which oxygen is not extracted at all.[57]

Several important technical factors are associated with $AJDO_2$ monitoring. The side chosen (right or left jugular bulb) for monitoring is important and can be affected by the side of the brain with the most injury regardless of whether it is the side of dominant venous drainage.[67–69] How high the tip of the catheter is positioned is another consideration and requires x-ray confirmation.[70] The speed at which samples are drawn also may affect the results.[71] Complications are uncommon and include carotid puncture[58,72] and subclinical internal jugular vein thrombosis.[72]

Ultimately, jugular bulb monitoring is geared toward the assessment of global CBF and cerebral oxygenation and can be useful in guiding therapeutic hyperventilation.[73,74] In severe TBI, there is enough evidence to recommend its use for titrating the level of hyperventilation[75]; however, some clinicians find jugular bulb monitoring to be cumbersome, to be prone to artifact, and to have other potential problems with poor data quality.[76–78] Because of all the problems involved with this technique, monitoring of $AJDO_2$ has not been universally accepted as a useful tool in the routine management of patients with head injuries, and the BTF 2016 update classifies the evidence for its support as Level III: "Jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 months post-injury."

Brain Tissue Oxygenation Monitoring

Brain tissue oxygen tension ($PbrO_2$) can be directly measured using a small flexible microcatheter (<0.5 mm in diameter) that is usually inserted into the frontal white matter and fixed onto a special bolt. The normal $PbrO_2$ is approximately 40 mm Hg.[79–83] Cerebral oxygen tension is generally reflective of CBF and local

oxygen extraction. In this sense, $PbrO_2$ may represent the "pool of oxygen" in brain tissue.[52,84,85] Changes in $PbrO_2$ can be used to monitor evolving disturbances of tissue metabolism.[76,86–88]

Ischemic damage seems to correlate to a $PbrO_2$ less than 8 to 10 mm Hg as measured by a Licox catheter (Integra Neuro Sciences, Plainsboro, NJ).[76] A systematic review of the literature on $PbrO_2$ monitoring found a total of 5676 patients across 6 studies where outcome measures, including mortality, Glasgow Outcome Scale, and Functional Independence Measure (FIM), at various time points showed inconsistent data to support the routine use of $PbrO_2$.[15] If $PbrO_2$ is being monitored, we recommend using it in conjunction with ICP and CPP monitoring and to set the threshold for intervention at $PbrO_2$ of 20 to 25 mmHg.

Local cerebral hypoxia in the presence of normal ICP, CPP, and mean blood pressure may be caused by insufficient arterial oxygenation,[86] a mismatch between supply (CBF) and demand ($CMRO_2$),[89] or hyperventilation-induced hypocapnia.[86,90] Hyperventilation can decrease $PbrO_2$ because of decreased CBF, which can negate the perceived benefit of improving ICP and CPP.[76,87,90–96] Hyperventilation has a particular risk of causing cerebral hypoxia when the partial pressure of carbon dioxide is less than or equal to 30 mm Hg, or within the first 24 hours[92,93] because of a further reduction of an already reduced CBF.[97] $PbrO_2$ has been shown not to be independently influenced by increases in CPP greater than 60 mm Hg,[78,87,96] which supports more recent evidence suggesting that maintaining a CPP greater than 60 mm Hg may be unnecessary,[98,99] and is consistent with current guidelines to keep CPP in the range of 60 to 70 mm Hg in severe TBI.[15]

When strategically placed, these monitors can detect local tissue hypoxia at the tip of the probe. An inherent problem with this technique (as with all focal monitors) is that placement of the probe into the area of interest becomes important.[52] There are rational arguments as to the best region to monitor. $PbrO_2$ values close to a contusion are smaller relative to a region that looks normal on a CT scan.[100] Some authors recommend monitoring the zone surrounding a contusion because of its high risk of tissue death. Other authors place the probes in uninjured brain with the idea being that a reduction in the $PbrO_2$ in the uninjured hemisphere is reflecting a diffuse decrease in arterial oxygenation, an increase in ICP, a decrease in CPP, overaggressive hyperventilation, or some other global event.[76]

Cerebral Microdialysis

Microdialysis is an established research tool to study the chemical composition of tissue extracellular fluids. The technology has been adapted for clinical use and to measure the extracellular concentration of standard neurochemicals at the insertion site within the brain tissue. This is achieved by the insertion of a double-lumen microcatheter fitted with a semipermeable membrane at the tip into or near the area of injured brain. Artificial CSF perfusate is pumped through the perfusion lumen at a standard rate of 0.3 μL/min and passes along the inside of the semipermeable membrane at the catheter tip. The chemical substances diffuse across the membrane according to their concentration gradient and the dialysate fluid is collected from the microdialysis catheter at a constant rate for analysis. Sampling can be done at 20-minute to 1-hour intervals. The concentration of extracellular glucose, lactate, pyruvate, glycerol, or glutamate can be measured from the dialysate at the bedside or in the laboratory, and lactate:pyruvate ratio (LPR) is a helpful calculation to estimate ischemia. The technology can also measure the concentration of other substances, such as proteins, cytokines, antibiotics, or drugs.[101] The normal value range for these substances are glucose ~2 mM, lactate ~2 mM, pyruvate ~120 μM, LPR 15 to 20, glycerol ~20 μM, and glutamate less than 10 μM.

Glucose levels should be interpreted in association with serum glucose levels. In the setting of ischemia or decreased cerebral perfusion, the **microdialysis** glucose (MD-glucose) level is low, the MD-lactate level is high, the LPR is high, and the MD-glutamate and MD-glycerol levels are also elevated owing to cell toxicity and destruction, respectively.

Microdialysis is a powerful research and clinical tool; however, its use has been limited to academic centers, and high-level evidence to support its use or correlate it with improved outcome is lacking.[15]

Summary

Most intracranial monitoring techniques are used for circumstances involving increased ICP, which has proven to be useful, reliable, and straightforward. As such, ICP and CPP monitoring has become a standard of care and both are widely used. It is much more difficult to obtain continuous, clinically useful information with CBF monitoring methods, and these methods have found limited use outside academic institutions. Newer advanced neuromonitoring techniques such as brain tissue oxygen monitoring and cerebral microdialysis are promising; however, evidence to justify their widespread use and impact on outcomes remains to be seen.

Key Points

- The primary objective concerning ICU management of patients with brain injuries is the prevention and management of secondary injury in an effort to prevent ischemia.
- ICP monitoring should be considered for patients with TBI and a Glasgow Coma Scale score of 8 or less.
- ICP monitoring in severe TBI has become routine because it facilitates rational management and provides prognostic information.
- It is crucial not to assign undue weight to a normal ICP if other clinical information suggests otherwise.
- A normal adult mean ICP is 10 mm Hg or less with transient physiologic elevations above this value, and normal CPP is generally 60 to 80 mm Hg.
- Ventriculostomies and fiberoptic intraparenchymal monitors are the mainstays of ICP monitoring devices.
- Local cerebral hypoxia in the presence of normal ICP, CPP, and mean blood pressure may be caused by insufficient arterial oxygenation, a mismatch between supply (CBF) and demand ($CMRO_2$), or hyperventilation-induced hypocapnia.
- Hyperventilation has a particular risk of causing cerebral hypoxia when the partial pressure of carbon dioxide is less than or equal to 30 mm Hg, or within the first 24 hours.
- Maintain CPP in the range of 60 to 70 mm Hg in severe TBI.

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Review Questions

1. Which of the following statements regarding fiberoptic intracranial pressure (ICP) monitors and ventriculostomies is most correct?

a. Either device allows drainage of CSF.
b. The infection rates are equal in both devices.
c. The drift in measurements is equal in both.
d. Ventriculostomy is considered the gold standard for ICP monitoring.

Answer: d. Ventriculostomy is considered the gold standard for ICP monitoring and, in addition to measuring ICP, it allows for cerebral spinal fluid (CSF) drainage as an intervention to lower ICP. There is, however, a slightly higher risk of infection associated with ventriculostomy. Therefore a protocol for infection control should be in place for intravenous antibiotics before insertion, externalizing the drain 5 cm from the insertion site and the use of antibiotic-impregnated catheters are all measures that lower infection rate. The fiberoptic ICP monitor has the potential for drift (±0.6 mm Hg/day) and therefore the ICP measurements could become inaccurate after several days of insertion.

2. Which one of the following statements is most correct?

a. CPP (cerebral perfusion pressure) = MAP (mean arterial pressure) − ICP (intracranial pressure).
b. CBF (cerebral blood flow) can be accurately inferred from CPP despite brain injury.
c. The 2016 Brain Trauma Foundation guidelines for traumatic brain injury management recommend maintaining a CPP of 80 to 90 mm Hg.
d. Local brain swelling increases blood flow in that area.

Answer: d. The CPP is measured by subtracting the ICP from the MAP: CPP = MAP − ICP. CBF can be inferred from the CPP in the normal physiologic state. However, in the setting of brain injury when autoregulation is impaired, the CBF could be significantly increased for a given CPP or it could be decreased in the setting of local swelling or injury. The 2016 Brain Trauma Foundation recommendations are to maintain CPP of 60 to 70 mm Hg.

3. In a 26-year-old patient with severe head injury and a Glasgow Coma Scale score of 7, an emergent computed tomography scan showed blossoming contusions in the left frontal and temporal lobes with uncal herniation, and he received emergent left craniectomy. He now has a right-sided ventriculostomy. Which of the following statements is correct?

a. The ICP waves may be dampened or lose their triphasic character.
b. In the setting of craniectomy, we can accept higher ICP measurements before intervention.
c. The swelling over the craniectomy site is a reliable indicator of the ICP.
d. The risk of ventriculostomy site infection is high in this setting, and continuous prophylactic antibiotics should be given.

Answer: a. In the setting of craniectomy the ICP waves may be dampened or may lose the characteristic triphasic wave appearance. The mean ICP values, however, are useful in assessing the ICP and can guide management. ICP and CPP management protocols do not change after craniectomy, and high ICPs should be managed accordingly. The scalp and soft tissues over the craniectomy site can swell after surgery, and swelling in itself is not a reliable indicator of increased ICP. There is currently no evidence to support continued prophylactic antibiotics use to prevent ventriculostomy site infection.

17

Gastrointestinal Endoscopy

KEVIN C. GORDON AND ADAM B. ELFANT

CHAPTER OUTLINE

History
Endoscopic Equipment
Anesthesia
Esophagogastroduodenoscopy
Wireless Capsule Endoscopy
Enteroscopy
Colonoscopy
Endoscopic Retrograde Cholangiopancreatography
Endoscopic Ultrasound
Endoscopy in the Pregnant Patient

History

The first gastroscopy procedure was performed in 1868 by German physician Adolph Kussmaul, with passage of a rigid metal tube down a patient's esophagus into the stomach. In 1932, Rudolph Schindler, in collaboration with a German engineer, Georg Wolff, developed a semiflexible instrument with a flexible distal shaft. Although this device was hailed as the first safe, workable gastroscope, it was not without limitation, including incomplete visualization of the esophagus and stomach, patient discomfort, and absence of photographic capability.[1,2] Fiberoptics were introduced into the endoscope in 1957 by Basil Hirschowitz, and in the 1960s and 1970s advancements were made with endoscope length, improved visualization, and greater control. Video cameras and monitors were subsequently incorporated into endoscopic technology, allowing others to view what was previously available only to the endoscopist.

Early experience with rigid and semiflexible proctosigmoidoscopes and colonoscopes was disappointing owing to the tortuous nature of the left colon, and early fiberoptic instruments fared no better. Bergein Overholt made adjustments in torque and control to develop a prototype flexible fiberoptic instrument in 1963.[3] The first total colonoscopy was performed in Sardinia, Italy, in 1965. Luciano Provenzale and Antonio Revignas instructed a patient to swallow a piece of polyvinyl tubing, which ultimately emerged from the anus. They attached a side-viewing gastroscope and gently pulled it through the entire colon to the cecum.[3] Further refinements were achieved in England, the United States, and Japan, and in 1969 Hiromi Shinya performed the first polypectomy, removing a 1.5-cm pedunculated polyp from the sigmoid colon of a 70-year-old Chinese gentleman.[4] Subsequently, colonoscopy has become a routine procedure performed by gastroenterologists and other health care providers.

Endoscopic cannulation of the duodenal ampulla was first accomplished in Chicago by William S. McCune and colleagues in 1968 and is considered the first reported case of endoscopic retrograde cholangiopancreatography (ERCP).[5] Sphincterotomy was initially performed in 1974, facilitating removal of common bile duct stones[6] and ushering in a new era of therapeutic pancreaticobiliary endoscopy.

The first transrectal ultrasound examination was performed by physician John Julian Wild and electrical engineer John Reid in 1956, when they developed the ultrasound probe.[7] The incorporation of ultrasound into a standard endoscope occurred in 1976, when Lutz and Rosch passed an ultrasound probe through the accessory port of an endoscope. Further improvements were achieved by Strohm and colleagues and Eugene DiMagno and coworkers, who introduced their own prototype echoendoscopes in 1980.[8] The first endoscopic ultrasound (EUS)-guided fine-needle aspiration was performed on a submucosal gastric lesion in 1991 by Giancarlo Caletti.[8]

Novel innovative endoscopic techniques continue to expand the field of gastroenterology. Peroral endoscopic myomoty was the first endoscopic procedure to go beyond the gastrointestinal (GI) lumen for therapeutic intervention. This was first performed by Inoue et al. in 2008 in Japan to treat severe achalasia. In 2010, Santiago Horgan continued the trend of extraluminal therapy by removing a gallbladder transorally using natural orifice transluminal endoscopic surgery.[8a] Endoscopic bariatric therapy is providing adjunctive therapy for obesity treatment, starting with transoral gastroplasty in 2008 by Eagon and Jonnalagadda in the United States.[8b] Development of antiobesity therapies are continuing to blur the lines between traditional surgical bariatric and endoscopic modalities.[9]

Endoscopic Equipment

Today's endoscopes have a control section that is grasped with the left hand to allow for scope control and passage of therapeutic instruments. An insertion tube extends from the bottom of the control section and is grasped with the right hand and inserted into the patient. Buttons on the control section allow for suction, insufflation, and washing of the lens. Channel ports distal to the hand controls on the control section allow for the passage of various accessories. Four-way tip deflection is accomplished through manipulation of control knobs, which are attached to a series of

TABLE 17.1 Levels of Sedation and Anesthesia

Anesthesia Management Component	Minimal Sedation (Anxiolysis)	Moderate Sedation (Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Adapted from American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology.* 2002;96:1004–1017.

cables that run the length of the insertion tube. The distal end of all endoscopes contains lenses for imaging and channel openings for air, water, suction, and passage of instruments.

EUS equipment differs from that of standard endoscopes in that an ultrasound transducer is incorporated into the distal end of the insertion tube. The transducer emits sound waves that are directed at adjacent tissues that deflect different acoustic qualities back to the transducer. Radial and linear echoendoscopes are currently available. Interventional procedures, such as fine-needle aspiration, therapeutic injections, placement of radiopaque markers to guide radiotherapy, as well as stent deployment, may be performed safely.[10]

All video endoscopes have an image sensor called a charge-coupled device (CCD) mounted at the tip of the endoscope, which transmits an image to a video processor for display. Advances in CCD technology have resulted in the current high-resolution or high-definition endoscopes, which produce signal image resolutions that range from 850,000 pixels to more than 1 million pixels, allowing for detailed inspection of the GI mucosa.[11]

The wireless video capsule is a small disposable unit containing a small camera, short focal length lens, light source, two batteries, and a radio telemetry transmitter.[12] There are presently three types of video capsules: an esophagus-specific capsule incorporating two CCD chips oriented at 180 degrees, a small bowel video capsule using a single CCD chip with an 8-hour battery capacity, and experimental colonic video capsules. Two to six frames per second are captured by the small bowel camera and transmitted to a data recorder that is carried by the patient. The colonic video capsule can record up to 35 frames per second with a battery life of 10 hours or longer. Data are downloaded from the recorder to a personal computer and interpreted. Handheld devices have also been developed to allow real-time monitoring of video capsule images.

Anesthesia

The choice of anesthesia is based on the patient profile, the endoscopic procedure, and the preference of the endoscopist, anesthesiologist, and patient. Essential patient information includes prior adverse events from anesthesia, current medications, pertinent medical history, cardiopulmonary status, age, allergies, body habitus, and social history. Patients with alcohol or narcotic dependency may require high doses of opiates and benzodiazepines. Agents such as propofol may facilitate their sedation. Pregnancy should be excluded in any woman of childbearing age. The level of sedation required depends on the endoscopic procedure and expected length of time necessary to complete it. Flexible sigmoidoscopy and esophagogastroduodenoscopy (EGD) may require minimal or moderate sedation, whereas more complex and lengthier procedures, such as ERCP and EUS, may require deep sedation or even general anesthesia. Table 17.1 illustrates the different depths of sedation as defined by The American Society of Anesthesiologists Task Force.[13]

Regardless of the type of sedation, cardiopulmonary status should be monitored at all times. Standard equipment should include a pulse oximeter, continuous electrocardiogram, and cyclical blood pressure monitoring. Personnel trained in airway support should always be present. The cardiopulmonary complication rate is 0.005% for EGD and 0.01% for colonoscopy.[14]

Four medication classes are commonly used during endoscopic procedures: pharyngeal topical anesthesia, benzodiazepines, opiates, and propofol. Pharyngeal anesthetics, such as lidocaine, benzocaine, and tetracaine, are used to suppress the gag reflex during upper GI tract procedures. These agents, applied by spray or gargling, are active for approximately 1 hour. Potential risks include aspiration owing to loss of gag reflex and, rarely, methemoglobinemia.[15]

Benzodiazepines, such as midazolam and diazepam, are used to induce relaxation and amnesia by binding to receptors of the postsynaptic gamma-aminobutyric acid neurons. Both have similar properties, with the latter possessing a longer half-life and milder amnestic properties.[16] Onset of action occurs in 1 to 2.5 minutes with intravenous midazolam and 8 minutes with diazepam.[17] Adverse reactions include respiratory depression and hypotension. Overdoses can be reversed with flumazenil, although caution should be used because seizures secondary to acute withdrawal may occur.

Opiates such as fentanyl and meperidine are used for analgesia and sedation. A synergistic effect occurs when opiates are given concurrently with intravenous benzodiazepines. Fentanyl has a rapid onset (1.5 minutes) with a short duration of action (0.5–1 hour), whereas meperidine has an onset of 5 minutes and lasts 3 to 5 hours.[17] Common adverse reactions include respiratory depression, hypotension, constipation, nausea, and vomiting. Overdosage can be reversed with naloxone, an opioid antagonist. Long-term opiate users may experience acute withdrawal symptoms with naloxone. Serotonin syndrome may occur if monoamine oxidase inhibitors are used with meperidine.

Propofol, an ultrashort-acting anesthetic agent, has been increasingly used in recent years.[18] Propofol has a rapid onset of action, deeper level of sedation, and more rapid recovery time compared with narcotics and benzodiazepines.[19] Propofol use during

• BOX 17.1 Indications for Esophagogastroduodenoscopy

Persistent upper abdominal symptoms despite appropriate therapy
Upper abdominal symptoms associated with signs or symptoms suggesting serious organic disease (anorexia, weight loss) or new-onset symptoms in patients older than 50 years of age
Dysphagia or odynophagia
Esophageal reflux symptoms (persistent or recurrent despite appropriate therapy)
Persistent vomiting of unknown cause
Familial adenomatous polyposis syndromes
Confirmation and specific histologic diagnosis of radiologically shown lesions
  Suspected neoplastic lesions
  Gastric or esophageal ulcer
  Upper tract stricture or obstruction
Gastrointestinal bleeding
  Active or recent bleed
  Suspected bleed (chronic blood loss, iron deficiency anemia)
Sampling of tissue or fluid
Documentation or treatment of varices (banding, sclerotherapy)
Assessment of acute injury after caustic ingestion
Treatment of bleeding lesions such as ulcers, tumors, vascular abnormalities (electrocoagulation, heater probe, laser photocoagulation, injection therapy)
Removal of foreign bodies
Removal of selected polypoid lesions
Dilation of stenotic lesions
Placement of feeding or drainage tubes (percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy)
Management of achalasia (botulinum toxin, balloon dilation)
Palliative treatment of neoplasms (laser, multipolar electrocoagulation, stent placement)
Surveillance for malignancy in patients with premalignant conditions (Barrett esophagus)

Adapted from ASGE Standards of Practice Committee, Early DS, Ben-Menahem T, et al. Appropriate use of gastrointestinal endoscopy. Gastrointest Endosc. *2012;75:1127–1131.*

• BOX 17.2 Contraindications to Esophagogastroduodenoscopy

Risk to patient's health or life judged to outweigh most favorable benefits of procedure
Conditions in which adequate patient cooperation or consent cannot be obtained
Perforated viscus—known or suspected

Adapted from ASGE Standards of Practice Committee, Early DS, Ben-Menahem T, et al. Appropriate use of gastrointestinal endoscopy. Gastrointest Endosc. *2012;75:1127–1131.*

colonoscopy may carry a lower risk of cardiopulmonary complications compared with traditional agents.[20] Controversy exists as to its cost-effectiveness and the requirement that it be administered exclusively under the supervision of an anesthesiologist.

Esophagogastroduodenoscopy

EGD is one of the most commonly performed procedures in the world and has become the primary tool for evaluating the esophagus, stomach, and proximal duodenum. EGD is performed for a wide variety of indications and has both diagnostic and therapeutic roles (Box 17.1). There are relatively few contraindications to upper endoscopy (Box 17.2).

EGD is a safe procedure. Perforation occurs in approximately 0.04% of diagnostic endoscopies and up to 10% with therapeutic interventions, including dilation and endoscopic mucosal resection.[21] Clinically significant bleeding is a rare adverse event and may occur as a result of Mallory-Weiss tear, cautery injury, sclerotherapy injection, and after biopsy or polypectomy.

Before undergoing elective EGD, patients should be fasting for at least 6 hours. Motility agents, such as erythromycin, may be beneficial in clearing the stomach of blood or food.[22] In situations of possible airway compromise, elective intubation is reasonable. In a meta-analysis evaluating prophylactic intubation before endoscopy for upper GI bleeding, there was a higher rate of aspiration, pneumonia, and hospital length of stay in the intubated patients group.[23] Without published guidelines to direct use of endotracheal intubation in this group of patients, it is important to weight the risks and benefits of intubation for individual cases. Alternatives to intubation may include pre-endoscopy lavage, overtube placement, or the use of large-caliber endoscopes for suction.

Before administration of anesthesia, patients should be in the left lateral position, with the head elevated and supported by a pillow. Monitoring devices for vital signs, electrocardiogram, and pulse oximetry are attached, supplemental oxygen should be administered, and a bite guard should be placed in the mouth.

In addition to diagnostic capabilities, therapeutic interventions may be performed during upper endoscopy, particularly in the setting of GI hemorrhage. Several modalities are available for treating GI bleeding, including thermal cautery, electrocautery, needle injection, rubber band ligation, mechanical clips, laser therapy, argon plasma coagulation, and tissue adhesives.

Thermal cautery probes deliver predetermined pulses of heat (250°C) to an endoscopic catheter tip, which is transferred to tissue on contact.[24] Thermal probe coagulation can be applied to peptic ulcers, vascular lesions, and Mallory-Weiss tears. Another option for contact thermal coagulation is monopolar or bipolar electrocautery. With electrocautery, electrical current flows from electrode tip through contacted tissue. Monopolar cautery requires attaching an electrical ground to the patient and may cause burn injuries and tissue stickiness. Monopolar cautery is typically not used for hemostasis, but serves a role in snare polypectomy. Bipolar cautery consists of two active electrodes incorporated into a single catheter probe, allowing electrical current to pass from one electrode through the tissue and back to the other electrode. Consequently, bipolar cauterization allows for improved control of coagulation depth.

Injection therapy for nonvariceal and variceal bleeding is performed with sclerotherapy injector needles. Solutions commonly used are epinephrine in saline solution (1:10,000) and sclerosing agents, such as polidocanol and ethanolamine. Epinephrine reduces bleeding by vasoconstriction, vessel tamponade, and platelet aggregation.[25,26] The potential exists for systemic side effects from submucosal injections as plasma epinephrine levels can transiently increase four to five times above basal levels.[27] Sclerosing agents achieve hemostasis through inflammation and sclerosis and have been used in peptic ulcer hemorrhage and variceal bleeding. Mediastinitis, perforation, stricture formation, and infection are among reported complications.[28]

Injector needles are also used in nonbleeding situations. Polyps and superficial mucosal lesions can be raised with submucosal injection of saline solution, epinephrine, or osmotic agents before polypectomy. This technique reduces the likelihood of

postpolypectomy hemorrhage or perforation.[29] Lesions requiring surgery can be tattooed with ink to facilitate localization by the surgeon.

Rubber band ligation is an effective tool for hemostasis. The delivery system is loaded onto the endoscope tip, and current models allow for deployment of multiple rubber bands before reloading. For variceal bleeding, endoscopic variceal ligation has become the treatment of choice and is superior to endoscopic sclerotherapy in speed of variceal eradication, decreased risk of recurrent bleeding, and fewer complications.[30] Endoscopic banding may be used to treat gastric varices, bleeding peptic ulcers, Dieulafoy lesions, postpolypectomy hemorrhage, and internal hemorrhoids.

Metal clips, or endoclips, have been used successfully for GI bleeding,[31] closure of perforations,[32] anastomotic leaks,[33] and prevention of postpolypectomy hemorrhage.[34] The potential for significant tissue injury is small as only the mucosal and submucosal layers are involved in the grasping.[35] The procedure may be technically challenging if massive bleeding is present, or the angle of approach is tangential to the target lesion.[36]

Laser therapy, using neodymium:yttrium-aluminum-garnet (Nd:YAG) or argon, is delivered through probes passed via the endoscope to treat bleeding lesions and for tumor ablation. Nd:YAG and argon lasers differ in the width and depth of tissue effect, with the former having the greater effect.[37] Advantages of laser therapy include improved accuracy and no requirement of direct contact with the desired target.

Argon plasma coagulation is a noncontact method of hemostasis that delivers argon gas through a catheter probe. The argon gas is ionized, delivering thermal energy to adjacent target tissue. Large areas and tissue not in direct view, owing to the tangential arcing nature of the argon gas, can be treated rapidly. Clinical uses include adjunctive ablative therapy after piecemeal resection of colonic polyps, radiation proctopathy, GI vascular lesions, bleeding peptic ulcers, Barrett esophagus ablation, and palliation of GI malignancies.[38,39]

Tissue adhesives constitute a newer class of agents for GI hemostasis. The major types of tissue adhesives are fibrin sealants and cyanoacrylate. Fibrin sealants form a coagulum through the interaction of fibrinogen, factor XIII, and thrombin.[40] Extensively used in the surgical fields for tissue adhesion, hemostasis, and wound care, fibrin sealants have been used endoscopically in bleeding peptic ulcers,[41] variceal bleeding,[42] and for closure of GI fistulas.[43] Cyanoacrylate is synthetic glue that rapidly polymerizes into a solid complex when in contact with water or blood.[44] Cyanoacrylate has been successfully used for ablation of esophageal and gastric varices.[45,46] Serious complications of tissue adhesives include embolization and infarction.[47]

In addition to hemostasis, upper endoscopy is routinely used for other therapeutic situations. Foreign object ingestion and food bolus impaction occur commonly. Although most esophageal foreign bodies pass spontaneously, up to 20% of cases may require endoscopic intervention. Various types of endoscopy, ranging from rigid to flexible, and equipment (Box 17.3) are available for foreign body retrieval. An overtube is available for airway protection and frequent esophageal intubations. Retrieval should be performed within 24 hours or more urgently if the ingested object is sharp, is a disc battery, or is causing the patient pain or difficulty in handling secretions. If it is not possible to remove the object endoscopically and it is less than 2.5 cm, the object can be gently maneuvered into the stomach, from which spontaneous passage usually occurs.[48] Unsuccessful removal or obstruction requires surgical evaluation.

• BOX 17.3 Devices Used for Foreign Body Retrieval

Overtube
Pronged forceps
Tooth forceps
Nets
Baskets
Retrieval loops
Magnetic extractors

Adapted from Nelson DB, Bosco JJ, Curtis WD, et al. The ASGE technology status evaluation report. Endoscopic retrieval devices. February 1999. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. *1999;50:932–934.*

Esophageal narrowing is a common reason for recurrent food impaction. Narrowing may occur from benign conditions, such as peptic strictures, Schatzki rings, eosinophilic esophagitis, or malignancy affecting luminal diameter. Endoscopic dilation can be performed on anatomic narrowings of the esophagus, pylorus, and anastomotic strictures. Four types of dilators are currently available: tip-weighted push bougies (Maloney or Hurst), wire-guided dilators (Savary-Gilliard or American), through-the-scope dilating balloons, and clear optical dilators that allow direct endoscopic visualization. Dilation is indicated in patients with achalasia, although recurrence is common, and clinical efficacy is decreased with subsequent dilations.[49] In general, endoscopic dilation increases the risk of perforation, with reported rates between 0.1% and 0.4%.[50]

Endoscopic stenting with endoprosthesis can be performed in a wide variety of clinical scenarios. Stenting is performed for fistula closure, anastomotic leaks,[51] malignant and nonmalignant perforations.[52,53] In addition, malignant obstructive lesions of the esophagus, stomach, duodenum, and colon can be stented for palliation or preoperative dilation. Stents vary in size, material (plastic or metal mesh), and by the presence or absence of a covering. Complications include increased reflux if the gastroesophageal junction is involved, bleeding, perforation, and stent migration.

Radiofrequency ablation of the distal esophagus has been developed as a treatment for low- and high-grade dysplasia in Barrett esophagus. The HALO system (Barrx Medical, Inc., Sunnyvale, CA) consists of a balloon that contains 60 separate 250-μm electrodes circumferentially oriented on its outer surface, with electrodes separated by a distance of 250 μm. Immediately adjacent electrodes function as bipolar devices that deliver heat to the mucosa at a controlled depth. Radiofrequency energy is delivered through the electrodes, which causes superficial tissue destruction circumferentially over a length of 3 cm. If focal ablation is needed, 60-degree, 90-degree, and ultralong focal ablation catheters are available.[54]

Percutaneous endoscopic gastrostomy (PEG) tube placement is a common procedure for endoscopists. The purpose of PEG tube placement is to improve quality of life, shorten hospitalization, prevent aspiration, improve nutritional and functional status, and prolong survival.[55] Controversy exists as to whether PEG tube placement is beneficial in patients with terminal anorexia-cachexia syndromes or in permanent vegetative states.[56,57] In addition to providing nutritional support, PEG placement has been used for long-term gastric decompression and recurrent gastric volvulus management. Placement is contraindicated if the anterior abdominal wall cannot be brought into contact with the anterior gastric wall, such as in morbid obesity and significant ascites. Complications,

although infrequent, include wound infection, necrotizing fasciitis, peritonitis, septicemia, peristomal leakage, device dislodgment, bowel perforation, and fistula formation.[57] Antibiotic prophylaxis is recommended for patients undergoing percutaneous feeding tube placement. Possible implantation metastasis in patients with head and neck cancer has been reported.[58] Pneumoperitoneum is seen in 40% of cases, but is usually asymptomatic and eventually resolves spontaneously.[59]

Wireless Capsule Endoscopy

Wireless video capsule endoscopy (VCE) is a safe, noninvasive method for visualizing the entire small bowel. The capsule examination typically is performed in an ambulatory setting. Preparation involves an overnight fast. Although data are conflicting, a bowel preparation has been shown to improve visualization and results in a higher rate of capsules reaching the small intestine.[60,61] Metoclopramide also may be beneficial in ensuring a complete small bowel evaluation before expiration of the battery life.[62] After swallowing the pill, the patient can leave the outpatient office, resume nonstrenuous daily activity, and eat 4 hours later. The data recorder is returned after 8 hours.

Common indications for VCE are evaluating obscure GI bleeding, suspected Crohn disease, small intestinal tumors and polyps, chronic diarrhea, malabsorption disorders, and abdominal pain.[63,64] VCE has been shown to be superior to push enteroscopy and small bowel barium radiography in detecting sources of obscure GI bleeding.[65] Superiority also was shown when VCE was compared with double-balloon enteroscopy.[66] A major limitation of VCE is the inability to perform therapeutic interventions.

Contraindications for VCE include swallowing disorders, known or suspected GI obstruction, stricture, fistula, pregnancy, and possibly cardiac pacemakers or implantable defibrillators. (Although listed as a contraindication by the manufacturer, more recent studies have shown no interference with cardiac pacemakers and implantable defibrillators by VCE.[67,68]) The capsule does not reach the cecum within recording time in 16% of cases. Abdominal x-ray study should be performed to evaluate for capsule retention, which occurs in 1.9% of all examinations, usually secondary to an anatomic abnormality, and may require endoscopic or surgical removal.[69,70] A patency system similar in size to a video capsule, but dissolvable if retained in the body, may be useful in screening high-risk patients for possible small bowel stenosis.[71] Patients with swallowing disorders or delayed gastric emptying may have the capsule endoscopically placed into the small bowel.

A variation of the small bowel video capsule exists to evaluate the esophagus. Although similar in design to the small bowel capsule, the esophageal video capsule incorporates a camera at each end, with each camera taking up to 35 frames per second for the first 10 minutes, followed by 18 frames per second for the final 80 minutes. Fasting time is only 2 hours, and the examination time is less than 1 hour. The patient ingests the pill in a supine position and is gradually raised to an upright position at 2-minute intervals. The esophageal video capsule can be used to evaluate for Barrett disease, esophageal varices, and complications of gastroesophageal reflux disease.

Enteroscopy

With increasing use of wireless capsule endoscopy, the need for direct visualization and therapeutic intervention in the small bowel is growing. Endoscopic techniques are emerging that improve visualization, allow for therapeutic intervention, and are less invasive than prior designs. The diagnostic yield of balloon endoscopy may reach 70% to 80% with histologic sampling and endoscopic therapy in more than 50% of patients.

Introduced in 2001, double-balloon enteroscopy (DBE) uses two balloons, one at the tip of an enteroscope, and the other at the end of an overtube backloaded onto the enteroscope. Using alternating inflation and deflation of the balloons during sequential advancement of the scope and the overtube, the double-balloon enteroscope is progressively advanced through the small bowel. Using both oral and anal intubation, evaluation of the entire small bowel is possible. Single-balloon enteroscopy (SBE) was introduced in 2007, and like DBE, incorporates a backloaded overtube with a balloon at the tip. Unlike the DBE, the tip of the scope is deflected to anchor the scope against the bowel wall and permit advancement of the overtube. After advancement, the balloon on the overtube can be inflated, the intestine pleated over the overtube, and the scope advanced once again. Severe complications from DBE are described in 1% to 1.7% of patients, with pancreatitis the most common (0.3%), followed by bleeding and perforation.[72] In one meta-analysis study, 622 SBE procedures were studied and only 2 perforations (0.032%) occurred with no episodes of pancreatitis.[73]

Spiral enteroscopy was developed with the potential advantages of decreased time and increased control in examining the small bowel. The enteroscope is advanced into the small bowel by continuous rotation of the raised helix-fitted overtube, which pleats the small bowel mucosa over the overtube. An inner sleeve allows the independent motion of the overtube during advancement and withdrawal.[74] Spiral enteroscopy has demonstrated a complication rate of 0.4% with perforation found to be the leading severe complication.[75]

Several studies have been performed comparing various combinations of each of the three modalities. A meta-analysis comparing SBE of 375 patients demonstrated that DBE offers deeper penetration into the small bowel.[76] There was no significant difference between DBE and SBE in therapeutic yield and complication rates. Spiral enteroscopy offers shorter procedure time when compared with balloon-assisted enteroscopy but no apparent difference in diagnostic yield.[77]

Colonoscopy

The colonoscope is used by general practitioners, surgeons, and gastroenterologists to evaluate the colon and distal ileum. A shorter version, the flexible sigmoidoscope, is available for rectum and sigmoid examination. Colonoscopy has replaced routine sigmoidoscopy and barium studies as the gold standard for large bowel evaluation. Indications range from colorectal screening and evaluation of anemia to therapeutic interventions such as polypectomy and palliative stenting (Box 17.4). Relative contraindications to colonoscopy are acute diverticulitis and suspected perforation.

Before colonoscopy, the patient should follow a clear liquid diet with subsequent fasting after bowel preparation. Several bowel preparations are commercially available, including polyethylene glycol, sodium-free polyethylene glycol, low-volume polyethylene glycol with bisacodyl, and tablet sodium phosphate.[78] Nausea, vomiting, and abdominal discomfort are common side effects among all bowel preparations. Sodium phosphate, owing to inducement of rapid volume changes, is contraindicated in patients with serum electrolyte abnormalities, advanced hepatic dysfunction, renal failure, recent myocardial infarction, unstable angina,

• BOX 17.4 Indications for Colonoscopy

Evaluation of abnormal imaging study
Evaluation of unexplained gastrointestinal bleeding
  Hematochezia
  Melena
  Presence of fecal occult blood
Unexplained iron deficiency anemia
Screening and surveillance for colonic neoplasia
Chronic inflammatory bowel disease
Clinically significant diarrhea of unexplained origin
Intraoperative identification of a lesion not apparent at surgery (polypectomy site, location of a bleeding site)
Treatment of bleeding from lesions such as vascular malformations, ulceration, neoplasia, and postpolypectomy site (electrocoagulation, heater probe, laser, or injection therapy)
Foreign body removal
Excision of polyp
Decompression of acute megacolon or sigmoid volvulus
Balloon dilation of stenotic lesions
Palliative treatment of stenosing or bleeding neoplasms (laser, electrocoagulation, stenting)
Marking a neoplasm for localization during surgery

Adapted from Adapted from ASGE Standards of Practice Committee, Early DS, Ben-Menahem T, et al. Appropriate use of gastrointestinal endoscopy. Gastrointest Endosc. *2012;75:1127–1131.*

• BOX 17.5 Indications for Endoscopic Retrograde Cholangiopancreatography

Treatment of choledocholithiasis
Treatment of biliary pancreatitis
Evaluation and treatment of recurrent pancreatitis
Evaluation and treatment of ascending cholangitis
Tissue sampling of suspected biliary and pancreatic malignancies
Diagnosis of ampullary tumors
Malignant and benign biliary stricture management (sphincterotomy, dilation, stent placement)
Photodynamic therapy
Diagnosis and treatment of biliary and pancreatic duct injury and leak
Pancreatic pseudocyst (stent)
Stent removal
Biliary manometry
Endoscopic sphincterotomy in type I sphincter of Oddi dysfunction
Endoscopic sphincterotomy in type II sphincter of Oddi dysfunction with manometry-confirmed pressure >40 mm Hg

Adapted from Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and pancreas. Gastrointest Endosc. *2005;62:1–8.*

congestive heart failure, ileus, malabsorption, and ascites.[79] One meta-analysis demonstrated that the use of a split-dose polyethylene glycol for bowel preparation before colonoscopy significantly improved the number of satisfactory bowel preparations, increased patient compliance, and decreased nausea compared with the full-dose polyethylene glycol.[80] Inadequate bowel preparation has been attributed to failure to follow preparation instructions; later colonoscopy start time; inpatient status; procedural indication of constipation; use of tricyclic antidepressants; male gender; and history of cirrhosis, stroke, or dementia.[81] Patients undergoing flexible sigmoidoscopy usually do not require complete bowel purgation. An enema before the procedure can assist in clearing the distal colon if incomplete preparation is suspected.

Complete colonoscopic examination is achieved in approximately 94% of patients.[82] Advanced age, female gender, body mass index less than 25 kg/m^2, diverticular disease in women, and a history of constipation or reported laxative abuse in men are predictors of a technically difficult colonoscopy.[83] In general, complications from diagnostic colonoscopy are rare. Hemorrhage and perforation occur in 0.001% to 0.008% and 0.005% to 0.14% of patients, respectively.[84] Interventional procedures, such as polypectomy, can increase the risk of bleeding and perforation to 2% and 0.3%.[85] Polypectomy is one of the most common interventions during colonoscopy. Pedunculated or sessile polyps may be removed with biopsy forceps, snare cautery, or argon plasma coagulation. As noted earlier, complications may be reduced with submucosal injection of saline solution or epinephrine.

Common causes of colonic hemorrhage include diverticulosis, postpolypectomy bleeding, vascular malformations, and hemorrhoids. Diverticular and postpolypectomy bleeding may be controlled with epinephrine injection, heater probe, electrocautery, or metallic clips. Band ligation also may be effective in hemostasis of postpolypectomy bleeds. Vascular malformations may be ablated with heater probe, electrocautery, laser, argon plasma coagulation, and metallic clips. Hemorrhoidal bleeding is effectively controlled with elastic band ligation, either with a rigid proctoscope or with a flexible video endoscope.[86]

Anastomotic strictures may occur from inflammatory bowel disease or postsurgical resection. These strictures may be dilated with balloon dilators or managed with self-expanding metallic stents.[87] Endoluminal stenting may be used as palliation or as a bridge to surgery for near-obstructive malignant lesions.[88] Laser therapy is another option for tumor ablation.[89]

Colonic decompression and placement of temporary rectal tubes is indicated in patients with sigmoid or cecal volvulus and acute pseudo-obstruction. Foreign objects also may be removed endoscopically.

Endoscopic Retrograde Cholangiopancreatography

ERCP is used to evaluate and treat diseases of the pancreas, biliary tree, gallbladder, and liver. With the advent of highly diagnostic alternative modalities, such as magnetic resonance imaging and EUS, the role of ERCP has slowly evolved into a therapeutic rather than diagnostic tool (Box 17.5).[90] The procedure is performed with the patient under anesthesia while lying on the left side or prone. After oral intubation, the side-viewing duodenoscope is advanced into the second portion of the duodenum, where the papilla of Vater is located, and the papilla is subsequently cannulated using a variety of wires, catheters, or papillotomes. Glucagon may be beneficial to reduce peristalsis of the small bowel, facilitating cannulation of the bile duct. Secretin may be administered to assist in identification of the papilla of Vater in the setting of ulceration, scarring, or malignancy, or the minor papilla in cases of pancreas divisum. Visualization of the common bile duct or pancreatic duct is achieved with injection of contrast dye and radiographic fluoroscopy.[91]

Biliary obstruction secondary to choledocholithiasis may be managed by ERCP with successful stone extraction in 90% of cases.[91] Techniques for stone extraction involve biliary sphincterotomy or balloon sphincteroplasty, followed by stone removal using a soft balloon or wire basket. Significant coagulopathy should be

corrected if sphincterotomy is to be performed. Large stones may be fragmented before removal with mechanical, laser, or electrohydraulic lithotripsy. Inadequate bile drainage may require biliary stenting to prevent ascending cholangitis. Antibiotic prophylaxis is indicated in patients undergoing ERCP for suspected biliary obstruction where incomplete drainage is anticipated or in patients with sterile pancreatic fluid collections that communicate with the pancreatic duct.[92]

Bile duct stenting is used to alleviate obstruction caused by malignant and benign disorders and to treat bile duct injuries and leaks.[93] Pancreatic stents are used for pancreatic duct disruptions[94] and pseudocysts that communicate with the pancreatic duct.[95] Stents vary in diameter, length, material (plastic, metallic, and biodegradable), and occlusion rates.

Malignant and benign strictures may be dilated with hydrostatic balloons. ERCP also is used to obtain brush cytology, fine-needle aspiration, or biopsy specimens of a suspected malignancy. Sensitivity is typically low, ranging from 30% with brushings to 60% with all three methods combined.[96] Reports of photodynamic therapy for nonresectable cholangiocarcinoma have been described.[97] Manometry, the measurement of biliary and pancreatic sphincter pressures, may be used to evaluate sphincter of Oddi dysfunction, postcholecystectomy pain, and idiopathic pancreatitis.

Choledochoscopes and pancreatoscopes are small endoscopes that can be passed through a duodenoscope channel port into the common bile duct or pancreatic duct. This placement allows direct visualization of the duct lumen. Direct visualization of vasculature and lumen within a biliary stricture may help differentiate benign from malignant lesions.[98]

ERCP carries a substantial morbidity risk. Pancreatitis is the most common complication, occurring in 3% to 10% of cases.[99] Although the benefits of prophylactic administration of gabexate mesylate are controversial,[100,101] pancreatic stenting of high-risk patients seems to be efficacious.[102] Stenting improves pancreatic duct drainage. Several major independent risk factors for post-ERCP pancreatitis that have been identified with multivariate analysis include prior post-ERCP pancreatitis, endoscopic papillary large-balloon dilation of an intact sphincter, female sex, pancreatic sphincterotomy, and repetitive pancreatic cannulation. Other reported complications include hemorrhage, cholangitis, and perforation occurring at rates of 0.3 to 2%, 1%, and 0.08 to 0.6% respectively.[103]

Endoscopic Ultrasound

EUS, a combination of endoscopy and ultrasonography, is used for evaluation of luminal walls and structures adjacent to the GI tract. In addition, high-frequency ultrasound probes that can be passed through the channel port of standard endoscopes are commercially available.[104]

A common application of EUS is evaluation of benign and malignant mucosal and submucosal lesions. EUS is used routinely for detection and staging of esophageal, gastric, ampullary, pancreaticobiliary, colorectal, and lung neoplasms. EUS also is used to evaluate chronic pancreatitis and biliary disorders, such as calculi. In general, EUS is an extremely sensitive tool and is often superior to computed tomography or magnetic resonance imaging for diagnosis and staging of neoplasia.[105] An advantage of EUS over these noninvasive modalities is the ability to perform therapeutic interventions when needed. Fine-needle aspiration can be done with EUS, which also can be used for pseudocyst drainage, celiac plexus blocks, cholangiography, pancreatography, and tumor ablation.[106] Despite the low risk of bacteremia after EUS fine-needle aspiration, patients undergoing EUS with aspiration of a cystic lesion along the GI tract should receive antibiotic prophylaxis.[92]

Preparation of the patient is similar to that for standard endoscopy. Complications from instrumentation vary, depending on the clinical scenario. Perforation rates, usually cervical esophageal in origin, occur in 0.03%.[107] Pancreatitis, hemorrhage, and bile peritonitis also have been reported.[108]

Endoscopic management of peripancreatic fluid collections has always been technically challenging. Newer lumen-opposing metal stents provide transluminal drainage of pancreatic pseudocysts, pancreatic abscesses, or walled-off pancreatic necrosis and are deployed under EUS guidance.

Endoscopy in the Pregnant Patient

Endoscopy in the general population is commonplace and widely regarded as safe. Endoscopy during pregnancy raises the unique concern of fetal safety and poses the potential risks of teratogenesis or premature induction of labor from medications, hypoxemia, and hemodynamic fluctuations. A lack of quality research into the safety of these procedures during pregnancy adds to the uncertainty of performing endoscopic procedures in this population.[109]

In controlled studies, no differences were seen between pregnant and nonpregnant patients undergoing EGD[110] or in fetal outcomes regardless of a history of EGD during pregnancy.[111] Acute upper GI bleeding, dysphagia associated with involuntary weight loss, and suspected GI mass have all been suggested as acceptable indications for EGD in the pregnant patient. Data surrounding colonoscopy during pregnancy are less robust, limited to small studies, case series, and case reports, and therefore accurate estimation of risk is not possible. Colonoscopy should be considered for unknown colonic mass or stricture, severe uncontrolled colonic hemorrhage, as an alternative to surgery in colonic pseudo-obstruction, and when required before colonic surgery.[109]

ERCP is associated with unique risks that must be appreciated when considering performing the procedure on a pregnant patient. Procedural time is often longer, requiring increased doses of anesthetic medications compared with EGD. ERCP also places the patient at risk for postprocedural complications, including bleeding and perforation from sphincterotomy and post-ERCP pancreatitis. ERCP during pregnancy also introduces a theoretical risk from fetal radiation exposure during fluoroscopy. Despite these risks, it is felt that ERCP can safely be performed during pregnancy as the literature has consistently demonstrated a high maternal success rate, a low procedural complication rate, and generally favorable fetal outcomes.[109] Additionally, although estimates of fetal radiation exposure vary, with careful technique, doses of radiation can be limited to less than the 5-rad threshold often used to minimize risk of fetal anomalies or pregnancy loss.[112] Indications for ERCP during pregnancy include choledocholithiasis with obstructive jaundice, ascending cholangitis, or gallstone pancreatitis, or the presence of biliary or pancreatic ductal injury.[109]

When considering GI endoscopy in the pregnant patient the physician must ultimately weigh the risks of performing the procedure to the fetus against the benefits to the mother. Guidelines exist that offer suggestions to help minimize these risks, such as limiting procedures to patients with strong indications, choosing medications that are safe during pregnancy, close involvement of obstetric staff, and performance of the procedure by an experienced endoscopist. In situations in which therapeutic intervention is necessary, endoscopy may offer a safe alternative to surgery.[113]

Key Points

- Endoscopy serves a diagnostic and a therapeutic role in the management of patients.
- Informed consent must be obtained before any elective endoscopic procedure.
- Perforation and bleeding are the major complications of endoscopy. Although standard endoscopy is generally low risk, interventional procedures increase the rate of complications. A benefit versus risk analysis must be done before any procedure.
- Cardiopulmonary decompensation is a possible complication of anesthesia.
- Endoscopy is the most effective technique to identify and control GI hemorrhage.
- Endoscopy plays a crucial role in the palliative care of patients with GI tract malignancy.
- ERCP has evolved into a therapeutic tool for treating pancreaticobiliary disease.
- Endoscopy in the pregnant patient can be done safely but should be limited to patients with strong indications.

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Review Questions

1. A 25-year-old female with no past medical history and two prior full-term pregnancies presents with intermittent right upper quadrant pain for the past 3 weeks. She is currently 20 weeks into her third pregnancy. Physical examination reveals mild discomfort to right upper quadrant palpation. Right upper quadrant ultrasound revealed cholelithiasis and two small filling defects in the common bile duct (CBD), with the largest measuring 0.5 cm in length. Liver function test results show the following levels: aspartate aminotransferase 62 U/L, alanine aminotransferase 82 U/L, total bilirubin 4.1 g/dL, direct bilirubin 1.2 g/dL, and alkaline phosphate 60 U/L. What would the next step in management be?

- **a.** Proceed to endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy for CBD stone extraction
- **b.** Proceed to ERCP with plastic stent placement followed by a repeat ERCP 6 weeks after delivery with sphincterotomy for CBD stone extraction
- **c.** Follow clinically and if develops worsening signs, then proceed to ERCP with sphincterotomy and CBD stone extraction.
- **d.** No further intervention as these stones will likely pass

Answer: a. Stent occlusion or migration can precipitate cholangitis and a second procedure is potentially needed during the pregnancy. If limited fluoroscopy time can be observed, a therapeutic sphincterotomy with stone extraction can facilitate stone passage and potentially limit any further complications of the pregnancy.

2. Which of the following is *not* a contraindication for video capsule endoscopy?

- **a.** Crohn disease with known stricture in small bowel
- **b.** Current pregnancy
- **c.** Known or suspected small bowel fistulas
- **d.** Rapid small bowel transit time

Answer: d. The passage time of the video capsule does not influence the ability to use this tool to help with diagnosis.

3. A 63-year-old male with hypertension, type 2 diabetes, obesity, and obstructive sleep apnea presents to the emergency department with complaints of acute sharp abdominal pain in the epigastrium with new esophageal reflux for the past 1 month. He had been taking a nonsteroidal antiinflammatory drug for back pain several times a day for the past 3 months. Upon presentation his heart rate is 110 beats/min, blood pressure is 90/60 mm Hg, and respirations are 28 breaths/min. He is slightly lethargic and diaphoretic. When you encounter the patient, he begins to vomit bright red blood. What is correct regarding intubation of this patient?

- **a.** Intubation should happen after the endoscopy if there is an active bleeding source.
- **b.** Intravenous proton pump inhibitors and octreotide should be started immediately and you should proceed directly to esophagogastroduodenoscopy without intubation.
- **c.** Intubation before endoscopy can help facilitate the passage of the endoscope and should be performed with the majority of acute upper gastrointestinal (GI) bleeding cases.
- **d.** Prophylactic intubation prior to endoscopy for upper GI bleeding can result in a higher rate of pneumonia in intubated patients.

Answer: d. A meta-analysis has evaluated intubation before endoscopy for upper GI bleeding. It found a higher rate of aspiration, pneumonia, and hospital length of stay in the electively intubated patients. It is recommended to weigh risks and benefits of intubation for each individual case.

18

Bedside Ultrasonography in the Critically Ill Patient

NITIN PURI AND PAUL MAYO

CHAPTER OUTLINE

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- Parasternal Short-Axis Mid-Ventricular View
- Apical Four-Chamber
- Subcostal Long-Axis View
- Inferior Vena Cava Longitudinal View

Utility of Basic Critical Care Echocardiography

Advanced Critical Care Echocardiography

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- A-Lines
- B-Lines
- Consolidation
- Pleural Effusion

Clinical Applications of Thoracic Ultrasonography
- Thoracic Ultrasonography Compared to Chest Radiography
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- Evaluation for Pneumonia
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- Evaluation for Chest Tube Removal
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- Prediction of Extubation Failure
- Evaluation of Respiratory Failure
- Evaluation for Cardiogenic Pulmonary Edema
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- Ultrasonography for Diagnosis of DVT
- Equipment Requirements and Scanning Technique
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Abdominal Ultrasonography
- Equipment Requirements and Scanning Techniques
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Ultrasonography for Guidance of Critical Care Procedures
- Ultrasonography for Guidance of Vascular Access
- Ultrasonography for Guidance of Thoracentesis, Paracentesis, and Pericardiocentesis

Quality Assurance and Imaging Archival Systems

Conclusions

Ultrasonography is useful to guide the diagnosis and management of critical illness. The intensivist who uses critical care ultrasonography (CCUS) assumes all responsibility for image acquisition, image interpretation, and the immediate application of the results at the bedside of the critically ill patient. This is different from standard ultrasonography, where a technician acquires the image and a radiologist or cardiologist provides interpretation. This latter approach results in a delay in performance of the scan, delay in its interpretation, and delay in transmission of results. This is compounded by the consultant typically having incomplete knowledge of the clinical facts of the case. In performing CCUS, the intensivist integrates the imaging results into the entire clinical picture, best understood by the front-line clinician. The use of CCUS has expanded rapidly over the past 2 decades. It is increasingly part of critical care training in North America as the Accreditation Council for Graduate Medical Education (ACGME) mandates knowledge of CCUS as a part of critical care fellowship training (ACGME program requirements for graduate medical education in critical care medicine are available at https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/142_critical_care_medicine_2017-07-01.pdf?ver=2017-04-27-145212-687). Thousands of attending-level intensivists have taken courses on CCUS provided by the professional societies, and the critical care societies have issued guidelines defining best practice and

competency requirements.[1,2] The International Expert Statement on Training Standards in CCUS specifies that "basic-level critical care echocardiography and general critical care ultrasound should be a required part of the training of every ICU physician."[3]

Basic Ultrasound Terminology and Probe Characterization

Echogenicity refers to the ability of a structure to reflect or transmit ultrasound waves. Different echogenicity between structures allows specific anatomy to be identified and localized (Box 18.1). It is important for intensivists to have knowledge of probe frequency to allow the choice of the appropriate probe for best resolution. High-frequency probes provide superior resolution but less penetration. A high-frequency probe is used to image superficial structures (e.g., vascular imaging), whereas a mid-range frequency probe is used to image deeper structures (e.g., cardiac or thoracic imaging). Curvilinear probes generate a wider image than linear probes and are used to visualize deeper structures (Table 18.1).

Basic Critical Care Echocardiography

The American College of Chest Physicians and La Société de Réanimation de Langue Française statement divides competence in critical care echocardiography (CCE) into two levels: basic and advanced. The basic CCE examination includes five standard views: the parasternal long-axis (PSLAX), the parasternal short-axis (PSSAX), the apical four-chamber (AP4), the subcostal long-axis (SCLAX), and the inferior vena cava (IVC) in longitudinal axis.[1] The intensivist uses basic CCE to qualitatively examine the anatomy and function of the heart.

Basic CCE is the cornerstone for the evaluation of cardiopulmonary failure, where it is used immediately, repeatedly, and serially by the front-line intensivist to establish diagnosis and guide management at the bedside of the critically ill patient.[4] Advanced critical care echocardiography (ACCE) requires the intensivist to have competence in echocardiography at a similar level to a cardiologist.[5] The National Board of Echocardiography (NBE), in cooperation with other professional societies, is developing national-level certification in ACCE. The first NBE ACCE examination is scheduled to be given in early 2019. Intensivists interested in ACCE may consult the NBE website or their professional societies for information on the process of certification. This chapter focuses on basic CCUS.

• BOX 18.1 Ultrasound Echogenicity

Hyperechoic: appears white
Hypoechoic: appears gray
Anechoic: appears black

TABLE 18.1 Frequency Probes

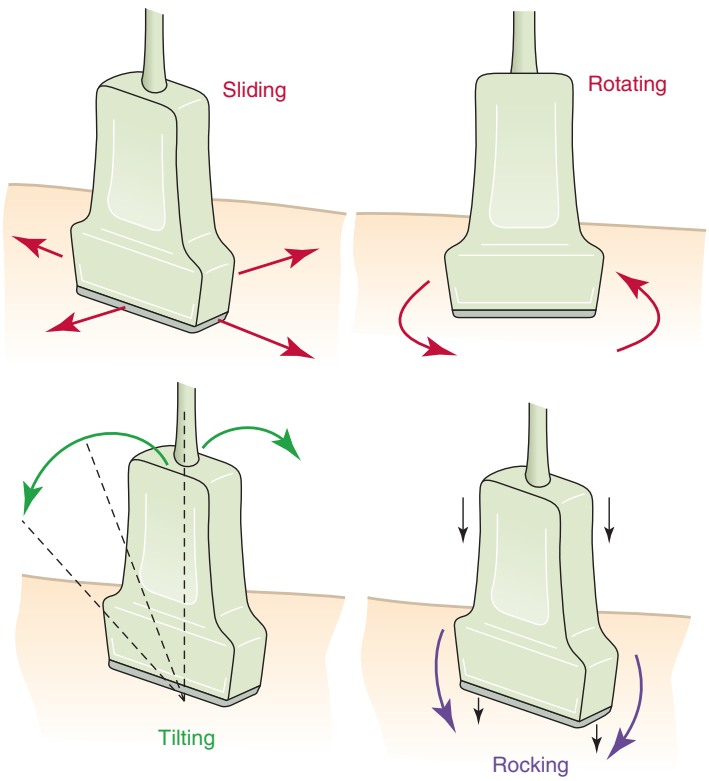
	Frequency	Optimal Structure Visualized	Probe Type
Linear	5–15 MHz	Vessels, nerves	Linear
Phased-array	0–5 MHz	Cardiac, thoracic Abdominal Imaging	Curvilinear

Performance of the CCE Examination

Basic CCE is performed with a phased-array probe (2–5 MHz). The probe is used with sufficient coupling gel (a conductive medium for sound waves generated by the transducer), and the machine is placed on the same side as the examiner to allow for easy machine control. The probe is held with part of the probe hand touching the patient to provide a stable image. The probe marker is placed on the right side of the screen, the gain (controls brightness of ultrasound image by amplifying the signal of ultrasound waves) is set to the appropriate level, and the depth is adjusted to place the target of interest in the center of the screen. The tomographic plane is a cross-sectional plane through the body. The tomographic plane of the probe is adjusted as according to the following steps[6] (Fig. 18.1):

1. Moving: The probe is moved from one place to another on the chest wall.
2. Angling: The probe is angled perpendicular along the axis of the tomographic plane.
3. Tilting: The probe is tilted along the axis of the tomographic plane.
4. Rotating: The probe is rotated without moving, angling, or tilting.

The main limitation of CCE is related to patient factors such as obesity, edema, heavy musculature, or surgical wounds/dressings



• **Fig. 18.1** Transducer movements. (From Soni NJ, Arntfield R, Kory P. *Point-of-Care Ultrasound.* Philadelphia: Elsevier; 2014.)

that may degrade image quality. The patient may be difficult to position for optimal imaging because of body size or surrounding equipment. The operator should attempt all the views; if one view fails, another may yield important information. The examination is performed in the same sequence every time to standardize scanning tactics and avoid omitting a view. The quality of the examination is influenced by the skill of the operator, so inadequate training can degrade image quality.

The Basic CCE Examination

Parasternal Long-Axis View (Fig. 18.2, Video 18.1)

The transducer is positioned to the left of sternum perpendicular to the skin surface in the left third to fifth intercostal space with the index marker of the probe pointing toward the right shoulder. The intercostal space that yields the best image is variable. The tomographic plane is adjusted so that it bisects the aortic valve (AV), the mitral valve, and the left ventricular (LV) cavity in its longest axis. The PSLAX view is used for qualitative assessment of LV function, right ventricular (RV) outflow tract size, LV wall thickness and function, septal kinetics, evaluation of AV/mitral valve anatomy, left atrial (LA) size, the descending aorta, and the pericardial space.[7]

Parasternal Short-Axis Mid-Ventricular View (Fig. 18.3, Video 18.2)

From the PSLAX view, the probe is now rotated 90 degrees clockwise without tilting or angling to obtain a cross-sectional view of the heart with the index marker of the probe pointing toward the left shoulder. By angling the probe along a right shoulder–to–left hip axis, the tomographic plane is adjusted to obtain a cross-sectional view of the left ventricle at the papillary muscle level. The PSSAX view is used for qualitative assessment of LV function, LV segmental wall function, LV/RV chamber size, RV/LV wall thickness, septal kinetics, and the pericardial space.

Apical Four-Chamber (Fig. 18.4, Video 18.4)

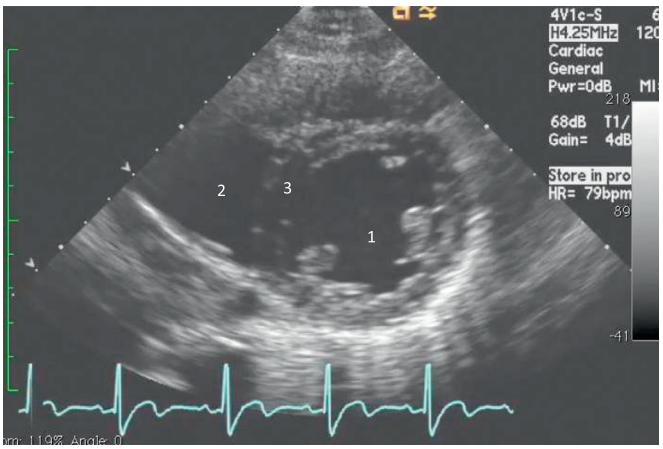
The transducer is positioned at the apex of the left ventricle (approximately sixth intercostal space midclavicular line) with the probe marker pointing toward the left axilla. The optimal patient position is the left lateral decubitus position, although this may not be possible in the critically ill patient. The tomographic plane is adjusted so that the intraventricular septum is oriented vertically in the center of the screen; thus it bisects the apex, the ventricles, and the atria. The AP4 view is used for qualitative assessment of LV function, RV/LV size ratio, RV/LV wall thickness, LV segmental wall function, septal kinetics, right atrium (RA)/LA chamber size, and evaluation of tricuspid valve (TV)/MV anatomy.

Subcostal Long-Axis View (Fig. 18.5, Video 18.7)

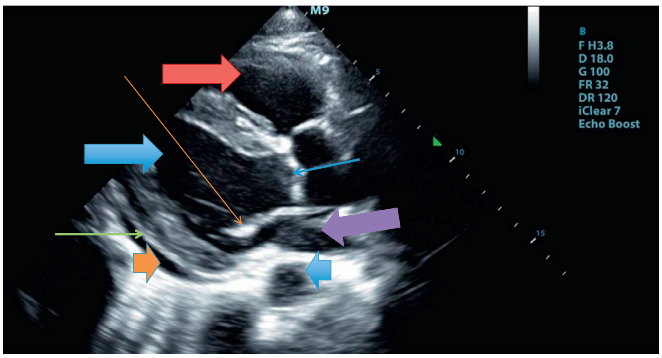
With the patient lying supine, the probe is placed immediately below the xiphoid process with the index marker pointing toward the lower lateral left chest. The tomographic plane is adjusted to yield a four-chamber view of the heart. The SCLAX view is used for qualitative assessment of LV function, RV/LV size ratio, RV/LV wall thickness, LV segmental wall function, septal kinetics, and the pericardial space.

Inferior Vena Cava Longitudinal View (Fig. 18.6, see Video 18.1)

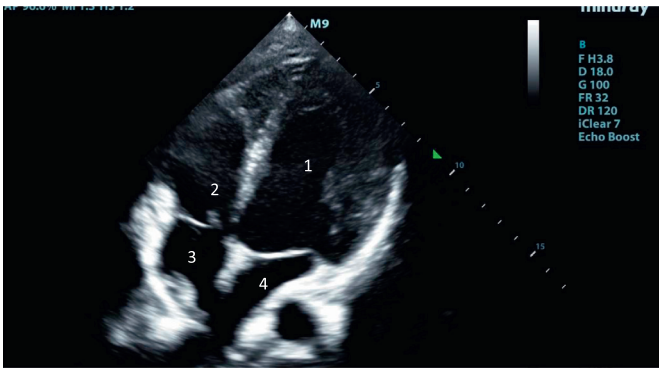
From the SCLAX, the transducer is rotated counterclockwise so that the index marker is pointing toward the 12-o'clock position, followed by angling of the tomographic plane toward the right to obtain a long-axis view of the IVC. The tomographic plane is



• **Fig. 18.3** Parasternal short-axis midventricular view. *1,* Left ventricle; *2,* right ventricle; *3,* intraventricular septum.



• **Fig. 18.2** Parasternal long-axis view. *Blue arrow,* Left ventricle; *red arrow,* right ventricle; *purple arrow,* left atrium; *blue arrowhead,* descending thoracic aorta; *orange arrowhead,* small pericardial effusion; *thin blue arrow,* aortic valve; *thin orange arrow,* mitral valve; *thin green arrow,* pericardium.



• **Fig. 18.4** Apical four-chamber view. *1,* Left ventricle; *2,* right ventricle; *3,* right atrium; *4,* left atrium.

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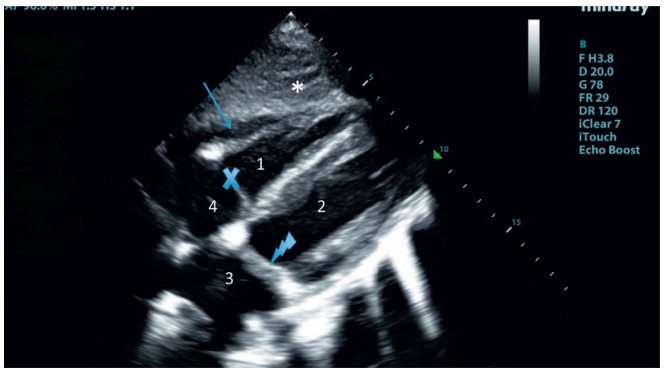


• **Fig. 18.5** Subcostal long-axis view. *1,* Right ventricle; *2,* left ventricle; *3,* right atrium; *4,* left atrium; *asterisk,* liver; *blue arrow*, small pericardial effusion; *X,* mitral valve; *lightning bolt,* tricuspid valve.

• BOX 18.2 Basic Critical Care Echocardiography

Identify imminently life-threatening processes
Categorize the mechanism of shock
Develop management strategy
Look for coexisting diagnosis that will complicate management
Follow the evolution of disease

adjusted to bisect the middle of the IVC. The IVC view is used for determination of volume responsiveness.

Utility of Basic Critical Care Echocardiography

Basic CCE has the following uses:

1. Identification of an immediately life-threatening cause of shock (Box 18.2)
   Basic echocardiography may identify an immediately life-threatening cause of shock such as massive pulmonary embolism, pericardial tamponade, catastrophic valve failure, or severe reduction of LV contractility. The possibility of a life-threatening process with effective treatment is more rapidly identified by the performance of immediate basic CCE for the patient in shock.
2. Categorization of the cause for shock state and guidance of management
   The basic CCE examination permits the critical care clinician to identify the category of shock as hypovolemic, obstructive, cardiogenic, or distributive (or a combination). This guides management strategy and the search for an underlying etiology.
3. Response to therapy and evolution of disease
   Basic CCE is repeated over time to follow response to treatment and the evolution of the disease process, given that critical illness and its treatment represent a dynamic process. Owing to its ease of use, the intensivist can perform the basic ultrasound examination as often as required after the initial scan.
4. Identification of a coexisting diagnosis
   Older patients and/or patients with chronic illness may develop hemodynamic failure where the management of the acute process is complicated by coexisting disease. The basic CCE examination is useful to identify a chronic (e.g., aortic stenosis) process that complicates the management of the primary cause of the acute hemodynamic failure.

Advanced Critical Care Echocardiography

The reader is referred to the International Consensus Statement for a full discussion of ACCE.[5] Although competence in basic CCE is a core skill for the intensivist, the need for competence in ACCE is determined by individual practice requirements. The National Board of Echocardiography is to offer North American certification in ACCE. The certification process will include a high-stakes board examination and a challenging requirement for competence in image acquisition.[8]

Thoracic Ultrasonography

Thoracic ultrasonography of the lung and pleural space is simple to perform, easy to learn, and has strong clinical utility for the intensivist. It is a low-cost imaging modality without ionizing radiation that can be performed immediately, repeatedly, and in a goal-directed fashion at point of care with a portable multipurpose device.

Equipment Requirements and Scanning Technique

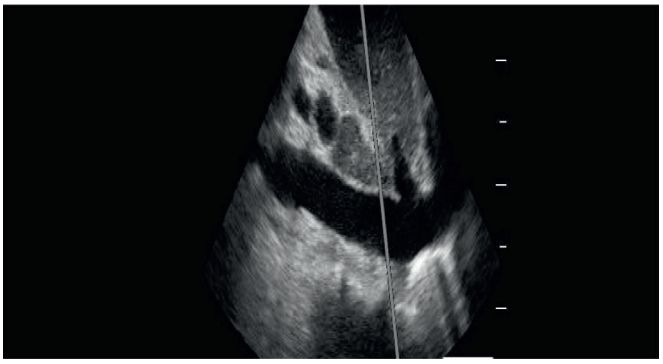
Thoracic ultrasonography is performed with a 3.5- to 5.0-MHz cardiac probe, which has a small footprint that fits well between rib interspaces. A larger curvilinear probe may also be used. The 7.5-MHz linear vascular probe is used to image pleural surface morphology, as it has better resolution than the lower frequency cardiac probe, although it lacks penetration into deeper tissues. Many portable ultrasonography machines have a lung preset that optimizes image quality for thoracic scanning. If not available, the operator may need to adjust machine settings for optimal image quality.

The probe is held perpendicular to the skin surface with the tomographic plane in the longitudinal axis and the probe indicator pointing in cephalad direction. The probe is adjusted such that the tomographic plane is directed through a rib interspace. An effective approach to examining the thorax is to move the probe across the chest wall in a series of scan lines to examine adjacent interspaces. The posterior thorax is an important area to examine, as pleural effusions and consolidations are found in the dependent thorax. To scan the posterior thoracic in the supine patient, the probe is pressed into the mattress and angled anteriorly; or the patient may be rolled to a lateral decubitus position to fully expose the posterior thorax.

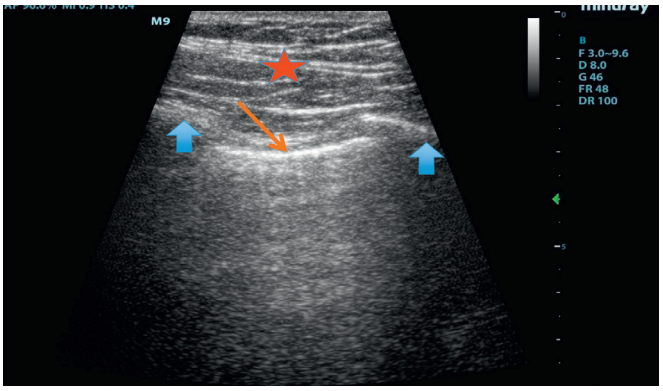
Lung Sliding

The pleural line represents the apposition of the parietal and visceral pleural surfaces. Normally the two pleural surfaces move against each other in synchrony with the respiratory cycle. This results in the finding of lung sliding, which is a mobile shimmering respirophasic movement of the pleural line (Fig. 18.7, see Video 18.2).[9] Cardiac pulsation also results in cardiophasic movement of the visceral pleura against the parietal pleural, which is termed *lung pulse.*[10,11] The findings of lung sliding and lung pulse exclude the presence of a pneumothorax at the site of probe application.[11] Multiple anterior rib interspaces may be rapidly examined. This allows the operator to quickly rule out pneumothorax.

Although the presence of lung sliding effectively rules out pneumothorax, the absence of lung sliding does not necessarily indicate that the patient has a pneumothorax because the absence of lung sliding may occur in conditions other than pneumothorax. A



• **Fig. 18.6** Inferior vena cava, longitudinal view.



• **Fig. 18.7** Lung sliding. *Orange line,* Visceral parietal pleura; *blue arrows,* ribs; *red star,* muscle wall; *green arrowhead,* area of focus for the ultrasound machine.

process that reduces air entry into the lung may cause loss of lung sliding. For example, severe pneumonia, apnea, or acute respiratory distress syndrome will result in the absence of lung sliding, as will an occlusion of a mainstem bronchus (e.g., mainstem intubation with endotracheal tube inflation blocking the contralateral mainstem bronchus, blood clot, mucous plug, foreign body, or tumor mass). Pleural symphysis (cicatricial, inflammatory, therapeutic, or neoplastic) causes loss of lung sliding. The *absence* of lung sliding indicates the possibility of pneumothorax, whereas the *presence* of lung sliding and/or lung pulse rules out a pneumothorax.

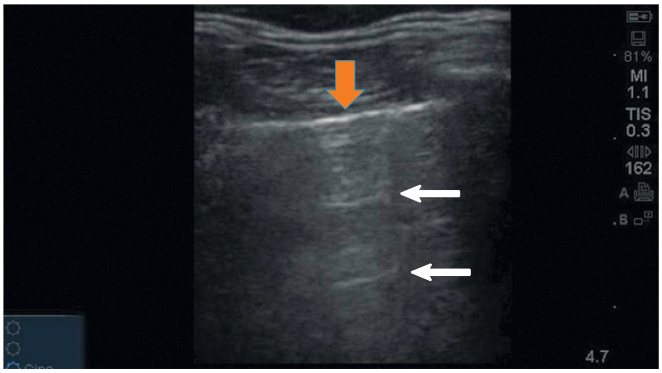
A-Lines (Fig. 18.8, Video 18.3)

Normally aerated lung is distinguished by the presence of A-lines. An "A-line" is a horizontally oriented line that is located deep to the pleural line at a depth equal or a multiplicative of the distance between the skin surface and the pleural line. A-lines can appear singly or multiply and, when multiple, are separated from one another by the same distance. In the presence of sliding lung, A-lines indicate normally aerated lung. When present without lung sliding, they suggest either air between the visceral and parietal pleura (e.g., a pneumothorax or some other cause for lack of lung sliding; see previous text). A-lines with lung sliding are strongly correlated with a normal aeration pattern on CT scan.[12]

B-Lines

Lung disease that involves the alveolar and/or interstitial compartment results in "B-lines." B-lines have several characteristics:

- They originate at the pleural interface.



• **Fig. 18.8** A-lines *(white arrows)*; *orange arrow*; visceral and parietal pleura.

- They move with the pleural interface.
- They are hyperechoic.
- They are vertical in orientation.
- They extend to the bottom of the screen.
- They erase A-lines.

B-lines are strongly correlated with alveolar or interstitial pattern abnormalities on CT scan (reticular pattern or ground-glass abnormality), and depending on their cause, they may be focal, scattered, or diffuse in distribution (Fig. 18.9, Video 18.4).[13,14]

Consolidation

On ultrasonographic examination, consolidated lung has tissue density with similar echogenicity as the liver or spleen. The finding of consolidation with lung ultrasonography is strongly correlated with the results of chest CT.[15] The distribution of the lung consolidation is readily identified with ultrasonography as being whole lung, lobar, or segmental in size with focal or multifocal distribution. If translobar in distribution, the consolidated lung may have sonographic air bronchograms within it that appear as hyperechoic foci representing small amounts of air in bronchi.

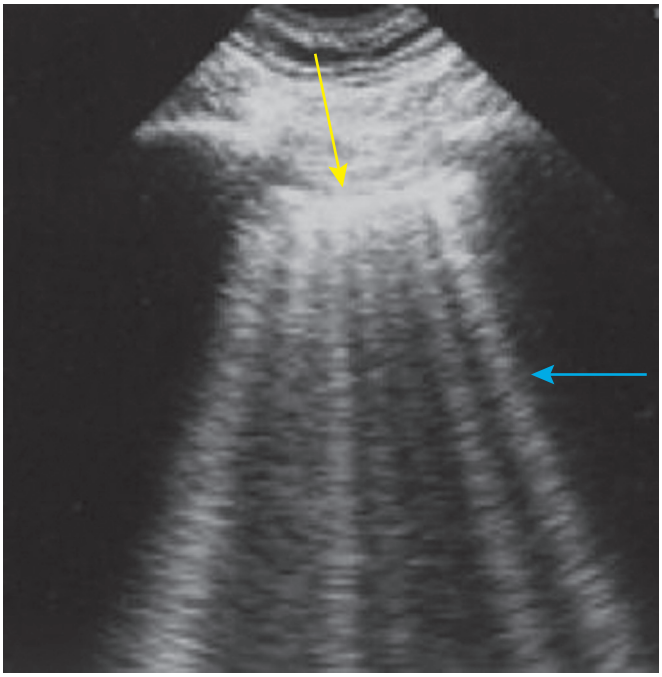
Pleural Effusion (Fig. 18.10, Video 18.5)

Pleural fluid is readily detected with thoracic ultrasonography. Unless the fluid is loculated, it assumes a dependent position within the thorax. Thus in the supine patient, the operator focuses the examination for fluid to the dependent thorax, which is posterior in location. Pleural fluid is indicated by the presence of a relatively hypoechoic space that is defined by typical anatomic boundaries (inside of chest wall, diaphragm, and surface of lung) in association with characteristic dynamic findings (diaphragmatic movement, lung movement, mobile echogenic elements within the pleural effusion). Identification of pleural fluid allows the operator to further characterize it (anechoic or containing internal echogenicity) and to identify a safe site and trajectory for device insertion.[16]

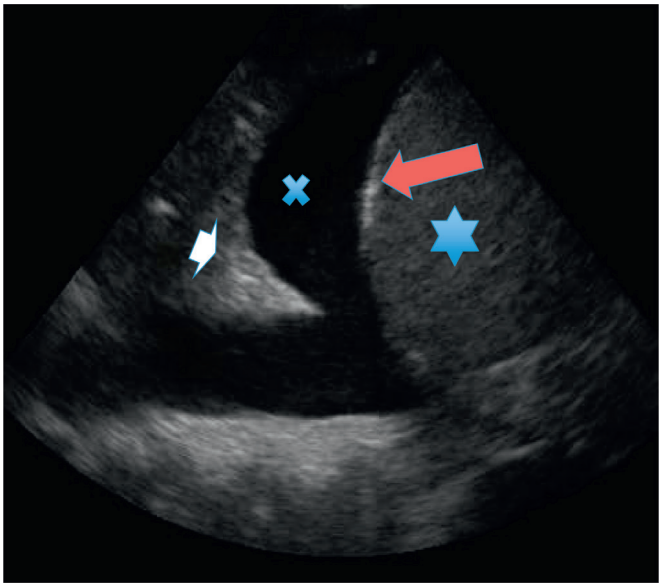
Clinical Applications of Thoracic Ultrasonography

Thoracic Ultrasonography Compared to Chest Radiography

Thoracic ultrasonography is superior to chest radiography for identification of pneumothorax, normal aeration pattern, alveolar/



• **Fig. 18.9** B-lines *(blue arrow)*; *yellow arrow* ,visceral and parietal pleura.



• **Fig. 18.10** Pleural effusion. *White arrow,* Lung; *X,* pleural fluid; *red arrow,* diaphragm; *star,* spleen.

interstitial abnormality, and pleural effusion. It also has operational characteristics that are similar to chest CT for identification of these abnormalities.[17,18] Its ease of use, portability, and cost profile favor its use over chest radiography, and whenever possible, chest CT. With this understanding, thoracic ultrasonography may be used as a primary imaging modality in the intensive care unit (ICU) instead of chest radiography.

Evaluation for Pneumothorax

In the supine patient, air within the pleural space typically collects in the anterior thorax. The intensivist can rapidly rule out a generalized (versus loculated) pneumothorax by detecting lung sliding over multiple anterior rib spaces. Thoracic ultrasonography is superior to chest radiography for detection of pneumothorax.[19–21]

Evaluation for Pneumonia

Lung ultrasonography has utility for diagnosis of pneumonia and for following its progression.[19,22,23] The effect of antibiotic treatment on ventilator-associated pneumonia can be observed with lung ultrasonography.[24] The combination of sputum analysis with lung ultrasonography has utility for the diagnosis of ventilator-associated pneumonia.[25]

Evaluation of Pneumonia Versus Atelectasis

The finding of dynamic air bronchograms with consolidated lung is a characteristic feature of pneumonia, whereas their absence increases the likelihood that the consolidation results from atelectasis (Fig. 18.11, Video 18.6).[26]

Guidance of Thoracic Procedures

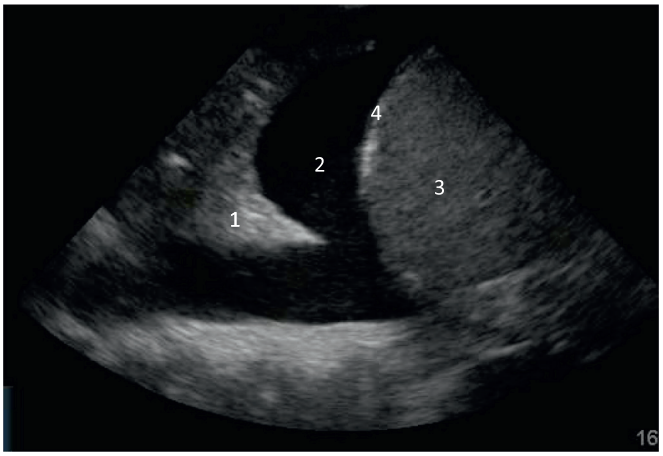
Thoracic ultrasonography increases procedure success rate and reduces the frequency of postprocedure pneumothoraces, bleeding complications, and the need for postprocedure chest radiography.[27,28] With ultrasonographic guidance, thoracentesis may be performed with a low complication rate in patients using mechanical ventilatory support.[29] Bleeding complications are reduced in patients taking clopidogrel both for thoracentesis and percutaneous chest tube insertion when guided by ultrasonography.[30] In reference to central line placement, the combination of thoracic ultrasonography and echocardiography may be used to exclude procedure-related pneumothorax and to confirm central venous catheter tip position.[31]

Evaluation for Chest Tube Removal

Galbois et al. reported the utility of thoracic ultrasonography to observe full lung expansion after pleural drainage for pneumothorax as well as the time to chest tube removal.[32] Once the lung is shown to be fully inflated with thoracic ultrasonography, the chest tube is clamped. If the lung remains fully inflated after an appropriate period of time, the chest tube is removed. Study results indicated that this method was superior to standard chest radiography.

Evaluation for Pulmonary Embolism

Nazerian et al. were able to diagnose pulmonary embolism in patients in the emergency department with 90% sensitivity and 86.2% specificity by performing a combination of vascular, lung, and cardiac ultrasonography. The investigators evaluated patients for deep venous thrombosis (DVT), alternative causes of respiratory failure, and evidence of RV dysfunction.[33] Koenig et al. similarly used a combination of vascular, lung, and cardiac ultrasonography in hospitalized patients to show that point-of-care ultrasound could eliminate the need for unnecessary CT scans of the chest.[34] Reissig et al. reported that pulmonary emboli commonly result in small areas of consolidation immediately deep to the pleural interface with preferential distribution to the lower lobes of the lung.[35] Two meta-analyses show a pooled sensitivity and specificity of 80% to 87% and 82% to 93%, respectively, for diagnosis of pulmonary embolism with thoracic ultrasonography.[36,37]



• **Fig. 18.11** Atelectasis. *1,* Atelectatic lung; *2,* pleural effusion, *3,* spleen; *4,* diaphragm.

Evaluation of Lung Recruitment With PEEP

Bouhemad et al. reported on the utility of thoracic ultrasonography to evaluate lung recruitment with positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome.[38] Using a standardized scoring system that reflects the degree of lung aeration, they observed the effect of varying levels of PEEP on reaeration of compromised lung at varying PEEP levels. By varying PEEP levels from 0 to 15 cm H_2O, an improvement in aeration detected by lung ultrasonography was associated with a measured increase in lung volume. Lack of improvement in lung aeration score was associated with reduced augmentation of measured lung volume.

Prediction of Extubation Failure

Using the same scoring system described for their PEEP study, Soummer et al. reported that worsening of the lung aeration score during spontaneous breathing trial was associated with weaning failure.[39]

Evaluation of Respiratory Failure

Lichtenstein and Mezière described an algorithm based on thoracic ultrasonography for the evaluation of respiratory failure.[40] With a simple three-point examination of the chest and standardized findings, the algorithm identified the cause of the respiratory failure in a high proportion of cases. The authors found that thoracic ultrasonography was as effective as standard evaluation methods for identifying the etiology of respiratory distress for a wide variety of diseases with the advantage that it reduced time to diagnosis.[40] Batialle et al. reported that the combination of thoracic ultrasonography with echocardiography for evaluation of dyspnea improved diagnostic yield when compared with thoracic ultrasonography alone.[41]

Evaluation for Cardiogenic Pulmonary Edema

Lichtenstein et al. reported that the presence of an A-line pattern with lung sliding was associated with a pulmonary occlusion pressure below 18 mm Hg and likely less than 12 mm Hg.[42] The finding of an A-line pattern in the dyspneic patient therefore rules out cardiogenic pulmonary edema. To distinguish between B-lines derived from cardiogenic pulmonary edema and those caused by primary lung injury, Copetti et al. reported that B-lines caused by cardiogenic pulmonary edema are associated with a smooth pleural surface, whereas primary lung injury B-lines are associated with an irregular pleural surface.[43] Agricola et al. reported that during cardiac stress testing, the onset of dyspnea coincident with the sudden appearance of B-lines is consistent with onset of cardiogenic pulmonary edema precipitated by cardiac ischemia under exercise load.[44]

Evaluation of Endotracheal Tube Position

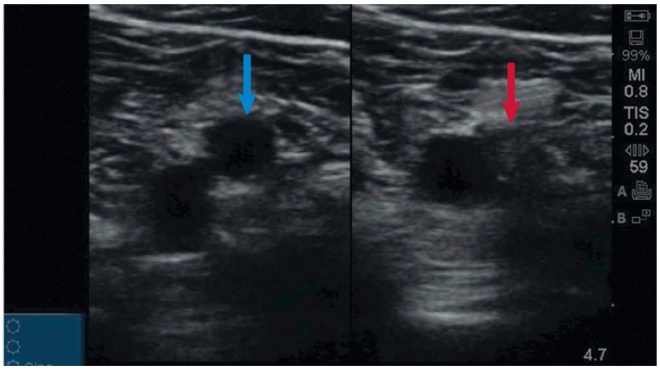
Lung ultrasonography is useful to assess endotracheal tube position. Bilateral lung sliding during bag-valve-mask (BVM) ventilation indicates successful tracheal intubation.[44,45] Unilateral mainstem intubation results in ipsilateral lung sliding with BVM ventilation and with contralateral lung pulse and absent lung sliding. Withdrawal of the endotracheal tube to a position above the carina results in bilateral lung sliding with BVM ventilation.[46]

Ultrasonography for Diagnosis of DVT

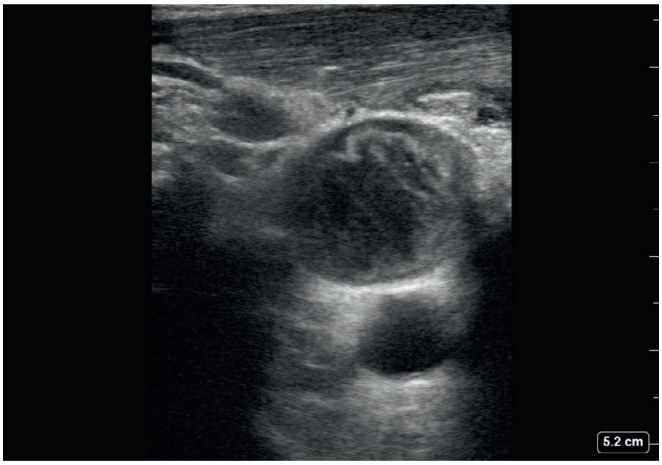
Ultrasonography is useful for the diagnosis of DVT. Trained intensivists perform ultrasonography compression studies with results similar to those performed by consultative radiology without typical delay in performance of the examination.[47] The front-line intensivist who performs the DVT study accrues major advantages. The examination is done immediately at point of care, it can be repeated as often as required, and it provides important clinical information that is promptly integrated into the management plan. Proficiency in the two-dimensional compression examination for DVT is a key part of competence in basic CCUS.

Equipment Requirements and Scanning Technique

The linear vascular probe (7.5 MHz) of the type used to guide vascular access is used to perform the examination. The scanning technique is the same regardless of the vessel being examined. The selected vein is imaged in its transverse axis. The transducer is placed perpendicular to the skin surface over the targeted vein. The examiner adjusts the tomographic plane to place the vein at the center of the ultrasonography machine screen. The orientation marker is set on the right side of the screen, and the probe marker is directed to the right side of the patient when examining the leg veins. A thrombus appears as an echogenic structure within the vein (Fig. 18.12, see Video 18.7). Absent a visible thrombus, the examiner performs a compression maneuver by pressing the probe down with the force vector perpendicular to the axis of the vein sufficient to deform the adjacent artery. Normal veins are fully compressible. Occasionally the thrombus will become visible only with the compression maneuver. Although the compression maneuver is best performed with the transverse view of the vein, the longitudinal view may be used to supplement the examination. The addition of Doppler to the examination (duplex and triplex) may afford no improvement in accuracy over the two-dimensional compression ultrasonography test.[48]



• **Fig. 18.12** Examination for a lower extremity deep vein thrombosus. *Blue arrow,* Vein; *red arrow,* vein collapse with compression.



• **Fig. 18.13** Deep vein thrombosus *(blue arrow)* in the internal jugular vein.

Examination for Lower Extremity DVT (Fig. 18.12, Video 18.8)

With the patient in the supine position, the leg is externally rotated. The examination is started in the inguinal region and follows an imaging sequence at defined anatomic levels of the upper leg venous system as follows:

1. Identification and compression of the proximal common femoral vein (CFV) and its paired artery (less compressible), with the CFV being medial to the common femoral artery.
2. Identification and compression of the CFV at its junction with the saphenous vein.
3. Identification and compression of the CFV at the level of the bifurcation of the common femoral artery into the femoral artery and deep femoral artery.
4. Identification and compression of the CFV at the level of the junction of the CFV and the deep femoral vein. Below this point, the CFV becomes the superficial femoral vein (SFV).
5. Identification and compression of the SFV. The SFV is deep to the femoral artery. There is debate as to how far down the thigh to continue the examination and compression of the SFV. It is uncommon for there to be a SFV thrombus in the absence of CFV or popliteal vein (PV) thrombus, so a complete examination of the entire course of the SFV may not be necessary.
6. Identification and compression of the PV. With the patient's knee flexed and leg externally rotated, the probe is positioned in the popliteal fossa to visualize and compress the PV. The PV is superficial to the popliteal artery.

Examination for Upper Extremity DVT

With the arm abducted and externally rotated, the brachial vein(s) and the adjacent brachial artery are identified in their transverse axis starting at the antecubital fossa. The brachial veins are often paired. The tomographic plane, oriented in the transverse axis to the vein, is moved proximally with examination for visible thrombus followed by compression at several points along the course of the brachial vein(s). In the proximal upper arm, the paired brachial vein(s) join to become the axillary vein. The examination continues as far into the axilla as possible.

Examination for Neck Vessel and Axillary DVT (Fig. 18.13)

Both the internal jugular vein (IJV) and SCV are imaged in their transverse axis and examined for visible thrombus followed by compression study along the length of the vessel. This is a standard part of assessment in preparation for IJV and SCV venous catheter insertion. Difficulty with compressing the SCV occurs in obese or muscular patients. Although no thrombus is present if the SCV is fully compressible along its course, absence of compression may be due to specific patient factors or the presence of an isoechoic thrombus.

Abdominal Ultrasonography

Competence in all aspects of abdominal ultrasonography is not needed by the critical care specialist. More advanced applications are under the purview of the expert-level radiologist, as they require a long training period that is unnecessary for the intensivist. Conceptually, this approach is similar to basic CCE. Implicit to competence in goal-directed abdominal ultrasonography is that the intensivist knows when to escalate to consultative radiology ultrasonography examination or abdominal CT. Goal-directed abdominal ultrasonography focuses on the evaluation of the urinary tract (kidney and bladder), identification of intraabdominal fluid, and evaluation of the aorta. A working knowledge of normal abdominal ultrasonography anatomy is required so that the intensivist can recognize abnormalities that require expert-level scanning.

Equipment Requirements and Scanning Techniques

Goal-directed abdominal ultrasonography is performed using a 3.5-Mz probe. Recent model portable ultrasonography machines in widespread use for CCUS offer the option of a curvilinear probe that is specifically designed for abdominal scanning. This probe design is not effective for cardiac scanning because of its size. Most manufacturers allow the phased-array cardiac probe to be rapidly configured for abdominal imaging. Purchase of a phased-array probe reduces equipment acquisition costs as only one probe is required to perform cardiac, thoracic, and abdominal scanning. The examination is performed using standard scanning planes that are specific to each organ system and requires knowledge of machine

controls, orthogonal views of the relevant target organs, and normal versus abnormal ultrasonography anatomy.

Kidney and Bladder Examination Technique

The evaluation of renal failure requires consideration of obstructive uropathy. Although obstructive uropathy is relatively rare, it is a potentially reversible cause that can be easily ruled out with ultrasonography. Bladder ultrasonography allows rapid evaluation of bladder volume, drainage catheter placement, and obstructive uropathy presenting as anuric renal failure that is remedied by manipulation of the drainage catheter.

The examination is performed with the patient in the supine position. The probe is positioned in the posterior axillary line over the lower lateral thorax in a longitudinal scanning axis. The tomographic plane is adjusted to obtain a coronal plane view of the right or left kidney. Once the kidney is identified, the probe is angled through the organ to fully image its anatomy. The size, cortical thickness/echogenicity, pelvicalyceal differentiation, and any pathologic findings are noted. Obstructive uropathy results in fluid collection with the collecting system. Although a primary indication for ultrasonography is identification of hydronephrosis, incidental pathology such as renal cyst, perinephric abscess, stone, or mass may be identified. The intensivist refers these findings to expert-level scanning by the radiology service.

The bladder is imaged by placing the probe immediately above the pubic bone in the midline. Using a transverse scanning plane, the tomographic plane is angled through the bladder to obtain a comprehensive view of the entire structure. Although the primary indication for ultrasonography is to identify urinary retention and to check the position of the drainage catheter, additional pathologic conditions may be identified that require referral to expert-level scanning by the radiology service.

Evaluation for Ascites

Ultrasonography allows the intensivist to identify, characterize, and access intraabdominal fluid. Identification of intraabdominal fluid has implications in urgent evaluation of the patient with abdominal trauma; thus ultrasonography for this application is now in standard use by the trauma team at the point of care. This has been codified in the focused assessment sonographic trauma (FAST) examination. In the medical patient, identification and characterization of ascites requires consideration of its etiology and management. This often requires ultrasonography-guided paracentesis.

Examination for Ascites

Whether performing a FAST examination on a trauma patient or for a less urgent indication on a medical patient, the examination technique is similar. Intraabdominal fluid is readily identified with ultrasonography. It collects in small amounts in the hepatorenal recess, the splenorenal recess, and the pelvis. It collects in larger amounts in the prehepatic and presplenic area, the subphrenic area, and the flanks bilaterally. Air-filled bowel floats on the ascites; characteristically, ultrasonography examination of the anterior abdomen detects air artifact with the fluid distributing in a dependent position.

The patient is in the supine position. The probe is placed in the right or left posterior axillary line using a longitudinal scanning axis over the lower lateral thorax, and the tomographic plane is adjusted to image the hepatorenal or splenorenal space for evidence of ascites manifested as a hypoechoic area. Prehepatic and subphrenic ascites can be identified by angling and/or tilting the probe. The FAST examination includes examination for pelvic ascites. This uses a technique similar to scanning the bladder with the depth setting adjusted to examine the area deep to the bladder. The examination for medical ascites includes the flank areas bilaterally, as this is the preferred site for performance of paracentesis.

Intraabdominal fluid has three characteristic features:

1. An anechoic or relatively hypoechoic space that is subtended by typical anatomic boundaries. This is the ascites.
2. Typical anatomic boundaries. These include bowel structures, the liver, or the spleen.
3. Dynamic changes. These include peristaltic movement of the bowel within the fluid and shape change of the fluid with application of force with the probe against the abdominal wall.

Examination of the Abdominal Aorta

Aortic pathology such as thrombus, atherosclerosis, dissection, or bleeding may be the primary cause for critical illness or may be detected as important secondary findings; therefore identification and characterization of the abdominal aorta is a component of goal-directed abdominal ultrasonography.

The patient is in the supine position. The probe is placed midline above the umbilicus in the transverse scanning plane. The tomographic plane is adjusted to obtain a transverse axis view of the abdominal aorta. The probe is then rotated in a clockwise direction to obtain a longitudinal view of the aorta with measurement of the diameter of the aorta and identification of any associated pathology. If bowel gas obscures the view, gentle downward pressure of the probe often clarifies the image.

Ultrasonography for Guidance of Critical Care Procedures

Ultrasonography can be used to guide a variety of critical care procedures, such as vascular access, pleural interventions, paracentesis, and pericardiocentesis. The widespread availability of high-quality bedside ultrasonography machines coupled with the intuitively obvious utility of the technique has resulted in widespread use of ultrasonography for guidance of procedures by critical care specialists. Independent of the literature that supports the utility of ultrasonography for this application, its widespread adoption must be predicated on a simple principle: there is an advantage to visualizing the anatomy that is relevant to the procedure rather than relying on anatomic landmarks and physical examination.

Ultrasonography for Guidance of Vascular Access

Central Venous Access

Ultrasonographic guidance of central venous access improves success rate and reduces complications at the internal jugular and femoral venous sites[49]; thus ultrasonographic guidance is now a standard of care owing to its advantages related to patient comfort, operator efficiency, safety, and ease of use.[50] Its use is supported by both national and international recommendations.[51–53]

Ultrasonography may be used in two ways to guide central venous access. In one method the operator scans the target area

to identify the appropriate site, angle, and depth for needle penetration into the vessel. The site is marked and the operator performs needle insertion with freehand technique (i.e., without real-time guidance of the needle). This "mark-and-stick" method is associated with a lower success rate and higher complication rate compared with real-time imaging throughout the needle insertion sequence, so real-time needle guidance is the preferred method.[54]

With real-time needle guidance technique, the target vessel may be imaged in either the short or long axis. Most studies describe the short-axis approach, but the long-axis approach has also been well validated. Operator preference determines which method to use. In the authors' experience, the short-axis approach seems to be in widespread use.

In using the short-axis view of the vessel, the needle tip is identified in the subcutaneous tissue well away from the vessel. It is then advanced forward under direct ultrasonographic control by moving the tomographic plane forward in tandem with the forward movement of the needle until the needle enters the vessel. The failure point with this method is that the operator may not maintain visualization of the needle tip as it is advanced toward the target vessel. This may result in adjacent organ injury. Identification and control of the needle tip are critical safety elements. We advise repeated deliberate practice on a task trainer (using a manikin to practice needle localization) before the first patient encounter.

In using the longitudinal view of the vessel, the entire needle is visualized while the operator advances it toward the target vessel. The failure point with this method is that the operator loses full visualization of the entire needle as it is advanced toward the vessel, and the barrel of the needle is misidentified as the needle tip. This may result in adjacent organ injury. Full visualization of the entire needle is a challenge to even a highly skilled operator. A solution to this problem is the use of a needle guide that attaches to the ultrasonographic probe. The needle is held by the device throughout the insertion sequence, so that it remains within the tomographic plane throughout the insertion process. As with the transverse view approach, we advise repeated deliberate practice on a task trainer before the first patient encounter.

Guidance of Internal Jugular Venous Access

Using the high-frequency linear vascular probe, the operator rules out pneumothorax bilaterally before the procedure by examining several anterior rib interspaces. The presence of lung sliding rules out pneumothorax before the start of the procedure. Before sterile skin preparation, both the right and left IJV are then examined in the transverse scanning plane along their length to check for anomalous anatomic position, small size, or a thrombus in the vessel. Although an ipsilateral IJV thrombus is a contraindication to catheter insertion, a contralateral thrombus is a relative contraindication to ipsilateral IJV access because of the possibility of formation of bilateral IJV thrombosis. Marked respiratory variation of IJV size may occur in patients with respiratory distress contraindicating an insertion attempt.

Following standard sterile preparation, the operator inserts the needle into the vessel using real-time ultrasonographic guidance of the needle. Most operators image the vessel in its transverse plane during insertion. After insertion of the guidewire, the operator documents wire position within the vessel before dilation, as the needle tip may have been deflected during wire insertion into adjacent carotid artery. Inadvertent dilation of the carotid artery is a serious complication of failed IJV access. The wire position is best identified by imaging the vessel in its longitudinal axis. After completion of the procedure, the operator examines several anterior rib interspaces to evaluate for the possibility of pneumothorax. The absence of ipsilateral lung sliding after the procedure when it was present immediately beforehand is diagnostic of a procedure-related pneumothorax.

Guidance of Subclavian Venous Access

The principles of ultrasonography guidance of IJV access (precheck and postcheck for pneumothorax, real-time needle guidance, and predilation check of wire position) apply equally to SCV access. The real-time needle guidance may be performed with the vessel visualized in either its longitudinal or transverse access according to operator preference. Because the SCV may not be easily compressible, the distinction between the SCV and the adjacent subclavian artery may be difficult. Observation of respirophasic variation of vessel size or the presence of a venous valve allows confident identification of the SCV. Flow augmentation within the vessel detected with color Doppler scanning upon squeezing the ipsilateral upper arm is characteristic of the SCV.

It often difficult to identify the wire within the SCV as the clavicle may block visualization of the lumen. Inadvertent dilation of the subclavian artery is a serious complication. An alternative method to confirm wire placement within the SCV before dilation is to image the inferior vena cava in the longitudinal axis. Identification of the wire within the IVC confirms appropriate placement within the SCV.

Whether from the IJV or SCV insertion site, correct placement of the catheter tip in the proximal superior vena cava may be confirmed with ultrasonography. Using either the subcostal long-axis view or the RV inflow view, the tip of the wire is identified and adjusted by the operator to rest at the juncture of the RA atrium and proximal superior vena cava (SVC). The catheter is then advanced over the wire until it is visible at the wire tip. After the wire is removed from the catheter lumen, the catheter tip may be further adjusted under ultrasonographic control for correct position.

Another method of confirming appropriate catheter tip position involves injection of agitated saline contrast (ASC) through the central line. Four patterns may be observed:

1. Immediate contrast opacification of the RA without laminar flow pattern. This indicates that the catheter tip position is within the RA and needs to be repositioned.
2. Immediate (<2 seconds) contrast entry into the RA with laminar flow pattern of contrast into the atrium from the SVC. This indicates appropriate catheter tip position and no need for repositioning.
3. Delayed (>2 seconds) contrast entry into right the atrium. This indicates that the catheter is above the level of the SVC and needs to be repositioned.
4. Lack of contrast entry into the RA. This indicates that the catheter tip is not within the venous circulation. Inadvertent arterial cannulation is a possibility.

The use of ASC to determine catheter position has been compared with chest radiography with strong concordance of results. Vezzani et al. reported that a laminar inflow pattern of ASC into the RA from the SVC that occurred within 2 seconds of the injection indicated appropriate catheter tip position. Right atrial placement was indicated by direct visualization of the catheter tip in the RA or by immediate opacification of the RA with use of ASC.[55] Delayed or absent entry of ACS into the RA was associated with malposition of the catheter. Weekes et al. confirmed these results in two additional studies.[56] Both investigations also included

examination for postprocedure pneumothorax using ultrasonography. Duran-Gehring et al. confirmed these findings while including adjustment of catheter position under ultrasonographic control and postprocedure check for pneumothorax.[57]

Provided the operator is able to obtain good-quality images of the cardiac chambers and pleural interface, ultrasonography can replace postprocedure chest radiography for purposes of checking catheter tip position and to rule out procedure-related pneumothorax; the limitation is that patient-specific factors such as body habitus or surgical dressings may degrade image quality to the extent that a chest radiograph is still required.

Guidance of Femoral Venous Access

The use of real-time ultrasonographic guidance for femoral venous access improves success rate and reduces complication of femoral venous access.[58] The vessel is imaged in its transverse access and the needle is guided into vessel using an out-of-plane technique. The standard needle entry point is just below the inguinal ligament where the common femoral vein lies medial to the common femoral artery. Much below this point, the femoral vein is posterior to the artery. As with the IJV and SCV, the operator checks for wire position before dilation.

Peripheral Venous Access

The use of real-time ultrasonography for guidance of difficult peripheral venous access improves the procedure success rate.[59] As the target vessel is often small, the procedure requires a high skill level of needle control. Operator preference determines whether the target vessel is imaged in its longitudinal or transverse axis.

Guidance of Arterial Access

The use of real-time ultrasonographic guidance for arterial access improves success rate and reduces complications.[60]

Ultrasonography for Guidance of Thoracentesis, Paracentesis, and Pericardiocentesis

Ultrasonography has a prime role in the performance of thoracentesis, paracentesis, and pericardiocentesis. Inadvertent injury to adjacent organs during performance of any of these may result in serious complications or death of the patient; therefore the front-line intensivist deploys ultrasonography on a routine basis to reduce the complication rate and improve success rate in these common procedures.

Although each of these procedures has different indications, contraindications, equipment requirements, and complications, the use of ultrasonography for guidance of the procedures shares a common principle: identification of a safe site, depth, and angle for needle insertion into the designated target without injury to adjacent organs. For large collections such as pleural, ascitic, or pericardial fluid, once a safe trajectory for needle insertion has been determined with ultrasonography, the procedure can be safely performed without real-time needle guidance using a mark-and-stick technique. Unlike vascular access, in which the preferred probe is a linear high-frequency probe, a lower-frequency probe is standard for body imaging because of its penetration. The phased-array cardiac probe is useful owing to its small footprint that allows easy scanning between rib spaces. Alternatively, a curvilinear probe designed for abdominal scanning may be used to guide paracentesis, although this probe design is not well suited for thoracic imaging.

Guidance of Thoracentesis

Regardless of whether ultrasonography is used to guide a simple diagnostic thoracentesis or to insert a pleural drainage device that requires wire insertion as part of the procedure, ultrasonography has a prime role in guidance of all pleural procedures. Its use is associated with a reduction of pneumothorax rate,[61] and it allows safe thoracic access in the patient using mechanical ventilatory support during which visceral pleural injury may result in tension pneumothorax.[29] Inadvertent subdiaphragmatic and cardiac injuries are rare, but potentially lethal, complications of pleural access. These can be avoided by use of ultrasonography to identify the relevant anatomy surrounding the pleural fluid collection.

Safe guidance of pleural access requires the operator to identify the pleural effusion (reviewed in the pleural ultrasonography section of this chapter) and to identify a safe site, depth, and angle for needle insertion that avoids injury to adjacent organs, such as the heart, liver, spleen, aorta, or mediastinal structures. Once identified, the site is marked and the depth required for needle penetration is measured from the frozen screen image. After equipment setup and sterile preparation are completed, the needle/syringe assembly is inserted by duplicating the angle of the probe used to identify the safe trajectory for insertion. For the operator to have a clear memory of this critical angle, a confirmatory scan is performed immediately before sterile preparation of the skin. No patient movement is permitted between the final confirmatory scan and needle insertion, as this may result in movement of the fluid within the thoracic cavity with a change in target location. It is inappropriate for the scan to be performed in the radiology suite with a skin mark applied followed by transfer of the patient to the ICU for needle insertion. The intensivist performs both the scan and the needle insertion at the bedside.

As with IJV and SCV access, the operator checks for pneumothorax both before and after thoracentesis as a routine practice. The absence of pneumothorax by ultrasonography examination obviates the need for postprocedure chest radiography. Both wire and final device position may be verified with ultrasonography according to operator preference. Kanai et al. have proposed that the trajectory for needle insertion be examined with the vascular probe to check for the rare occurrence of an aberrantly positioned intercostal vessel.[62] Although this has not been validated in a prospective study design, it can be done easily and could reduce the occurrence of a rare complication of thoracentesis.

Guidance of Paracentesis

Safe guidance of paracentesis requires the operator to identify the ascites (reviewed in the "Abdominal Ultrasonography" section) and to identify a safe site, depth, and angle for needle insertion that avoids injury to adjacent organs such as the liver, spleen, or intestine. The site is marked and the depth required for needle penetration is measured from the frozen screen image. The needle/syringe assembly is inserted by duplicating the angle of the probe used to identify the safe trajectory for insertion. No patient movement is permitted between the final confirmatory scan and needle insertion, as this may result in movement of the fluid within the thoracic cavity with a change in target location. The intensivist performs both the scan and the needle insertion at the bedside.

Guidance of Pericardiocentesis

Tsang et al. reported 1127 serial pericardiocenteses performed under ultrasonographic guidance with a very low complication rate.[63] This definitive study established that ultrasonography is the best

method to guide pericardiocentesis. The alternative—fluoroscopic guidance—is an inferior method as it does not allow a three-dimensional view of the heart, the pericardial effusion, the lung, or the liver that is obtained from the multiple tomographic planes achieved with dynamic ultrasonographic imaging at the bedside. Fluoroscopy allows identification of the position of the heart but is otherwise limited. Another outmoded technique used in conjunction with fluoroscopic guidance is the attachment of an electrocardiographic lead to the needle. Contact with the myocardium yields a current of injury on the electrocardiogram tracing indicating that the needle has been inserted too far. Rather than being preventive, this method detects the complication at the time of its occurrence. The use of ultrasonography for guidance of pericardiocentesis avoids the failure points intrinsic to fluoroscopic guidance.

As with thoracentesis and paracentesis, the operator establishes a safe site, depth, and angle for needle insertion with attention to the position of the liver and myocardium. The lung is identified by the presence of air artifact. Aerated lung blocks visualization of underlying structures, so the presence of air artifact at the site of probe placement contraindicates needle insertion. The liver is of particular concern when planning the needle trajectory from the subcostal approach because it will frequently block safe access to the pericardial effusion. When the parasternal approach is used, there is risk of injury to the internal mammary artery. The vascular probe is used to examine the planned needle trajectory to avoid this complication. When ultrasonographic control is used, the best trajectory for needle insertion is predicated on locating the greatest depth of the effusion in association with avoidance of adjacent organ injury. In the study by Tsang et al., 21% of pericardiocenteses were performed from the subcostal approach; the para-apical approach was used in the majority of cases.[63] With identification of a safe trajectory for needle insertion into the pericardial effusion, the site is marked and the depth required for needle penetration into the pericardial effusion is measured from the frozen screen image. After equipment setup and sterile preparation are completed, the needle/syringe assembly is inserted by duplicating the angle of the probe used to identify the safe trajectory for insertion. Myocardial or coronary artery laceration are lethal complications of pericardiocentesis, so the operator must precisely duplicate the angle of the probe when inserting the needle and limit the depth of insertion to that determined by measurement from the ultrasonographic image. Tsang et al. performed pericardiocentesis without real-time needle guidance with a high degree of safety. It may be useful to have a probe cover prepositioned in the sterile field—not for real-time needle guidance but in case the insertion is unsuccessful with need to adjust site, depth, and/or angle for access. After placement of the pericardial drainage device, its position is confirmed with ultrasonography by injection of ASC.

Ultrasonography can be used to guide other critical care procedures, such as lumbar puncture, transthoracic needle aspiration/biopsy, lymph node aspiration/biopsy, timing of chest tube removal, percutaneous drainage of lung abscess, pacemaker insertion, pulmonary catheter insertion, and gastric tube insertion.

Visualization of Vena Cava Diameter for Guidance of Fluid Resuscitation

The use of the IVC collapsibility index (based on respiratory cycle changes in the IVC diameter) to guide fluid resuscitation in mechanically ventilated patients gained clinical prominence over the past 10 years.[64] Recent data question the level of accuracy of the IVC collapsibility index in predicting fluid responsiveness while supporting the superior vena cava collapsibility index as more accurate and clinically useful than the IVC index.[65,66] Measurement of the SVC collapsibility index requires a transesophageal probe.

Quality Assurance and Imaging Archival Systems

As CCUS becomes a standard part of critical care fellowship training and routine practice by the front-line intensivist, quality assurance of scanning activity is a mandatory component of both training and clinical operations. This requires a well-designed imaging archival system. Review of images is needed for training purposes. Access to image files is required for clinical function, quality assurance, and billing purposes. There are several options for image archiving. One method is to interface CCUS imaging with the hospital radiology picture and archiving system (PACS). Although this method is an optimal solution, there may be impediments in achieving a CCUS-PACS connection. As an alternative solution, some CCUS programs use an ICU-based system for image archival. The typical system consists of a local hard drive that has wireless connectivity with the ICU-based machines. The system is compliant with the Health Insurance Portability and Accountability Act (HIPPA) and is relatively low cost. The system is well designed for image review, documentation purposes, quality assurance, and billing functions. Another solution, absent PACS connection or a local ICU system, is that the critical care team may simply download images from the ICU machine with a flash drive and transfer them to a hospital computer. This is a suboptimal solution associated with a high probability of data loss, difficulty in accessing the images, and risk of noncompliance with HIPPA regulations.

Conclusions

1. Ultrasonography is useful to guide the diagnosis and management of critical illness.
2. The intensivist who uses CCUS assumes all responsibility for image acquisition, image interpretation, and the immediate application of the results at the bedside of the critically ill patient.
3. Training in CCUS focuses on image acquisition, image interpretation, and the cognitive base of well-defined elements of echocardiography, thoracic ultrasonography (lung and pleura), ultrasonography for detection of DVT, screening abdominal ultrasonography, and ultrasonographic guidance of procedures.

Key Points

- The use of critical care ultrasonography is an integral part of the care of ICU patients.
- Professional societies formulated guidelines on training requirements and scope of practice intensivists.
- Basic critical care echocardiography is useful for identification, characterization, and management of the cause of shock.
- Thoracic ultrasound is based on artifacts, including A-lines, which are horizontal reflections of visceroparietal pleura with

no clinical significance, and B-lines. which are vertical lines resonating from the visceroparietal pleura that can represent pathology.
- Lung sliding consists of two pleural surfaces moving against each other in synchrony with the respiratory cycle. The absence of lung sliding may represent a pneumothorax.
- A simple three-point ultrasound examination of the chest identifies the cause of the respiratory failure in a high proportion of cases.
- Vascular ultrasonography performed by an intensivist is used to identify DVT thrombosis with high sensitivity and specificity and shortens the time to diagnosis.
- Screening abdominal ultrasonography is used to identify intraabdominal pathology.
- Ultrasonography used to guide bedside procedures, including central lines, thoracentesis, and paracentesis, decreases complications.

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Review Questions

1. Which of the following statements is true?

a. The parasternal long-axis view (PSLAX) is best obtained at the sixth intercostal space in the midclavicular line.

b. In the apical four-chamber (AP4) view the tomographic plane is adjusted so the interventricular septum is oriented vertically.

c. The subcostal long axis view (SCLAX) is usually the most difficult view to obtain in mechanically ventilated patients.

d. The parasternal long axis view (PSSAX) is obtained by rotating 90 degrees from the AP4 view.

Answer: b. The AP4 view is best obtained at the midclavicular line in the sixth intercostal space. The PSLAX view is best obtained between the third and fifth intercostal spaces with the indicator on the probe facing the patient's right shoulder. The SCLAX view is often the easiest to obtain in intubated patients owing to the heart-lung interactions. The PSSAX is obtained by rotating 90 degrees from the PSLAX view. To obtain an accurate AP4 view the intraventricular septum should be vertical.

2. Which finding does not rule out a pneumothorax?

a. Lung pulse

b. A-lines

c. B-lines

d. Lung sliding

Answer: b. The pleural line represents the apposition of the parietal and visceral pleural surfaces. Lung sliding is two pleural surfaces moving against each other in synchrony and that rules out a pneumothorax. Cardiac pulsations that result in cardiophashic movement of the visceral pleural against the parietal pleura are called lung pulses and this finding rules out a pneumothorax. B-lines are vertical lines that originate at the pleural surface and extend to the bottom of the screen and their presence rules out a pneumothorax. A-lines are horizontally oriented lines that are located deep to the pleural line, but their presence does not rule out a pneumothorax.

3. Which of the following statements is true?

a. The mark-and-stick method for obtaining venous access has a success rate equal to real-time guidance of needle placement in the internal jugular vein (IJV).

b. Short-axis visualization of the IJV is associated with a higher success rate than long-axis visualization of the vein during placement of a central line.

c. The use of real-time ultrasonography does not improve the success rate for difficult peripheral venous access.

d. Ultrasound guidance decreases thoracentesis complications in mechanically ventilated patients.

Answer: d. Real-time ultrasound guidance improves the success rate and lessens complications when placing IJV central venous access. Short-axis and long-axis real-time visualization of the IJV have equivalent success rates during placement of central lines. Real-time ultrasonography improves peripheral intravenous success rates. Ultrasound guidance during thoracentesis in mechanically ventilated patients decreases complications related to the procedure.

19

Continuous Renal Replacement Therapy

OLEKSA G. REWA AND SEAN M. BAGSHAW

CHAPTER OUTLINE

Physiologic Principles
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Acute kidney injury (AKI) occurs in 50% to 70% of all patients admitted to the intensive care unit (ICU), with approximately 20% to 30% of these patients receiving renal replacement therapy (RRT).[1] The incidence of dialysis-requiring AKI has steadily increased.[2] Among those critically ill patients with more severe AKI treated with RRT, continuous renal replacement therapy (CRRT) remains the most common modality prescribed in ICU settings worldwide.[3]

The establishment of CRRT evolved as a treatment of hemodynamically unstable patients unable to tolerate or achieve adequate therapy with conventional intermittent RRT (IRRT) or peritoneal dialysis. In general, CRRT offers many theoretical advantages over IRRT in ICU settings, including better hemodynamic tolerance, enhanced fluid balance, and enhanced uremic solute homeostasis and renal recovery; however, the superiority of CRRT relative to IRRT remains controversial. CRRT technology has undergone marked advances over time to improve efficiency, safety, and bedside simplicity.[4]

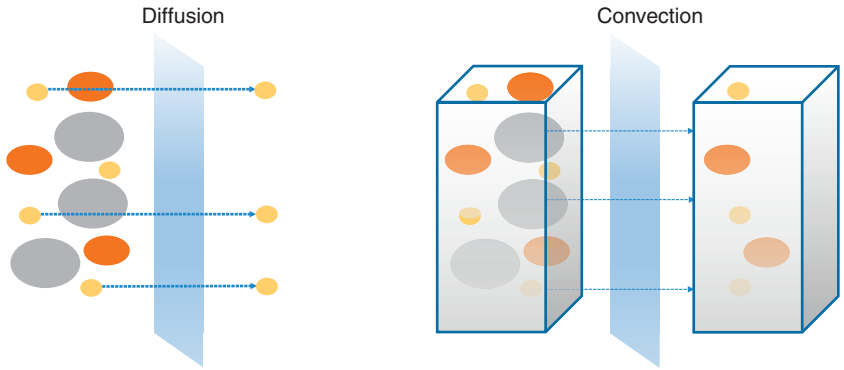
Physiologic Principles

CRRT uses a semipermeable membrane to alter the molecular composition and concentration of blood to restore the body back toward homeostatic balance. Blood flows along one side of the semipermeable membrane and a wash solution, dialysate, flows on the opposite side of the membrane. CRRT relies on two physical forces—*diffusion* and *convection*—either in isolation or in combination (Fig. 19.1).

In *diffusion*, the net movement of solute is dependent on the diffusivity of the solute and solvent, membrane permeability, membrane surface area, and concentration gradient, as governed by Fick's law. Other membrane characteristics also play a role: thickness, pore size, and electrostatic charge. To maximize the concentration gradient between the blood and dialysate, the dialysate runs countercurrent to the flow of blood. Any substance that is in higher concentration in the blood than the dialysate flows "down" its concentration gradient (e.g., creatinine, urea) and leaves the blood and flows into the dialysate. Conversely, any solute that is in higher concentration in the dialysate (e.g., bicarbonate) leaves the dialysate, crosses the semipermeable membrane, and enters the blood. Diffusion is most efficient in the clearance of low–molecular-weight (LMW) substances (<500 Da). This is particularly useful in correcting the imbalance in small molecule electrolytes (e.g., potassium [K], calcium [Ca], magnesium [Mg], phosphate [PO_4]). This form of transport occurs in continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF).

In *convection*, solutes move across a membrane in response to or following solvent flux (i.e., hydrostatic pressure is applied on the blood side of the membrane) or drag: solutes are moving along with the solvent containing them. *Solvent drag* is limited only by the pore size or electrostatic charge of any semipermeable membrane that is applied across the passage of the solution. In convection, the concentration of a solute is similar on either side of the membrane. Convection is more efficient at the clearance of high–molecular-weight substances (HMW) (500–5000 Da). Convective removal of plasma water from blood across a large-pore, semipermeable membrane results in an *ultrafiltrate* with a solute composition equivalent to plasma water. This occurs in both continuous venovenous hemofiltration (CVVH) and CVVHDF.

Fluid removal is termed *ultrafiltration* (UF). UF uses hydrostatic pressure, which is applied across a semipermeable membrane. This is a form of convective removal of solute. The clearance of molecules in UF is dependent on the volume of fluid removed.



• **Fig. 19.1** Forms of solute and water transport in continuous renal replacement therapy. Diffusion is depicted on the left. Solute is passively transported across a semipermeable membrane where molecules move from an area of higher concentration to an area of lower concentration. It is best for lower–molecular-weight solute clearance. Convection is depicted on the right. Solute is actively transported across the semipermeable membrane with the solvent (i.e., solvent drag) in response to the positive transmembrane pressure. It is best for higher–molecular-weight solute clearance.

It may be applied in isolation (in volumes usually <5 L/day) or in combination with other blood clearance techniques, such as dialysis. UF can occur in all forms of CRRT. To maintain isovolemia, each unit volume that is removed by UF is replaced with a balanced solution that is devoid of the metabolic waste and uremic solute.

Notwithstanding the mechanisms of plasma water and solute movement in CRRT, there are several parameters that can be used to characterize the performance of CRRT. *Clearance* is used to estimate the solute clearance of the blood and can be defined by the following formula:

$$K = N/C_b,$$

where K is solute clearance, N is the mass removal rate, and C_b is the blood solute concentration. In CRRT, the mass removal rate is estimated by measuring the actual amount of solute appearing in the effluent (i.e., the "waste" CRRT fluid) and is the product of effluent flow rate and the effluent concentration of the solute. This applies when diffusion occurs (i.e., CVVHD and CVVHDF). In CVVH, where no dialysate is used, clearance occurs by means of the solvent drag and is the product of the *sieving coefficient* (SC) and the UF rate. The SC represents the degree to which a membrane (i.e., filter) permits the passage of a certain solute. It can be represented by the following formula:

$$SC = C_{UF}/C_p,$$

where C_{UF} is the solute concentration in the ultrafiltrate and C_P is the concentration in the plasma. The SCs of LMW substances, such as urea and creatinine, approach 1.0 (i.e., cleared completely), whereas the SCs of HMW substances are more variable depending on the size of the substance and the membrane characteristics.

Another form of clearance of the blood is through a process called *adsorption*. This refers to molecules in the blood adhering to the semipermeable membrane. This process is dependent on the molecules contained in the blood and the composition of the semipermeable membrane. Adsorption is usually time dependent (i.e., as the semipermeable membrane is used over time, it will become saturated with a given molecule). The process begins anew when the membrane is changed (approximately every 72 hours). Selected inflammatory mediators and drugs may be cleared through this process.

CRRT is the continuous extracorporeal purification of blood (i.e., hemofiltration, dialysis, and UF) intended to support lost intrinsic kidney function. CRRT is performed through a centrally inserted double lumen-venous catheter where blood is driven by a pump through a semipermeable membrane via an extracorporeal circuit.

Principles of Ultrafiltration

Targeting fluid balance by removal is one of the most common indications for CRRT. In prescribing UF, a specific volume of fluid loss per unit of time should be determined. UF by CRRT is intended to be slow and continuous. The steady, constant loss of fluid at a rate that does not exceed the plasma-refill rate gives CRRT its superior hemodynamic stability compared with conventional intermittent hemodialysis (IHD). If extremely rapid UF in a short time frame is the therapeutic intent, intermittent forms of pump-driven UF are more efficient and therefore the treatment of choice. Common UF rates range from 50 to 400 mL/h. Larger amounts may be obtained if there is a need for rapid fluid removal. Automated continuous machines control UF through a volume-driven system, establishing a fixed loss of a determined amount of fluid from the system over a given period of time (usually on an hourly basis). The blood flow rate (QB) has a significant effect on any UF system. During UF, plasma water is removed from the blood as it moves through the dialysis filter, thereby increasing the viscosity of blood in the filter, measured by the filtration fraction. If the viscosity increases excessively, the system will clot. Therefore whenever UF is being prescribed, an appropriate QB must be prescribed to accommodate the prescribed UF. Careful attention should be given to the amount of excess recirculation. Rates greater than 15% are associated with a greater incidence of clotting. This tendency is more evident at higher UF rates (>300 mL/h), at which the returning blood tends to have a higher hematocrit, creating a more viscous, afferent blood flow.

Principles of Hemofiltration

If excessive fluid removal occurs, additional fluid may be needed as replacement to maintain intravascular volume homeostasis. This is termed *hemofiltration* or plasma water exchange. Fluid replacement

TABLE 19.1 Comparison of Predilution and Postdilution Techniques for Continuous Renal Replacement Therapy

Feature	Predilution	Postdilution
Clearance	Less clearance per milliliter	High small solute clearance per milliliter
Efficiency	Reduced efficiency by 10%–15% and reduced filtration fraction	
Ultrafiltration rate limitations	Ultrafiltration rate not limited	Ultrafiltration rate limited by blood pressure and hemoconcentration (filtration fraction)
Blood viscosity	Low viscosity of the blood	High viscosity of the blood and increased risk of clotting

can be delivered into the blood circuit either prefilter, before UF has occurred (predilutional hemofiltration), or after fluid has been removed by the filter (postdilutional hemofiltration) (Table 19.1). In predilutional hemofiltration, ultrafiltrated fluid reflects the mixture of blood and replacement solution. Because the oncotic pressure of blood is reduced within the filter, a greater rate of fluid removal is possible at the same transmembrane hydrostatic pressure. This increased rate of fluid removal is offset by dilution of plasma solute. In other words, the overall mass transfer of uremic toxins is reduced, and higher rates of fluid exchange are required to compensate. It is common to have exchange rates of 30 to 40 L/day. Predilutional hemofiltration may also be used for patients with high hematocrit levels in an effort to reduce clotting episodes. Postdilutional fluid replacement has the advantage of being easier to perform, with lower rates of fluid exchange compared with the predilutional system. One problem with this form of replacement is the increased oncotic pressures at the venous end of the filter. With high rates of exchange or high degrees of access recirculation, blood viscosity may be increased, which may predispose to clotting. Therefore fluid exchange rates may be dictated by such factors as hematocrit, blood flow, and access recirculation. The system should be kept below a filtration fraction of 15% in postdilution and 30% in predilution hemofiltration for efficient operation and a lower risk of clotting.

Principles of Hemodialysis

In hemodialysis (HD), the flow of dialysate is countercurrent to that of blood to maximize transmembrane concentration differences across all blood concentrations and at all levels of the filter. Blood flow (100–300 mL/min) is maintained well above the usual dialysate flow rates (15–30 mL/min). By contrast, in IHD, blood flow, rather than dialysate flow, is the limiting factor in diffusive clearance. Clearance of LMW substances is "flow dependent" because there is little resistance to transmembrane movement posed by the porous membrane. Substances of higher MW (e.g., β_2-microglobulin, vitamin B_{12}) are relatively slow in crossing the dialyzer membrane and are "membrane-dependent" molecules. Using the high-flux membrane characteristics generally used with continuous therapies, substances with molecular weights (masses) of 20,000 to 30,000 Da are transferred at rates that have an inverse relationship to their molecular weights. LMW substances (i.e., electrolytes, urea, creatinine) easily cross membranes at a rate that is directly proportional to membrane surface area, temperature, and concentration difference, and inversely proportional to viscosity, distance from the membrane, and molecular size. Protein-bound solutes are not subject to the concentration gradients that drive the molecular transport across the membrane. This concept is the basis for altered drug kinetics when patients are subjected to continuous supportive therapy. In CVVHD, dialysate flow rates remain the most influential factor in determining urea clearance. Dialysate usually is delivered via pumps at rates of 15 to 40 mL/min. Given adequate blood flow through the circuit, one can see why the limiting factor for flow-dependent transfer is the relatively low dialysate flow rate. Blood flow and filter membrane have limited effects on the diffusion of molecules compared with the potential of dialysate flow changes. In addition to the dialysate inflow, the dialysate outflow also must be controlled. By setting the outflow rate higher than dialysate inflow rates, one can create a negative transmembrane pressure, promoting UF across the dialysis membrane. This difference in flow is used to establish the rate of UF. An increase or decrease in this flow difference would increase or decrease the rate of fluid loss.

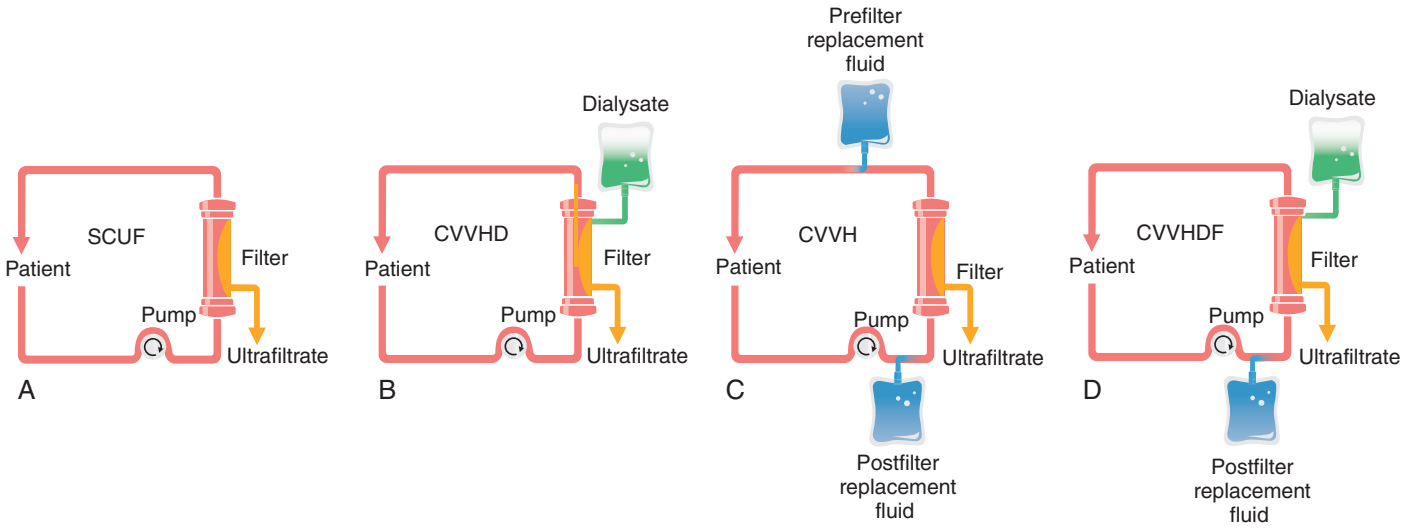
CRRT Modalities

The various modalities of CRRT are depicted in Fig. 19.2 and Table 19.2. CVVH is a form of CRRT where solute is cleared by convection and where the ultrafiltrate is either completely or partially replaced before (i.e., predilution) and/or after (i.e., postdilution) to the hemofilter (see Table 19.1). CVVHD is characterized by slow countercurrent dialysate flow into the dialysate compartment of the hemodialyzer, similar to traditional IHD. The main mechanism of solute removal is diffusion. CVVHDF combines hemofiltration and hemodialysis modalities. Solute clearance is achieved by both convective and diffusion mechanisms (Table 19.3). Slow continuous UF is based on the slow removal of plasma water (i.e., ultrafiltrate) only; there is no clearance of solutes. Table 19.2 summarizes the details of CRRT modalities.

Patient Selection and Timing of Initiation

There is no consensus on the optimal circumstances and timing for starting CRRT in critically ill patients.[5] The conventional "life-threatening" indications include volume overload, hyperkalemia, metabolic acidosis, uremia, and intoxication with a dialyzable compound (Box 19.1). Both patient-specific (i.e., reduced baseline kidney function) and provider-specific factors (i.e., perception of benefit) may influence the decision to start RRT. These may include use of CRRT to prevent AKI in patients with reduced kidney reserve (i.e., tumor lysis, myoglobinemia, nephrotoxic treatment), to prevent worsening nonrenal organ dysfunction owing to AKI, to help manage volume homeostasis (i.e., delivery nutritional support), and to compensate for respiratory acidosis in acute respiratory distress syndrome (ARDS).

Observational data and small clinical studies have suggested earlier CRRT may facilitate improved volume, acid-base, electrolyte, and uremic solute control.[6] Alternatively, an earlier start to CRRT may have disadvantages and be associated with risks, particularly for patients with marginal indications, including complications



• **Fig. 19.2** Summary of continuous renal replacement therapy (CRRT) modes showing the four primary CRRT modalities. A shows slow continuous ultrafiltration *(SCUF)* where only ultrafiltrate removal occurs. B shows continuous venovenous hemodialysis *(CVVHD).* C shows continuous venovenous hemofiltration *(CVVH)* with fluid replaced before *(Prefilter)* and after *(Postfilter)* replacement fluid. D shows continuous venovenous hemodiafiltration with fluid replaced postfilter *(CVVHDF).*

TABLE 19.2 Modalities of Continuous Renal Replacement Therapy

Feature	SCUF	CVVH	CVVHD	CVVHDF
Method of clearance	Convection	Convection	Diffusion	Convection and diffusion
Middle molecular size clearance	+	+++	+	+++
Replacement fluid	None	Present	None	Present
Dialysate	None	None	Present	Present
Effluent composition	Ultrafiltrate	Ultrafiltrate	Dialysate + ultrafiltrate	Dialysate + ultrafiltrate

+, Minimal; +++, considerable.
CVVH, Continuous venovenous hemofiltration; *CVVHD,* continuous venovenous hemodialysis; *CVVHDF,* continuous venovenous hemodiafiltration; *SCUF,* slow continuous ultrafiltration.

related to insertion and maintenance of vascular catheters, bloodstream infection, hemodynamic instability, and electrolyte abnormalities. Moreover, CRRT can also disrupt drug pharmacokinetics and increase bedside workload and health costs (Box 19.2).

Several recent randomized clinical trials have evaluated the optimal start for RRT in critically ill patients; however, findings have been contradictory (see Table 19.3). The ELAIN trial (Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury), a single-center study of 231 predominantly postsurgical ICU patients, found early compared with delayed start to RRT improved survival and kidney recovery in critically ill patients with AKI.[7] Alternatively, the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial, a multicenter study of 620 critically ill patients without an urgent indication for RRT found no difference in survival; however, it showed only approximately 50% of those allocated to the delayed strategy received RRT.[8] These trials have highlighted the complexity of decision making for when to start RRT.[6]

Discontinuation of CRRT

Relatively few studies have focused on the optimal timing and circumstances for liberation from CRRT. Failure to successfully discontinue CRRT is associated with increased mortality.[9] Most studies have generally shown restoration of spontaneous urine output (>500 mL/24 h) to have the greatest predictive value for weaning, whereas persistent oligura (<100 mL/8 hr) predicted resumption of CRRT.[9–12] Urine biochemistry may also have value for predicting successful RRT discontinuation.[13–15] Timed 2-hour creatinine clearance (in the 12 hours preceding CRRT cessation) and greater 24-hour urine creatinine excretion have shown association for successful CRRT discontinuation. Although some urinary markers have shown more accurate prediction ability for successful RRT discontinuation than urine output, studies evaluated were small and conducted in single-center settings; thus the findings might not be generalizable. Furosemide is often administered to increase urine output and try to facilitate RRT liberation[9]; however,

TABLE 19.3 Summary of Recent Randomized Trials of Timing of Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury

Trial	Bouman et al.[69]	Jamale et al.[70]	STARRT-AKI I[39]	HEROICS[36]	ELAIN[7]	AKIKI[8]
Center(s)	Single	Single	Multiple	Multiple	Single	Multiple
Patients (no.)	106	208	100	224	231	620
Population	Mixed—shock	Medical	Mixed	Cardiac surgical	Mixed	Mixed
Inclusion criteria	UO <30 mL/h × 6 h; CrCl <20 mL/min; MV	Severe AKI + increasing SCr and urea	SCr ≥100 μmol/L in females and 130 μmol/L in males; presence of severe AKI by any two of the following: twofold increase in SCr from baseline, urine output <6 mL/kg in 12 h, and/or whole blood NGAL ≥400 ng/mL; absence of urgent indications for RRT; and low likelihood of volume-responsive AKI	High-dose catecholamines or extracorporeal mechanical support within 24 h of surgery	KDIGO stage 2 AKI + NGAL >150 ng/mL *and* any one of the following: severe sepsis, use of vasoactives; refractory fluid overload; nonrenal organ dysfunction	KDIGO stage 3 AKI *and* receiving MV and/or vasoactive support
Early group	Within 12 h of eligibility	Urea >25 mmol/L or SCr >619 μmol/L	Within 8 hr of KDIGO stage 2	Immediate upon eligibility	Within 12 h of eligibility	Within 6 h of eligibility
Delayed group	Conventional criteria for RRT: urea >40 mmol/L; K >6.5 mmol/L; or severe pulmonary edema	Clinically indicated as judged by consensus of two clinicians	Conventional criteria for RRT: K >6.0 mmol/L; serum bicarbonate <10 mmol/L; Pa_{O_2}/Fi_{O_2} ratio <200 with infiltrates compatible with pulmonary edema	Conventional indications for RRT: KDIGO stage 3 AKI; urea >36 mmol/L; or life-threatening hyperkalemia	Within 12 h KDIGO stage 3 or conventional indications for RRT: urea >36 mmol/L; K >6.0 mmol/L; Mg >4 mmol/L; urine output <200 mL/12 hr or anuria; diuretic-resistant organ edema	Conventional criteria for RRT: severe hyperkalemia; severe pulmonary edema; severe acidosis; urea >40 mmol/L; oligoanuria >72 h
Mortality difference	NS	NS	NS	NS	Early > delayed (P = 0.03)	NS

AKI, Acute kidney injury; *AKIKI,* Artificial Kidney Initiation in Kidney Injury; *CrCl,* creatinine clearance; *ELAIN,* Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury; *HEROICS,* Hemofiltration to Rescue Severe Shock following Cardiac Surgery; *K,* potassium; *KDIGO,* Kidney Disease Improving Global Outcomes; *Mg,* magnesium; *MV,* mechanical ventilation; *NGAL,* neutrophil gelatinase-associated lipocalin; *NS,* not statistically significant; *RRT,* renal replacement therapy; *SCr,* serum creatinine; *START-AKI,* standard versus accelerated initiation of renal replacement therapy in acute kidney injury; *UO,* urine output.

a small trial failed to show furosemide improved recovery after CRRT cessation.[16] Limited data have not conclusively shown novel kidney damage and repair biomarkers provide added decision support on when to optimally attempt liberation from CRRT.[17,18]

Continuous RRT Versus Intermittent RRT

The clinical presentation and circumstances may favor either intermittent or continuous therapies (Table 19.4). There are many theoretical benefits that may favor the use of CRRT over intermittent forms of therapy, such as improved hemodynamic stability, faster resolution of fluid overload, and increased dialysis dose delivery (Table 19.5). Selected nonrenal indications favoring use of CRRT include fulminant hepatic failure, brain injury with risk of cerebral edema, and hyperammonemia (see Box 19.1).

The most important short-term advantage to CRRT over IRRT is the preservation and maintenance of hemodynamic stability. CRRT enables slower removal of solute and fluid from the intravascular space, permitting adequate time for vascular refilling from the interstitial and intracellular space, and theoretically minimizing iatrogenic episodes of hypotension. There are longer-term implications for renal recovery, with IHD-related instability potentially exacerbating or predisposing to recurrent episodes of kidney injury and disrupting repair and recovery. Data from rigorous, comparative studies, however, have shown variable conclusions.[19]

Robust data in support of the many theoretical advantages of CRRT are still lacking. In fact, Box 19.3 lists some of the limitations of CRRT. Interpretation of published data has been hampered by retrospective analysis, the use of historical control groups, incomplete randomization, incomplete descriptions of patient populations

• BOX 19.1 Indications for Renal Support

Absolute (Conventional) Indications

Pulmonary edema
Hyperkalemia
Metabolic acidosis
Uremic complications (i.e., encephalopathy, pericarditis, bleeding)
Toxin removal

Relative Indications

Medically refractory volume overload
Electrolyte imbalances
- Hyponatremia
- Hyperphosphatemia
- Hypermagnesia

Acid-base balance
- Metabolic acidosis
- Mixed acidosis/alkalosis
- Severe metabolic alkalosis

Nonrenal indications
- Lactic acidosis
- Myoglobinemia (i.e., crush injury)
- Tumor lysis syndrome
- Temperature control (i.e., hyperthermia/hypothermia)
- Hyperammonemia
- Nutritional support

Theoretical Indications

Immunomodulation

TABLE 19.4 Clinical Considerations in Continuous Renal Replacement Therapy Versus Intermittent Hemodialysis in the Intensive Care Unit

	METHOD OF DELIVERY	
Condition/Feature	Intermittent	Continuous
Hemodynamic instability	No/yes	Yes
High fluid requirements	No/yes	Yes
High potassium generation	Yes	No
High catabolism	Yes	Yes/no
Peripheral vascular disease	Yes	Yes/no
Global cardiac dysfunction	No/yes	Yes
Septic shock	No/yes	Yes
APACHE II score above 25	No/yes	Yes

APACHE, Acute Physiology and Chronic Health Evaluation.

and RRT dose delivery, and study group–control group heterogeneity.

In the absence of a robust evidence base to guide clinical decision making, clinicians must adopt a patient-centric view to provide the most effective and safe RRT option for a given patient at a given point during their critical illness. The fundamental indications for delivering renal support remain unchanged (see Box 19.1) and range from the most frequent request for volume homeostasis to more esoteric indications such as immunomodulation. Common considerations in choosing to apply intermittent or continuous support are listed in Table 19.4, being mindful of numerous relative advantages and disadvantages of each (see Table 19.5). A final consideration relates to timeliness and feasibility. CRRT can often be prescribed in collaboration with ICU and nephrology, can be started any day of the week at any time of day, and can be started and managed solely by an ICU nurse, whereas this may not always be possible with IRRT. Recent data have suggested critically ill patients receiving RRT can be safely mobilized and receive physiotherapy, including those with catheters in the femoral position.[20–22]

• BOX 19.2 Potential Complications of Continuous Renal Replacement Therapy

Access

Distal arterial insufficiency
Embolism (air, thrombus, foreign body)
Early
Early thrombosis
Infection
Hematoma (local/retroperitoneal)
Late
Angiocutaneous fistula
Stenosis
Aneurysm (pseudo/real)
Loss of potential long-term intermittent hemodialysis arteriovenous fistula/graft site

Blood Pump

Air embolism
Blood loss

Lines

Disconnection/hemorrhage
Infection
Thrombosis
Kinking

Kidney

Clotting
Membrane rupture
Backdiffusion of pyrogens from contaminated dialysate
Membrane hypersensitivity reaction

Therapy

Overanticoagulation/citrate intoxication
Electrolyte abnormalities
Amino acid losses
Fluid imbalance
Hypothermia

Prescription Variables

Continuous Hemodialysis Versus Continuous Hemofiltration

Both hemodialysis and hemofiltration are equally efficient in the removal of LMW solutes; however, there is uncertainty about the incremental benefit afforded by hemofiltration. Hemofiltration may remove a wider spectrum of solutes, including inflammatory mediators and cytokines that are not removed by hemodialysis, making hemofiltration attractive, although unproven, as a potentially

TABLE 19.5 Intermittent and Continuous Forms of Renal Replacement Therapy

Feature	MODALITY		
	IHD	SLED	CRRT
Setting	Hemodynamically stable	Hemodynamically unstable	Hemodynamically unstable Increased intracranial pressure
Advantages	Rapid removal of low–molecular-weight substances and toxins Time when not receiving treatment may be used for diagnostic or therapeutic procedures Reduced anticoagulation exposure Low cost	Hemodynamic stability Time when not receiving treatment may be used for diagnostic or therapeutic procedures Decreased anticoagulation requirements	Easy control of fluid balance Hemodynamic stability Continuous removal of toxins
Disadvantages	Hypotension with rapid fluid removal Dialysis disequilibrium with risk of cerebral edema Technically complex	Slower clearance of toxins Technically complex	Slower clearance of toxins May require anticoagulation Patient immobilization Hypothermia Increased costs

CRRT, Continuous renal replacement therapy; *IHD,* intermittent hemodialysis; *SLED,* sustained low-efficiency hemodialysis.

• BOX 19.3 Disadvantages of Continuous Renal Replacement Therapy

Anticoagulation
No rapid removal of electrolytes
Limited role in overdose
Relative hypothermia (masks a true fever)
Electrolyte depletion: K^+, PO_4^{3-}, Ca^{2+}, Mg^{2+}
Bleeding and thrombosis complications
Minimal removal of protein-bound substances
Membrane adsorption
Negative balance of selenium, copper, thiamine, Mg^{2+}, Ca^{2+}

Ca^{2+}, *Calcium ion;* K^+, *potassium ion;* Mg^{2+}, *magnesium ion;* PO_4^{3-}, *phosphate.*

adjuvant therapy for sepsis.[23] Mechanistic studies have shown the superiority of convective clearance in the removal of certain larger-sized MW solutes.[23–25] However, the effect of hemofiltration compared with hemodialysis on patient-relevant outcomes remains unclear.[26] A meta-analysis that compared hemofiltration and hemodialysis did not find any differences in patient survival or kidney recovery.[27] Pooled analysis did confirm; however, that hemofiltration was associated with greater removal of higher-MW solutes (i.e., β_2-microglobulin, vancomycin), but further found hemofilter survival may be extended by using hemodialysis, alone or in combination with hemofiltration, compared with hemofiltration alone.[27,28] Accordingly, the modality prescribed should be tailored to patient goals of therapy and institutional and provider expertise until further evidence becomes available.

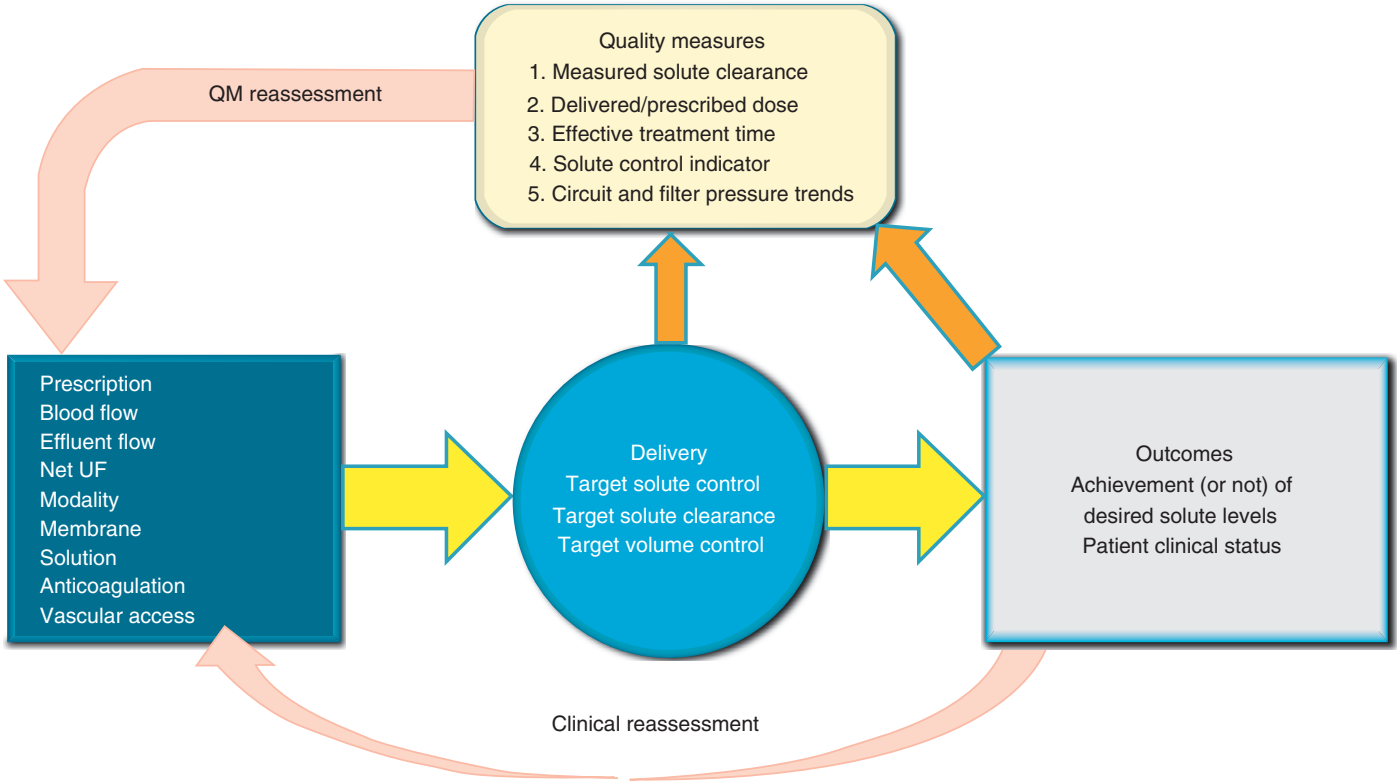
CRRT Prescribed and Delivered Dose

Dose in RRT refers to how much of a measure of the quantity of a representative marker solute is removed from a patient (i.e., reduction in serum creatinine, urea, or potassium or increase in serum bicarbonate over time during treatment with CRRT). Several trials had variably suggested that higher doses of CRRT improved outcomes in critically ill patients with AKI.[29–32] However, two large multicenter randomized clinical trials (ATN [Acute Renal Failure Trial Network] and RENAL [Randomized Evaluation of Normal versus Augmented Level Replacement Therapy]) failed to confirm these findings.[33,34] In the ATN study, CRRT was used in patients who were hemodynamically unstable while conventional IHD was used in patients who were hemodynamically stable.[33] Predilution CVVHDF was dosed to provide an effluent rate of 20 mL/kg per hour in the less intensive arm and 35 mL/kg per hour in the more intensive arm. In the RENAL study, patients were randomly assigned to postdilution CVVHDF at an effluent rate of 25 mL/kg per hour or 40 mL/kg per hour.[34] Neither study detected a survival or kidney recovery benefit from more intensive RRT, including across several subgroup analyses (e.g., sepsis). There is no evidence that high-volume hemofiltration (>35 mL/kg per hour) compared with conventional CRRT dose is beneficial in patients with septic or post-cardiac surgery vasoplegic shock.[35,36]

Accordingly, the current recommendation for a minimum dose of RRT supports the delivery of at least 20 to 25 mL/kg per hour of CVVH, CVVHD, or CVVHDF. However, patient-driven prescription should also be considered to ensure adequate metabolic, electrolyte, acid-base, and volume homeostasis.[37] Similarly, patients should receive a minimal dose of 20 to 25 mL/kg per hour with careful attention to ensuring that the target dose of therapy is actually delivered,[38] while recognizing that the prescription may need customizing to achieve these goals (Fig. 19.3). Both the RENAL and ATN trials showed that the delivered dose is often less than the prescribed dose. As such, this may practically translate into a prescribed dose of 25 to 30 mL/kg per hour if there was anticipation of treatment downtime or interruptions.

CRRT for Volume Control

The ability to control volume status is a fundamental consideration for CRRT initiation. Although studies have largely focused on timing of CRRT initiation based on serum creatinine or other metabolic thresholds,[7,8,39] a trigger based on a fluid accumulation threshold may be equally important in selected circumstances,



• **Fig. 19.3** Principles of continuous renal replacement therapy (CRRT) dose prescription. After the initial dose prescription, providers should reassess the response to the prescribed CRRT dose. This can be achieved by following select quality measures focused on dose delivery. Additionally, the patient's condition may change while undergoing CRRT, necessitating additional modifications. *QM,* quality measure; *UF,* ultrafiltration. (Reprinted with permission from Acute Dialysis Quality Initiative; www.ADQI.org.)

such as when fluid accumulation fails to respond to diuretic therapy or when their use compounds metabolic complications.[40,41] The primary therapeutic goal of CRRT in such settings is to allow for optimal nutrition, medication, and blood product administration, while concomitantly maintaining solute and volume homeostasis.[42] With respect to volume homeostasis, the decision to initiate CRRT should be based on the following four factors: (1) anticipated obligatory daily fluid requirement; (2) current and predicted output in terms of urine, chest tube, and/or other actual fluid losses; (3) likelihood of kidney function recovery in the subsequent 24 hours; and (4) the current fluid accumulation status. CRRT can prevent unavoidable fluid accumulation, maintain euvolemia, and facilitate organ support weaning (i.e., mechanical ventilation). CRRT enables hourly calculation and adjustment of UF and enables gradual fluid removal.

Technical Considerations

Access

Access for CRRT is accomplished through placement of a large (>12F) double-lumen central venous catheter. Preexisting arteriovenous fistulas or grafts in general are not used for CRRT, as this would require needles to be continuously placed in the fistula or graft, which may damage it.

Ultrasound guidance should be the reference technique for CRRT catheter placement.[4] A meta-analysis, evaluating a total of 830 catheters, showed reduced risk of catheter placement failure, higher rate of placement on the first attempt, decreased numbers of attempts, decreased time to successful placement, and a decreased rate of complications when compared with conventional anatomical landmark placement.[43]

Both the femoral and jugular venous routes are acceptable sites for catheter placement. Studies have shown similar rates of catheter-tip colonization and catheter-related bloodstream infection.[44,45] Placement of temporary catheters at the subclavian site are associated with risk of development of venous stenosis and are discouraged.[46]

Rates of catheter dysfunction were comparable between jugular and femoral locations with two notable exceptions.[47] First, catheter dysfunction and rate of recirculation may be higher with catheters in the femoral location, particularly with catheters less than 25 cm in length or with lower flow capacity.[47–49] Second, owing to anatomic differences, catheter placement in the left internal jugular vein was found to be associated with greater catheter dysfunction.[47] In patients in whom severe dysfunction develops, a catheter change is often required. Although guidewire exchange appears similar with respect to risk of catheter-tip colonization or infection compared with new site placement,[50] this strategy may be associated with a greater than threefold rate of catheter dysfunction.[51] The risk of catheter colonization and infection is strongly correlated to exposure time. Accordingly, the necessity of the RRT catheter should be reassessed daily and the catheter removed once RRT is no longer necessary.[5,52]

Tubing

Long tubing for blood transport increases exposure of blood to nonbiologic surfaces, which cools the blood and increases the risk of clotting. The presence of sampling ports, entry ports, and stopcocks may create blood turbulence. Negative preblood pump pressures can easily introduce air into the circuit from a dysfunctional afferent limb of a catheter and would carry the risk of air embolism were it not for the presence of an air trap in the efferent limb of the circuit.

Membrane

The details of membrane technology are beyond the scope of this chapter; however, the key highlights are presented here. The filter design in CRRT is hollow-fiber. The design consists of a blood compartment and a dialysate compartment, with respective inflow and outflow ports, separated by a semipermeable membrane. The hollow-fiber dialyzer consists of a tubular casing containing thousands of narrow capillary fibers through which blood flows between the arterial and venous header—two small spaces at either end of the filter where blood collects before and after running through the capillary fiber bundle. The capillaries, whose walls constitute the semipermeable membrane, are bathed in dialysate fluid, usually running in countercurrent fashion to blood flow. The hollow-fiber design allows for the maintenance of systemic blood pressure. However, if clots form at the arterial header, a large surface area of membrane for electrolyte exchange may become unavailable. Membranes may be made from (1) cellulose (e.g., cuprophane), (2) substituted cellulose (the free hydroxyl groups of cellulose, thought to activate complement, are bound to other substances, e.g., acetate in cellulose acetate membranes), (3) cellulosynthetic material (synthetic material incorporated with the cellulose polymer; e.g., Hemophan, Membrana Gmbh Solutions, Wuppertal, Germany), and (4) synthetic material (made of noncellulosic materials; e.g., polysulfone-polyacrylonitrile, polyamide, and polymethyl methacrylate). Nearly all conventional CRRT filter membranes now in use are biocompatible and synthetic.

Solutions

Replacement solutions take the form of either dialysate or replacement fluid. When hemofiltration is performed, replacement fluid composition dictates the resultant concentration of electrolytes. Similarly, knowing the composition of dialysate is important to determine to what equilibrium the electrolytes will settle. Calcium and magnesium levels should be monitored closely, and replacement should be initiated at an early stage. Because therapy is effective in removing phosphate and fluids generally do not contain phosphate, deficiencies develop, requiring supplementation. In general, these electrolytes are monitored every 12 to 24 hours.

Most fluids either contain lactate or bicarbonate as the base buffer. Other substances have also been considered, such as acetate or citrate. The use of citrate has an added advantage of being an anticoagulant. Acetate, although previously used in long-term HD, may give rise to vasodilation, myocardial depression, and increased oxygen consumption. As such, acetate should be avoided in CRRT. Lactate undergoes hepatic conversion to bicarbonate on an equimolar basis.[53] Although lactate is more stable than bicarbonate, there are theoretical disadvantages to its use in CRRT.[54] Although bicarbonate-based and lactate-based solutions can correct acidosis, bicarbonate is preferred because the metabolism of exogenous lactate may be impaired in critical illness, with accumulation giving rise to a paradoxical metabolic acidosis.[55] Hyperlactatemia carries with it potential negative hemodynamic effects and metabolic complications, including increased protein catabolism and reduced adenosine triphosphate regeneration.[56] Complications of lactate overload are more likely to develop in patients with hepatic dysfunction and organ hypoperfusion. Although lactate-based replacement dialysate solutions may be used safely in many critically ill patients, for the aforementioned reasons bicarbonate-buffered solutions may be preferable.[57]

Anticoagulation

Circuit clotting is the most frequent cause of therapy interruption in CRRT.[58] Various factors may account for the hypercoagulable state in a patient receiving CRRT. Anticoagulation during CRRT is necessary to preserve the life of the extracorporeal circuit, to maximize the CRRT dose, and to minimize blood loss caused by clotting during CRRT. Loss of the extracorporeal circuit increases bedside workload, increases costs, and may increase the risk of patient adverse events.

The ideal anticoagulant should have no effect on systemic hemostasis, no increase in hemorrhagic risk, be limited only to the extracorporeal circuit, optimize filter performance in circuit life, have a short half-life, be easily monitored, be easily reversible, and be inexpensive. Options for anticoagulation of the circuit include using no anticoagulation, unfractionated heparin, low-MW heparin, citrate, and in rare circumstances, thrombin inhibitors or prostaglandins. Box 19.4 lists current strategies to prevent circuit clotting. The most common anticoagulation used for CRRT worldwide remains unfractionated heparin.

The option of no anticoagulation is usually used in patients with intrinsic coagulopathies such as hepatic failure or thrombocytopenia. Circuits are usually primed with saline solution or heparin. Intermittent saline solution flushes may be used as well. The rates of filter clotting using this method vary widely; however, mean filter life is usually suboptimal between 12 and 48 hours.

Unfractionated heparin works by inactivating factors Xa and IIa. The half-life of unfractionated heparin is 90 minutes; however,

• BOX 19.4 Current Options to Prevent Continuous Renal Replacement Therapy Circuit Clotting

- Unfractionated heparin
  - Standard, prefilter
  - Regional
  - Low-dose, prefilter
  - Systemic
- Low–molecular-weight heparin
- Citrate
- No anticoagulation
  - Saline solution flushes
  - No intervention
- Prostacyclin
  - Epoporstenol
- Direct thrombin inhibitors
  - Hirudin
  - Argatroban
- Serine protease inhibitors
  - Nafamostat mesylate

this may be increased up to 3 hours in kidney failure. The use of protocolized unfractionated heparin involves continuous infusion at the arterial site of the circuit. Usually a bolus of 1000 to 5000 IU of heparin is used. Continuous infusion of heparin ranges between 5 and 20 units/kg per hour. In general, an activated partial thromboplastin time (aPTT) goal ranges between 1.5 and 2.0 times the normal. The reported circuit patency of this ranges between 18 and 48 hours. Advantages include the fact that it is effective, widely available, involves simple monitoring (i.e., aPTT), is easily reversed with protamine, is inexpensive, and has a relatively short half-life. Disadvantages include systemic bleeding, unpredictable kinetics, aPTT being an unreliable predictor for bleeding, heparin resistance, and heparin-induced thrombocytopenia.

Regional citrate anticoagulation works by chelating free calcium in the extracorporeal circuit and preventing activation of calcium-dependent coagulation. The anticoagulant effect of citrate is measured by ionized calcium levels. Anticoagulation is reversed by a calcium infusion. Citrate has a plasma half-life of 5 minutes and is rapidly metabolized by the liver, kidney, and muscle cells. The extracorporeal clearance of citrate is the same as that of urea (SC 0.87–1.0). In a typical circuit, blood from the patient is first infused with citrate, which chelates the free ionized calcium. This blood then enters the filter where a calcium-free dialysate is used. Postfilter ionized calcium is monitored and used to titrate the citrate rate to ensure anticoagulation. The goal is to maintain the ionized calcium at less than 0.40 mmol/L. The returning blood combines with the venous blood in the body, which normalizes the ionized calcium and prevents systemic anticoagulation. Calcium is infused through a separate central line to replace the calcium lost in the ultrafiltrate. Citrate is metabolized primarily in the liver to bicarbonate and the bound calcium is released. For CVVH, citrate may or may not be a component of the replacement fluid. Advantages of citrate are that it is regional and avoids bleeding complications. Disadvantages of citrate include metabolic complications. Metabolic consequences of citrate include metabolic alkalosis from citrate overdose or toxicity, metabolic acidosis in a setting of severe liver disease or hypoperfusion, hypernatremia from hyperosmolar citrate solutions (4% sodium citrate), and hypocalcemia and hypercalcemia from inappropriate calcium supplementation. The risk factors for citrate toxicity include fulminant hepatic failure or shock liver and nursing or pharmacy errors leading to overdose. The detection of citrate toxicity can be suspected when there is evidence of a rising anion gap, worsening metabolic acidosis, a falling systemic ionized calcium, escalating calcium infusion requirements, or a total calcium–systemic ionized calcium ratio greater than 2.5:1. Strategies to manage citrate toxicity include decreasing the citrate infusion rate, decreasing the blood pump speed, and increasing the dialysate flow rate. Another reported drawback to citrate was the necessity of complex protocols; however, recent data have reinforced that regional citrate anticoagulation is safe and more beneficial when compared with systemic heparin. Numerous trials have shown citrate yields no additional bleeding risk and leads to longer filter life compared with unfractionated heparin.[59,60]

LMW heparins have also been examined for their effect on circuit life. Prostacyclin, a potent, short-acting, endogenous inhibitor of platelet aggregation, has also been studied. Direct thrombin inhibitors such as argatroban and hirudin have been used in response to heparin-induced thrombocytopenia. Bleeding may be treated with the fresh frozen plasma transfusion. Clinical experience with various agents and strategies influence choice. Table 19.6 summarizes the advantages and disadvantages of selected anticoagulants.

Complications and Troubleshooting

CRRT is complex and complications can occur (see Box 19.2). CRRT machines have built-in alarms and sensors that can identify selected complications as they occur so that they may be promptly recognized and appropriate action taken (Table 19.7). Perhaps the most frequent problems encountered are electrolyte derangements. With the use of hemofiltration, as noted earlier, the replacement solution determines the final electrolyte outcome. The replacement solution must reflect the desired sodium, chloride, and bicarbonate concentrations in the patient's serum and the relative loss via the hemofilter. There are selected substances readily cleared but not routinely included in replacement solutions, including selected amino acids, trace elements, minerals, and phosphate.[61] These require monitoring and supplementation. In selected circumstances,

TABLE 19.6 Anticoagulation Options for Continuous Renal Replacement Therapy

Feature	None	Heparin (Unfractionated)	Low–Molecular-Weight Heparin	Citrate
Advantages	1. Reduced risk of bleeding	1. Widely available 2. Commonly used 3. Short half-life 4. Available reversal agent 5. Monitoring accomplished with routine tests (aPTT) 6. Low cost	1. Reduced risk of HIT 2. Predictable kinetics (weight-based dosing) 3. Monitoring not required	1. Strict regional anticoagulation—reduced risk of bleeding 2. Improved hemofilter lifespan
Disadvantages	1. Risk of blood loss and clotting of system 2. Microthrombi in filter may decrease efficiency	1. Narrow therapeutic index—risk of bleeding 2. Heparin resistance 3. HIT	1. Risk of accumulation in kidney failure 2. If monitoring required, then a nonroutine test is necessary (anti-factor Xa) 3. Incomplete reversal by protamine 4. May be more expensive UH	1. Citrate may accumulate in patients with hepatic dysfunction and shock 2. Metabolic complications (acidosis, alkalosis, hypernatremia, hypocalcemia, hypercalcemia) 3. Increased complexity requires a strict protocol

aPTT, Activated partial thromboplastin time; *HIT,* heparin-induced thrombocytopenia; *UH,* unfractionated heparin.

TABLE 19.7 Summary of Potential Complications During Continuous Renal Replacement Therapy

Alarm	Possible Causes	Actions
High transmembrane pressure	1. Clogging filter 2. Kinked catheter	1. Check filter for clots 2. Check catheter position
High venous pressure	1. Kinked catheter 2. Clotted line	1. Check catheter position 2. Declot vascular access
Low arterial pressure	1. Kinked catheter 2. Clotted line 3. Hypovolemia	1. Check catheter position 2. Declot vascular access 3. Stop ultrafiltration and decrease blood flow rate
Line disconnection	1. Line disconnected from patient 2. Circuit kinked before pressure sensor 3. Clotted line excluding pressure sensor	1. Check circuit and patient for disconnection 2. Evaluate circuit for change

the composition of the replacement and dialysate solutions may need to be altered to achieve target electrolyte concentrations.

Multiorgan Support Technologies With CRRT

CRRT may be used with other organ-supporting technologies. These include specific therapies for sepsis, ARDS, and liver failure.

Endotoxin is a lipopolysaccharide and an outer membrane molecule essential for all gram-negative bacteria. It is the causative agent in gram-negative bacteria believed to mediate septic shock. Sorbents composed of polymyxin B–immobilized fibers have been used to adsorb endotoxin in sepsis. CRRT therapy with polymyxin B–immobilized fibers has shown improvements in hemodynamic profile and organ dysfunction; however, it has not been shown to improve patient outcomes. Several additional sorbent and novel high-flux hemofilters have been developed and shown to clear inflammatory mediators; however, their impact on patient outcomes is uncertain.[62,63]

Albumin dialysis, through the Molecular Adsorbent Recirculating System (MARS, Gambro/Baxter International, Deerfield, IL), may be integrated into a conventional CRRT circuit for patients with advanced liver failure or in selected overdoses (i.e., calcium-channel blockers).[64] MARS uses albumin as a dialysate and contains charcoal and anion-exchange cartridges to clear protein-bound toxins. Data from small trials have shown MARS clears drugs and toxins (i.e., phenytoin, digoxin), bilirubin and bile acids, and reduces hepatic encephalopathy and hepatorenal syndrome; however, it has not been proven to improve transplant-free survival.

CRRT can be configured to deliver therapeutic plasmapheresis (TPE). TPE is the removal of plasma and is usually exchanged with albumin or fresh frozen plasma. TPE may be indicated for microangiopathies in which antibodies, immune complexes, or cryoglobulins are contributing to multiorgan dysfunction. A small clinical trial has shown improved survival in patients with septic shock with use of TPE[65]; however, further corroborative studies are needed. Recently TPE was also shown to improve survival in fulminant hepatic failure with multiorgan dysfunction.[66]

In ARDS, lung-protective mechanical ventilation targets low tidal volumes; however, it may be limited by significant hypercapnia and respiratory acidosis. A low-flow extracorporeal carbon dioxide removal circuit may be integrated in parallel with a conventional CRRT circuit to remove excess carbon dioxide and enable delivery of lung-protective ventilation.[67]

Quality Assurance and Improvement for CRRT

To ensure effective, safe, and timely CRRT, programs must measure and review their own CRRT data. Selected quality indicators should be routinely captured for all patients receiving CRRT to monitor and benchmark performance and identify areas for improvement (Table 19.8).[68] Programs should establish regional committees to review data and engage in quality improvement initiatives to continuously aim to provide high-quality CRRT care.

Key Points

- CRRT has many theoretical advantages over IHD, particularly maintenance of hemodynamic stability, enhanced fluid removal, and increased dose delivery. However, evidence has not shown patient outcome advantage.
- CRRT modality (diffusion vs. convection) has not shown an advantage in patient outcome. However, hemofiltration (CVVH/CVVHDF) is associated with greater clearance of larger MW solute and shorter filter survival compared with hemodialysis (CVVHD).
- CRRT prescription would typically include the following: a blood flow rate 150 to 350 mL/min; a cumulative replacement and/or dialysate flow rate 20 to 25 mL/kg per hour (effluent); and an UF rate determined by the daily fluid balance goal of the patient. Considering treatment downtime is common, the delivered dose may be less than the prescribed dose and the prescribed dose increased accordingly.
- Many strategies are available for anticoagulation of the extracorporeal circuit. Heparin, citrate, and no anticoagulation are the most commonly used. Education and standardized protocols should be used to prevent adverse events and complications.
- There is no consensus on the best strategy for when to initiate CRRT in the absence of absolute (or life-threatening or medically refractory) complications of AKI. Both patient- and provider-specific factors should be used to individualize the decision to start CRRT.
- There is no consensus on the optimal time to discontinue CRRT; however, the most reliable measure for successful discontinuation is spontaneous urine output.

TABLE 19.8 Summary of Suggested Core Quality Indicators for a Continuous Renal Replacement Therapy Program

Quality Indicator	Donabedian Framework[a]	Definition	Proposed Benchmark
Education and training	Structure	CRRT programs have formal processes for training and certification of bedside staff	Annual
CRRT order and anticoagulation set protocols	Structure	CRRT programs have standardized order sets for CRRT prescription and anticoagulation monitoring	Present
Filter life span	Structure	The proportion of filters that last 72 hours before being changed, censored for planned circuit disruption. Filter change is dictated by elevated TMPs <250 mm Hg for greater than 5 min	>60% of filters
LMW solute clearance	Process	Change or relative stability in small solutes (SCr, urea) over time	Stable or increase of <10% over 24 h
Delivered dose	Process	The percentage of the prescribed dose that is delivered to the patient	>80%
Downtime	Process	The amount of time CRRT was not operating per 24-h period	<20%
Fluid management	Process	The percentage of prescribed ultrafiltrate removed from the patient daily	>80%
Time prescription to Initiation	Process	The time gap from the time of CRRT prescription to CRRT initiation	<4 h
Bleeding	Outcome	Any bleeding that requires the transfusion of PRBCs during the delivery of CRRT	No events

[a]The Donabedian Framework promotes the evaluation and classification of quality indicators across structure, process and outcome measures.
CRRT, Continuous renal replacement therapy; *SCr,* serum creatinine; *TMPs,* transmembrane pressure.

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Review Questions

1. A 70-kg 63-year-old male presents to the emergency department with community-acquired pneumonia and decreased level of consciousness. He is intubated and becomes markedly hemodynamically unstable. He is given 10 L of intravenous crystalloid before left internal jugular central venous catheter insertion and initiation of high-dose vasopressor therapy. He is immediately transferred to the intensive care unit (ICU) for ongoing management. Following ICU admission, the patient remains anuric despite ongoing fluid therapy with a total fluid intake of 250 mL/h. Blood work reveals a potassium level of 5.6 mmol/L, creatinine 1.8 mg/dL, and carbon dioxide 20 mmol/L. The decision to initiate renal replacement therapy (RRT) is made. Which of the following statements is correct?

a. The primary indication for RRT is for ongoing fluid management.

b. A right subclavian dialysis catheter should be inserted for RRT.

c. Intermittent renal replacement therapy should be initiated as this is the patient's first dialysis treatment.

d. Ultrasound guidance for catheter insertion is unnecessary as the priority is rapid initiation of RRT.

Answer: a. Ultrasound guidance is the reference technique for catheter placement. This decreases the risk of catheter placement failure and complications. Additionally, while theoretically decreasing the risk of infection, placement of temporary catheters at the subclavian site should be avoided owing to the risk of venous stenosis; either femoral or jugular sites are more preferable. Although smaller catheters convey a smaller puncture site, large catheters (>12F) are necessary to ensure sufficient blood flow. Continuous RRT (CRRT) would be preferential initial therapy over intermittent RRT in this clinical situation as the patient is receiving high-dose vasopressors. Traditional indications for RRT include volume overload, hyperkalemia, metabolic acidosis, uremia, and intoxication with a dialyzable compound. In this case, the patient has received a large fluid challenge (<20–30 mL/kg) and has ongoing large fluid requirements (~250 mL/h). As he is anuric, unable to manage his fluid status on his own, and not likely to imminently recover kidney function, RRT is necessary for ongoing volume management.

2. On day 2 of ICU admission, blood culture reveals gram-negative bacilli. Additionally, although the patient's vasopressor requirements are improving, the patient has worsening hypoxemia with a PaO_2/FIO_2 (partial pressure of oxygen–fraction of inspired oxygen) ratio of 105. Which one of the following statements is most correct?

a. High volume continuous hemofiltration should be initiated to clear inflammatory mediators and improve the patient's septic shock.

b. A prescribed dose of 35 mL/kg per hour should be initiated in anticipation of treatment downtime or interruptions.

c. Unfractionated heparin anticoagulation should be used as it is the most common form of anticoagulation used and leads to longer filter life compared with regional citrate anticoagulation.

d. Ultrafiltration should be initiated at 25 mL/h to initiate fluid removal to improve oxygenation while not exceeding the plasma-refill rate.

Answer: d. Although endotoxins and other inflammatory mediators can be cleared with high-volume hemofiltration, there is no evidence for improved patient outcomes. Furthermore, the evidence would support a minimal delivered CRRT dose of 20 to 25 mL/kg per hour. To ensure the target dose of therapy is actually delivered, this often translates into a prescribed dose of 25 to 30 mL/kg per hour. The choice of anticoagulation in RRT is important; unfractionated heparin has been shown to have shorter filter life compared with regional citrate. Hence, although it is the most common anticoagulation used for CRRT, regional citrate anticoagulation is preferable to extend filter life span and circuit survival. Finally, fluid management remains an important principle for CRRT. Initial ultrafiltration should occur at a low rate (e.g., 25 mL/h), which may be increased according to the patient's clinical status. This slow continuous initial rate of ultrafiltration optimizes hemodynamic stability by not exceeding the plasma-refill rate.

3. By ICU day 5, the patient is hemodynamically stable, is producing 30 mL/h of clear urine, and his gas exchange is improving. He is still currently receiving CRRT with an ultrafiltration rate of −100 mL/h. Which of the following is most correct?

a. The patient is likely recovering kidney function based on his urine output.

b. The patient should continue CRRT until he has recovered sufficient kidney function to be discharged from the ICU.

c. The patient should be subject to a furosemide challenge to increase urine output and facilitate CRRT liberation.

d. Blood and urine should be screened for kidney damage and repair biomarkers to provide additional decision support on timing for liberation from CRRT.

Answer: a. It is important to continuously screen patients for kidney recovery, and RRT should be discontinued as soon as clinically appropriate. There is evidence to support several parameters that may predict successful discontinuation of CRRT. These include restoration of urine output (>500 mL/24 h) (without diuretic exposure), an increased 2-hour creatinine clearance, and an increase in 24-hour urine creatinine excretion. There is no evidence that a furosemide challenge or continuous infusion can predict or facilitate CRRT liberation. There is also limited evidence for use of kidney damage and repair biomarkers to guide CRRT discontinuation.

20

Use of Sedatives, Analgesics, and Neuromuscular Blockers

CURTIS N. SESSLER, KRISTIN MILLER, AND KATIE M. ROCAWICH

CHAPTER OUTLINE

Considerations in Managing Sedation, Analgesia, and NMB in the ICU

Pain Management in the Intensive Care Unit
- Nonopioid and Atypical Agents
- Regional Anesthesia and Analgesia
- Complementary Techniques

Sedation Management
- Sedative Drug Therapy
- Management of Sedation

Neuromuscular Blocking Agents
- Comparison of Neuromuscular Blocking Agents
- Monitoring
- Complications of Neuromuscular Blocking Agents

Summary and Conclusions

Considerations in Managing Sedation, Analgesia, and NMB in the ICU

Critically ill patients often experience unpleasant sensations, including pain, anxiety, dyspnea, and other forms of distress.[1–3] This is particularly true for mechanically ventilated patients who make up a significant proportion of patients in intensive care units (ICUs). The ICU environment, and ICU care in general, is widely regarded as not ideally suited to patient comfort. For example, most patients have a variety of indwelling tubes and vascular catheters and some have surgical incisions. Further, sleep disruption is common, sound and light levels are often excessive, and patient communication and mobility is impaired. Core principles of ICU care are to provide comfort to our patients and to relieve their suffering.[4–7] Although nonpharmacologic interventions can improve patient comfort,[8] clinicians have relied on administration of analgesic and sedative medications to reduce the sensation of pain and anxiety, to control agitation, and to enhance tolerance of the ICU environment.[9–11] However, clinical experience and research has demonstrated the hazards associated with excessive or unnecessarily prolonged sedation and the importance of accurately achieving targeted analgesia and sedation.[12–15] Clinical practice guidelines from the Society of Critical Care Medicine (SCCM)[4] and other guidelines and reviews on sedation and analgesia[16–21] highlight the importance of adopting a management approach that is patient-focused and strives to use the lowest effective dose of medications, maintaining light levels of sedation in ICU patients as clinically feasible. The past decade has also brought a greater appreciation of the importance of development of delirium in the ICU on long-term outcomes including downstream cognitive dysfunction.[4,22–27] The topic of ICU delirium is reviewed in detail elsewhere in this textbook (see Chapter 69). Finally, the use of neuromuscular blocking agents (NMBAs) to achieve therapeutic paralysis is undergoing reevaluation, particularly for optimizing management of acute respiratory distress syndrome (ARDS).[28–31] The use of sedatives, analgesics, and NMBAs in managing critically ill patients is reviewed in this chapter.

Surveys and clinical reports indicate that the majority of ICU patients experience pain, dyspnea, or other forms of distress and receive sedative and/or analgesic medications.[9–11,32] Some key terms and definitions related to patient distress and neurobehavioral abnormalities in ICU patients are presented in Box 20.1. Much of the discomfort is related to various stressors. In one case series, pain, inability to sleep, and the presence of tubes in the nose or mouth were the most prominent stressors reported by recovering ICU patients.[3] Clearly, providing relief from these and other issues is an important goal of analgesic and sedative therapy. Consequences of suboptimal analgesia and sedative therapy can include problems related to inadequately controlled pain and anxiety or excessive sedation.

Agitation, regarded as excessive motor activity associated with internal tension, is perhaps the most widely recognized manifestation of uncontrolled anxiety or pain, because it can result in dramatic events, such as self-removal of important tubes and catheters, or even violence directed toward care providers. Overt agitation is a common occurrence among critically ill patients with rates as high as 20% of patient-shifts and nearly three-quarters of patients during ICU stay.[33–36] Self-removal of critical indwelling tubes and vascular catheters is the most common manifestation of overt agitation, placing the patient in peril from loss of an artificial airway and positive-pressure ventilation, abrupt cessation of infusion of critical medications such vasopressors, and/or the risk and discomfort associated with reinsertion of tubes and lines.[37] In prospective studies, device removal rates range widely from 22 to 157 events per 1000 patient-days[38,39] and have an associated added cost.[40] Documentation of patient agitation has become commonplace with the broad use of scales that address both sedation and agitation.[41] In addition to device removal and care provider assault, agitation is often accompanied by an intense stress response with catecholamine surge, resulting in tachycardia, hypertension, and tachypnea.[42,43]

• BOX 20.1 Terms for Patient Distress and Neurobehavioral Abnormalities in the Critically Ill

Agitation: Excessive motor activity associated with internal tension. The motor activity usually is nonpurposeful but may be irrationally purposeful and counterproductive.
Anxiety: A sustained state of apprehension with accompanying autonomic arousal in response to a real or perceived threat.
Apprehension: The subjective experience of dread and foreboding.
Autonomic arousal: Stimulation of the sympathetic and parasympathetic nervous systems and the autonomically controlled humoral axes. Autonomic arousal is manifested physically by tachycardia, systolic hypertension, hyperventilation, and diaphoresis.
Cognitive dysfunction: Reduced memory and analytical skills, confusion, and impaired judgment.
Coma: A state of unarousable unresponsiveness.
Defensive withdrawal: A physical and psychological reaction to an unpleasant situation manifested by avoidance, reduced responsiveness, and hypervigilance.
Delirium: An acute, potentially reversible impairment of consciousness and cognitive function that fluctuates in severity. Manifestations include apprehension, agitation, cognitive distortion, abnormal thought processes (including hallucinations), and impairments of short-term memory, arousal, and attention.
Distress: A global term for suffering, strain, or misery affecting the body or the mind.
Dyspnea: The experience of difficulty or distress in breathing.
Obtundation: Pathologic drowsiness, often accompanied during wakefulness by reduced attention and interest in the environment.
Pain: An unpleasant sensory or emotional experience associated with either actual or potential tissue damage that typically leads to evasive action.
Patient-ventilator asynchrony: An erratic breathing pattern in mechanically ventilated patients characterized by suboptimal matching of patient respiratory drive and mechanics with ventilator function.
Stress response: Reactions of the body and the mind to threats or forces of a deleterious nature that tend to upset physiologic homeostasis.
Stupor: A sustained state of spontaneous unarousability interruptible only by vigorous, direct external stimulation.

Modified with permission from Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med. *2001;22:211–225.*

Withdrawal of continuous infusion sedative and analgesic medications to promote awakening is associated with a twofold to fourfold increase in circulating catecholamines,[44] and can produce evidence of withdrawal that peaks within 6 hours.[45] Adrenergic stress response has been linked to hypercoagulability, glucose intolerance, increased catabolism, immunosuppression, sleep disturbance, and delirium. Furthermore, this can precipitate adverse events such as myocardial ischemia, increased intracranial pressure (ICP), tachyarrhythmias, and complications of uncontrolled hypertension in susceptible individuals.[46] Finally, it is also worth considering that overt agitation can be a marker for extreme distress that has a cause which may be life-threatening and/or rapidly resolves upon recognition and management.[19,33,34] Endotracheal tube malposition or obstruction, severe chest pain from myocardial ischemia, and tension pneumothorax are examples of conditions for which severe agitation in the nonverbal patient may be an important clue to an urgent dangerous situation. In fact, agitation was a common clinical antecedent before cardiopulmonary arrest in one study.[47]

Although the primary effects of analgesic and sedative medications are the relief of pain, anxiety, agitation, and related problems, such relief is usually accompanied by a reduced level of consciousness. Excessive and/or unnecessarily prolonged impaired sensorium is associated with additional complications—as a result of excessively deep sedation (i.e., pressure sores or nerve compression from reduced movement) or as a result of sedation-related delayed recovery from critical illness and mechanical ventilation with higher rates of complications and interventions related to longer ICU length of stay (LOS). In addition, long-term neuropsychological consequences of ICU sedation are increasingly recognized.[27] Accordingly, it is critical to take a structured approach to managing analgesia and sedation that includes carefully examining the specific patient-focused goals of therapy, using validated tools for evaluation and monitoring, and implementing management that explicitly targets using the lowest effective dose of the best analgesic and sedative medications for the specific patient. Some important components for analgesia and sedation management gleaned from prior reviews and current clinical practice guidelines are listed in Box 20.2.[4,16–21]

Analgesia and sedation are most effective when they are patient-focused because each patient and circumstances have unique features that may influence the response to therapy. Some of the predisposing and precipitating conditions that can contribute to the development of anxiety, pain, and delirium are noted in Fig. 20.1.[16,33] For example, a variety of underlying medical conditions—such as alcohol or substance abuse,[48] psychiatric disorders, and chronic pain—can influence the likelihood of developing anxiety, pain, or delirium and can affect the response to therapy.[35] Further, inadvertent discontinuation of home medications, such as opioids, benzodiazepines, or antipsychotic medications, because of lack of awareness of their prior use is not uncommon with unscheduled ICU admissions and is an important reason to perform detailed medication reconciliation with patients and their family members. Although the notion that "ICU psychosis" is actually caused by the ICU is misleading, it is clear that excessive noise, light, and repeated patient awakening to check vital signs or perform tests at night is common, contributes to fragmented sleep, and can provoke anxiety and delirium.[49–52] Sleep hygiene is clearly important and simple interventions such as patient use of earplugs and periods of "quiet time" can decrease the incidence of delirium and sedative drug requirements.[53,54] Acute medical illness, surgical interventions; mechanical ventilation and the related interface (i.e., tracheostomy tube, endotracheal tube, oronasal mask); and nursing interventions such as suctioning and turning can contribute to pain and discomfort.[3,55] A variety of conditions and medications have been associated with development of delirium and/or agitation, as displayed in Box 20.3.[33]

Pain Management in the Intensive Care Unit

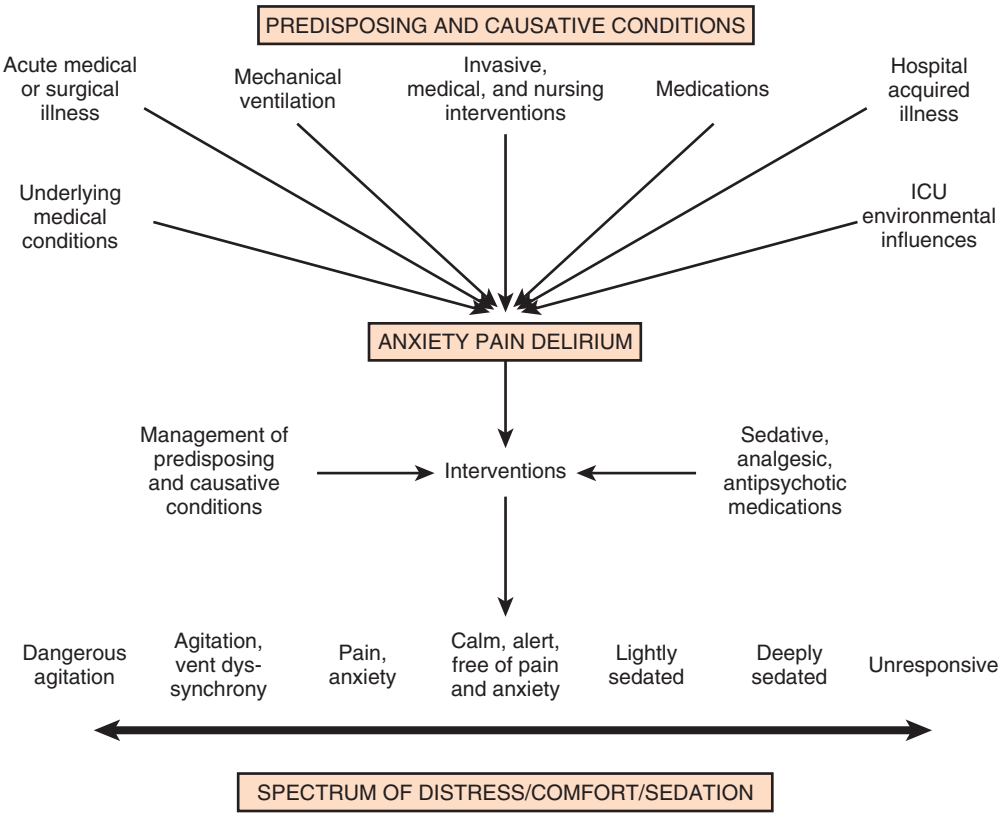
Pain is widely experienced in the ICU setting and can result from invasive procedures, surgery, and monitoring devices, as well as more direct stimuli from injury, inflammation, and immobility.[56] Treating pain is a core component of caregivers' responsibility to relieve suffering, but it also has physiologic benefits of relieving pain-induced altered glucose control, myocardial ischemia, immune system dysfunction, hypercoagulability, ventilator asynchrony, impaired ventilation, and disrupted sleep.[56] Mechanisms for these downstream effects include neurohormonal derangements, catecholamine release, and stress response.[56,57]

Effective treatment of pain begins with the assumption that pain is widely present and that caregivers should systematically evaluate each patient for the presence of pain and its intensity and characteristics on a repetitive basis.[4,6,8,56] Caregivers tend to

• BOX 20.2 Key Concepts for Management of Sedation and Analgesia

1. Develop a multiprofessional, structured approach for managing analgesia and sedation in your ICU. Use key user buy-in, education, protocols, order sets, ICU rounding checklists, and other tools such as implementation of the ABCDEF bundles to promote durable integration into patient care.
2. Perform patient assessment and optimize ICU environment:
   a. Identify predisposing and precipitating factors; manage correctable factors.
   b. Optimize patient comfort and tolerance of the ICU environment, including controlling light and noise, and promoting sleep.
   c. Optimize mechanical ventilation settings for patient-ventilator synchrony.
   d. Perform preemptive analgesia to alleviate pain associated with painful procedures.
3. Regularly perform and document structured patient evaluation and monitoring:
   a. Establish and communicate treatment goals.
   b. Assess presence and severity of pain, as well as response to therapy using self-report and/or a validated pain assessment tool.
   c. Assess level of sedation using a validated sedation scale, as well as response to therapy.
   d. Assess presence and severity of agitation using a validated agitation scale.
   e. Identify delirium using a validated delirium assessment instrument.
4. Implement a structured patient-focused management strategy:
   a. Select analgesic and sedative drugs based on patient needs and unique characteristics (such as alcohol or substance abuse), drug allergies, organ dysfunction (particularly renal or hepatic dysfunction), need for rapid onset and/or offset of action, anticipated duration of therapy, prior response to therapy, and published evidence.
   b. Focus first on analgesia, then sedation. Use opioids as primary analgesics but consider adding adjunctive agents or interventions.
   c. Evaluate and manage severe agitation, including search for causative factors, and rapidly intervene.
   d. Identify delirium, correct precipitating factors, and administer appropriate interventions and medications to reduce the intensity and duration of delirium.
   e. Titrate analgesic and sedative drugs to a defined target, using the lowest effective dose and aiming for light level of sedation.
   f. Implement a structured strategy to avoid accumulation of medications/metabolites: use scheduled interruption of medications, or intermittent dosing, of analgesic and sedative drugs. Perform daily SAT safety screen to select proper candidates for interruption of sedation.
   g. Link reductions in analgesic and sedative drugs to spontaneous breathing trials and to early mobilization, implementing the ABCDEF bundles.
   h. Avoid potential adverse effects of analgesic and sedative drugs; quickly identify and manage adverse effects that occur.
5. Recognize and take steps to ameliorate analgesic and sedative drug withdrawal during de-escalation of therapy.
6. De-escalate and discontinue sedative, opioid, and neuroleptic medications during recovery to reduce the likelihood of unnecessary long-term administration.

ICU, *Intensive care unit;* SAT, *spontaneous awakening trial. See text or Box 20.4 for explanation of ABCDEF bundle.*



• **Fig. 20.1** The spectrum of distress, comfort, and sedation. *ICU,* Intensive care unit. (With permission from Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. *Chest.* 2008;133:552—565.)

• BOX 20.3 Conditions and Medications Associated With Agitation and Delirium

Conditions

Central nervous system disorders—stroke
Infections—sepsis, encephalitis
Withdrawal from sedative agent (alcohol, benzodiazepine, opioid, nicotine)
Medication intoxication (central nervous system stimulants)
Metabolic disorders (hypoglycemia, thyrotoxicosis)
Electrolyte disorders (hyponatremia, hypermagnesemia)
Poisoning
Hypoxia
Endotracheal tube or tracheostomy tube malposition or occlusion
Patient-ventilator asynchrony
Pneumothorax
Pain: cardiac/vascular/gut ischemia, headache, distended viscus (i.e., bladder, bowel, indwelling tubes/catheters/devices, poor body/limb position)
Sleep deprivation

Medications

Antibiotics
Anticholinergics,
Anticonvulsants
Antihistamines
Benzodiazepines
Cardiovascular medications
Corticosteroids
Opioids
Nonsteroidal antiinflammatory agents

underrecognize pain and often fail to preemptively treat pain.[58] Accordingly, clinicians should err on the side of presuming pain is present—particularly when considering that it is far more effective to prevent and manage pain at an early stage than after it has become severe. Ideally, pain should be described in regard to location, duration, type, exacerbating and relieving factors, and intensity. Pain is sometimes conceptualized by subtypes, including somatic, visceral, and neuropathic, because manifestations and management can differ.[59] For example, somatic pain is typically dull and aching, often localized, and responds well to opioids and nonsteroidal antiinflammatory agents. In contrast, visceral pain is often cramping and colicky and may respond to anticholinergic therapy, whereas the burning and shooting neuropathic pain is often best treated with antidepressant and anticonvulsant agents.

Because pain is a subjective interpretation by an individual, the ability of that individual to convey the presence and magnitude of pain is of great value in guiding evaluation and management.[59] Detailed verbal communication by ICU patients is often limited; however, use of simple tools such as the numerical rating scale or a series of cartoon faces ranging from smiling to crying can facilitate communication by pointing or nodding in the nonverbal but cognitively intact patient.[60] A simple horizontal 0 to 10 numerical scale with an enlarged font was judged to be most feasible and valid in one study of pain intensity rating scales.[61] Other techniques to enhance the use of self-reporting of pain include adding descriptive words to the numerical scale, carefully explaining the tool and correct use with each encounter, providing glasses and hearing aids if necessary, allowing adequate time for instructions and patient response.[59] Use of a scale that incorporates descriptive pictures, such as the FACES scale, can facilitate self-reporting of pain intensity regardless of potential language barriers.

Many ICU patients are cognitively impaired and self-reporting pain intensity is not feasible. Accordingly, clinicians must rely on observed behaviors that correlate with self-reported pain or are associated with noxious stimuli.[55,58,62–64] Investigators have combined behaviors into structured assessment tools, often including facial expressions and body position and movement. Contraction of facial muscles associated with grimacing correlate particularly well with noxious stimuli.[65] Interestingly, much of the early work in pain assessment for noncommunicative ICU patients was in infants and young children, resulting in the development of the COMFORT Behavior scale,[66] the FLACC Observation (face, legs, activity, crying, and consolability) tool,[67] and others. Subsequently, a variety of pain assessment tools for nonverbal critically ill adults have been developed, validated, and critically reviewed.[59,68,69] In the 2013 SCCM guidelines,[4] published pain observation tools for adults in the ICU care were identified as the Critical-Care Pain Observation Tool (CPOT),[70] the Behavioral Pain Scale (BPS),[71] the Behavioral Pain Scale-Non-intubated (BPS-NI),[72] the Nonverbal Pain Scale (NVPS),[73] the Pain Behavioral Assessment Tool (PBAT),[74] and the Pain Assessment, Intervention, and Notation (PAIN) tool.[75] Extensive psychometric testing was performed, including examination of scale development, testing of reliability, testing of validity, feasibility, and scale relevance or impact of implementation on ICU patient outcomes yielding a maximum score of 25 and weighted score of 0 to 20. The CPOT had the highest weighted score of 14.7, followed by the BPS with 12.0,[4] and these two scales are recommended in the 2013 guidelines as the most valid and reliable behavioral pain scales for monitoring pain in adult medical, postoperative, or trauma ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable.[4] The CPOT and BPS are displayed in Tables 20.1 and 20.2.

Pain is often accompanied by changes in vital signs, with tachycardia, hypertension, and tachypnea being most common. However, changes in vital signs are inconsistently associated with pain, with many confounding factors that can mask anticipated changes, such as administration of β blockers, as well as lack of specificity with many other causes of tachycardia, hypertension, and tachypnea.[76] Accordingly, the 2013 guidelines recommend against the use of vital signs (or observational pain scales that include vital signs) alone for pain assessment in adult ICU patients.[4] However, it is acknowledged that vital signs may be an important cue to prompt further pain assessment.[4] Other potentially useful approaches include evaluating pain risk profile, use of surrogate (such as family members) report,[77] or performance of an analgesic trial.[56,59]

There are several important tenets for managing pain in the ICU. The first is that when initiating sedative treatment for mechanically ventilated ICU patients, analgesia should be the first step, followed by addition of a sedative-anxiolytic agent. This "analgesia-first" approach is suggested in the 2013 SCCM guidelines.[4,8,54] Second, the use of preemptive analgesia should be administered before performance of interventions, such as chest tube removal, that are associated with a high likelihood of producing pain.[4] It is more effective to prevent pain or manage it at an earlier and/or more mild stage than after pain has become severe.

Successful pain management in the ICU incorporates pharmacologic and nonpharmacologic treatment.[8] Parenteral opioids are the primary agents used to treat pain in the ICU setting, but use of selected nonopioid and atypical agents can enhance pain relief and may reduce adverse effects (AEs). The major parenteral opioids for continuous infusion in ICU patients, fentanyl, morphine, hydromorphone, and remifentanil (Table 20.3) are generally

TABLE 20.1 Critical Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

TABLE 20.2 Behavioral Pain Scale

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

From Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med.* 2001;29:2258–2263.

considered equivalent in regard to analgesic potential as well as class-based AEs such as respiratory depression or reduced level of consciousness. There are important differences among agents in regard to lipid solubility, volume of distribution (Vd), half-life, clearance, metabolism, and active metabolites that have important effects on onset, peak, and offset of action, potency, and the influence of renal or hepatic dysfunction.[8] Some of the medication features that can influence opioid selection for a particular patient are noted in Table 20.4. For example, morphine sulfate is metabolized to several active metabolites, including morphine-6-glucuronide that is as active as the parent compound and accumulates in renal failure, resulting in prolonged effects including not only analgesia but also somnolence and respiratory depression.[78] The rapid equilibration of fentanyl from plasma to lipid-rich brain tissue is responsible for its rapid onset of action but its high lipophilicity also contributes to a large Vd and delayed offset of action after prolonged infusion. Remifentanil has a small Vd and rapid clearance with metabolism by esterases yielding a short half-life and rapid offset of action that is independent of renal and hepatic function.[79,80] Several opioids not listed deserve mention. Meperidine has potential for neuroexcitatory AEs such as seizures[81] and is not recommended for ICU use.[4] Methadone can slow the development of tolerance to other opioid agents when coadministered but has unpredictable pharmacokinetics and is not administered by continuous infusion.[4] Methadone is also a potent precipitating agent for prolonging the rate-corrected QT interval.[82,83] Although opioids are most effective for pain management in the ICU patient, these agents have a well-documented propensity to produce AEs that are reviewed, along with comments for each AE, in Table 20.3.[8,56] Opioid-induced constipation is particularly common and can be ameliorated by using a stool softener, osmotic agent, stimulant laxative, and either enteral naloxone or subcutaneous injected methylnaltrexone.[84] Comprehensive pain management should include awareness of the likely AEs and how best to avoid them and/or to recognize and manage them.

It is often advantageous to use the lowest effective dose of an opioid analgesic, particularly when intolerable side effects are present. Additionally, there are clinical settings in which a nontraditional approach may be more effective, safer, and/or better tolerated. Use of alternative or complementary approaches such as adding nonopioid or atypical analgesic agents, use of epidural or other neuraxial alternatives to parenteral opioid, and use of complementary, nonpharmacologic interventions should be considered in selected cases.[8,56]

TABLE 20.3 Common Opioid Medications

Drug	Metabolism	Onset/Duration	Dosing	Titration	Advantages	Disadvantages
Fentanyl	Cytochrome P450 3A4	1–2 min/2–4 h (longer in liver failure)	Bolus: 25–50 μg IV push MD: 12.5–200 μg/h continuous infusion	Increase/decrease in increments of 25–50 μg every 5–30 min as needed; may be used to attain goal RASS or goal pain score	Less hypotension than morphine, short-acting, less accumulation with organ dysfunction than with other opiates	CYP 3A4 inhibitors may increase fentanyl effect; tolerance develops over time
Hydromorphone	Hepatic	5–10 min/2–4 h (longer in liver failure)	Bolus: 1–4 mg IV push MD: 0.25–50 mg/h (no real maximum dose)	Increase/decrease in increments of 1–4 mg every 15–30 min as needed; may be used to attain goal RASS or goal pain score	May be preferred in patients with tachyphylaxis to fentanyl, does not accumulate with renal dysfunction like morphine	Long-acting and very potent
Morphine	Conjugation; active metabolites that undergo renal excretion	5–10 min/2–4 h (longer in liver failure and ESRD)	Bolus: 2–4 mg IV push MD: 0.5–49 mg/h	Increase/decrease in increments of 1–4 mg every 15–30 min as needed; may be used to attain goal RASS or goal pain score	May be preferred in patients with tachyphylaxis to fentanyl	Accumulates with renal and hepatic dysfunction, hypotension owing to histamine release
Remifentanil	Plasma esterase	1–3 min/10–20 min	Bolus: 1 μg/kg over 1 minute IV push MD: 0.6–15 μg/kg per hour (use ideal body weight if >30% over ideal body weight)	Increase/decrease in increments of 1–2 μg/kg every 5–10 min as needed; may be used to attain goal RASS or goal pain score	No accumulation in hepatic or renal dysfunction	Can cause bradycardia, hypotension, and may increase intracranial pressure

CYP 3A4, Cytochrome P450 3A4; *ESRD*, end-stage renal disease; *IV*, intravenous; *MD*, maintenance dose; *RASS*, Richmond Agitation-Sedation Scale.

TABLE 20.4 Common Opioid Adverse Effects

Potential Adverse Effect	Comment
Allergy	Rare. Most common with morphine
Arrhythmias	QTc prolongation with methadone
CNS depression	Accumulation of active morphine metabolite in renal failure
Constipation	Start bowel regimen early if sustained opioid administration is likely. Enteral naloxone sometimes effective, but reverse analgesia; consider methylnaltrexone
Cough	Most common with fentanyl and similar agents
Dry mouth	Use oral lubricants
Histamine release	Uncommon with fentanyl and similar agents. Slow infusion rate. Treat with combination of H_1 and H_2 agonists
Hyperalgesia	Paradoxical increase in pain sensitivity, more common with short-acting opioids
Myoclonus	Consider reduced opioid dose or switch agent. Hydrate
Nausea/vomiting	Administer antiemetic until tolerance develops
Neurotoxicity	Avoid meperidine as has highest incidence. Can occur with morphine or hydromorphone, particularly at higher doses or in renal failure
Opioid dependency	Withdrawal symptoms can develop—usually coincides with clearance. Prevent by tapering, reinstitute agent if withdrawal occurs
Pruritus	Consider naloxone, serotonic antagonists such as ondansetron
Rigidity	Most common with fentanyl and similar agents, but can occur with any agent at high dose
Serotonin syndrome	Reported with meperidine and methadone. Avoid concomitant serotonic reuptake inhibitor

CNS, Central nervous system; *QTc*, rate-corrected QT interval.
Adapted from Erstad BL, Puntillo K, Gilbert HC, et al. Pain management principles in the critically ill. *Chest.* 2009;135:1075–1086.

Nonopioid and Atypical Agents

The use of nonopioid medications is best approached from the perspective of differentiating neuropathic pain for which anticonvulsants, antidepressants, and other agents play a primary role versus nonneuropathic pain for which opioids are the first-line therapy and other agents are used to reduce opioid dosage and reduce side effects. There is compelling evidence that the addition of oral gabapentin or carbamazepine to opioids provides superior pain relief for neuropathic pain in ICU patients compared with opioids alone,[85,86] and this is strongly recommended in this setting in the 2013 SCCM guidelines.[4] Pharmacotherapy for neuropathic pain has been extensively studied in randomized controlled trials (RCTs) in non-ICU patients, and medications including tricyclic antidepressants, selective serotonin receptor inhibitors, serotonin and norepinephrine reuptake inhibitors, anticonvulsants, tramadol, dextromethorphan, ketamine, topic capsaicin, lidocaine patch or gel, cannabinoids, and other agents have shown efficacy, albeit often in trials with small sample size and with associated side effects.[87]

Nonopioid adjuvant therapy in nonneuropathic pain can help reduce the quantity of opioids administered and potentially decrease the incidence and severity of opioid-related side effects. Such agents have been extensively studied in various noncritically ill populations—primarily postoperative patients—with efficacy demonstrated in meta-analyses of RCTs for corticosteroids, nonsteroidal antiinflammatory agents, acetaminophen, ketamine, and others.[88–91] There is relatively limited research in ICU patients and most of the RCTs performed with ICU patients have been in the postoperative setting. The drugs most studied in the ICU population are intravenous (IV) acetaminophen, cyclooxygenase inhibitors, and ketamine.[92–94] As a result of the limited evidence base in ICU patients, the 2013 SCCM guidelines generally support this approach as a weak recommendation for the addition of nonopiods for nonneuropathic pain.[4] The potential benefits as well as risks of no-opioids for ICU use are further discussed in recent reviews.[8,56]

Regional Anesthesia and Analgesia

Although systemic administration of opioids for pain management in the ICU is typically by the IV route, regional approaches can offer advantages in selected cases.[8] These options include continuous epidural analgesia and/or anesthesia (central neuraxial techniques) and continuous peripheral nerve or plexus block. With medication delivery in close proximity to the spinal cord or nerves, these techniques can promote parenteral opioid sparing, which is associated with less respiratory depression and gastrointestinal hypomotility and other benefits. However, these techniques introduce new issues related to needle and catheter placement and maintenance, as well as physiologic alterations related to local anesthetic block and/or epidural drug delivery. Critically ill patients are often at higher risk for complications owing to coagulopathy, thrombocytopenia, sepsis, and hemodynamic instability. Peripheral nerve blocks are particularly useful for anatomically localized pain such as limb injury or operation. However, of all the various regional anesthesia and analgesia (RAA) techniques, the greatest experience in ICU patients is with continuous epidural analgesia.

Similar to other pain management issues, there is more published research to support the use of RAA in noncritical care settings, and most ICU studies focus on postoperative patients or those who have sustained injury. The recent evidence-based review undertaken to develop the 2013 SCCM guidelines provides the most relevant and current basis for use of RAA in ICU patients.[4] Specific patient populations were examined, and only thoracic epidural anesthesia/analgesia for postoperative analgesia in patients undergoing abdominal aortic surgery received a strong recommendation as a superior alternative to IV opioids.[95] Interestingly, high-level evidence was also available to compare lumbar epidural analgesia to IV opioids in the same population and no benefit was demonstrated.[96] Patients with traumatic rib fractures are the other population for whom benefit from RAA was demonstrated for ICU patients. Specifically, use of thoracic epidural analgesia was associated with superior pain control and reduced incidence of pneumonia—but more hypotension—compared with parenteral opioids,[97,98] and its use is supported as a weak recommendation in this setting.[4] The evidence was insufficient to recommend thoracic

epidural analgesia for intrathoracic or nonvascular abdominal surgical procedures.[4] Similarly, the lack of high-quality research prevented a recommendation regarding the use of RAA for medical ICU patients.[4]

Complementary Techniques

Nonpharmacologic interventions such as music, relaxation, and provision of information can provide complementary pain relief and can be considered.[8,56,99–101] However, although these measures are low cost, easy to provide, and safe, they have a relatively weak body of evidence to support their routine use and they are not "high impact," providing only limited opioid-sparing or pain intensity reduction capability.[8,56,99]

Sedation Management

Sedative drugs have formed the cornerstone for patient comfort and tolerance of the ICU environment for decades by calming anxiety, providing amnesia, and controlling agitation. There have been changing paradigms from preferential use of moderate- to long-acting benzodiazepines and acceptance of prolonged deep sedation a decade ago, to patient-focused sedation with careful monitoring, analgesia first, and more recently to emphasis on use of nonbenzodiazepine sedative agents and using the lightest level of sedation possible.[4] Management of sedation should be preceded by examining individual patient characteristics and effective pain control. It incorporates establishing the goals of sedative therapy, monitoring of the depth of sedation, selecting and administrating the best agent(s) for the particular patient, and using protocolized management of sedation that includes structured elements to ensure use of the lowest effective dose and lightest level of sedation. Common goals of therapy include relief of anxiety, control of frank agitation, promotion of patient-ventilator synchrony, and elimination of awareness when NMBAs are used. Monitoring of the depth of sedation is now routinely performed in most ICUs and is applied to titrate medications to a targeted level of consciousness and to avoid excessive or prolonged sedation.

Monitoring the depth of sedation is most commonly performed by observing patient behaviors, often after varying levels of stimulation, using a structured sedation scale.[4,41,67,102] The domain being tested is that of arousal or level of consciousness and typically ranges from alert to comatose. Ramsay and coworkers developed the first widely used sedation scale for ICU patients: a six-level scale based on response to the assessor's voice and to physical stimulation.[103] Subsequent scale development has introduced assessment of agitation, ranging from calm to combative. Useful features of sedation-agitation scales include multidisciplinary development; ease of administration, recall, and interpretation; well-defined discrete criteria for each level; sufficient sedation levels for effective drug titration; assessment of agitation; demonstration of good interrater reliability for relevant patient populations; and evidence of validity.[41] Recently the SCCM guideline task force performed a careful analysis of the sedation scales that have undergone validation analysis in ICU patients, including the Ramsay Sedation Scale (RSS),[103] the New Sheffield Sedation Scale,[104] the Observer's Assessment of Alertness/Sedation Scale (OAA/S),[105] the Sedation Intensive Care Score (SEDIC),[106] the Motor Activity Assessment Scale (MAAS),[107] the Adaptation to the Intensive Care Environment (ATICE) tool,[108] the Minnesota Sedation Assessment Tool (MSAT),[109] the Vancouver Interaction and Calmness Scale (VICS),[110] the Sedation-Agitation Scale (SAS),[111] and the Richmond Agitation-Sedation Scale (RASS).[112] Of these, the RASS had the highest total weighted psychometric score (19 of 20 possible points), followed by the SAS (16.5 points), and these two instruments are recommended in the 2013 SCCM guidelines as the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients.[4] The RASS, developed by a multidisciplinary group led by Sessler, is displayed in Table 20.5.[112] The RASS incorporates assessment of arousal in response to two levels of stimulation (voice, physical), presence or absence of cognition, sustainability of response, and the presence and

TABLE 20.5 Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained (>10 s) awakening, with eye contact, to voice
–2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

Performed using a series of steps: observation of behaviors (score +4 to 0), followed (if necessary) by assessment of response to voice (score –1 to –3), followed (if necessary) by assessment of response to physical stimulation, such as shaking shoulder and then rubbing sternum if no response to shaking shoulder (score –4 to –5).

From Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166:1338–1344. Reproduced with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

TABLE 20.6 Sedation-Agitation Scale

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, attempts to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

ETT, Endotracheal tube.
From Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med.* 1999;27:1325–1329.

intensity of agitated behavior into a 10-level scale subcategorized with positive (agitation) and negative (sedation) values.[112] The SAS, developed by Riker and colleagues, is displayed in Table 20.6.[111] Both the RASS and SAS have been extensively tested for interrater reliability and validity in a cross section of ICU populations, correlated with subjective and objective measures of sedation, and evaluated for ease of use in clinical settings.[4,67,111–115] The introduction of a sedation scale into clinical practice has been demonstrated to result in higher quality sedation with fewer hours of oversedation, as well as reduced use of sedative and analgesic drug doses, shorter duration of mechanical ventilation, and reduced use of vasopressors.[116,117] Structured assessment and management of agitation and pain was similarly associated with less agitation, quicker extubation, and fewer nosocomial infections.[118]

Objective measures of cerebral function have been developed to quantify the level of consciousness as reflected by the cortical electrical activity based on processed electroencephalographic (EEG) signals.[67,119] Raw EEG signals are difficult to interpret, but proprietary mathematical algorithms have been developed and incorporated into commercially available devices to simplify interpretation of the power and frequency of the signal by converting this into a numerical display ranging from 0 (flat EEG) to 100 (fully alert). The Bispectral Index (BIS), Narcotrend Index (NI), Patient State Index (PSI), and State Entropy (SE) are examples of processed EEG monitors that have been used to assess level of consciousness in ICU patients.[4] The addition of assessing the "evoked potential" to an auditory signal (i.e., auditory evoked potentials)—displayed as the auditory evoked responses index (AAI)—incorporates measurement of latency and amplitude of the evoked electrical potential.[120] Collectively, these devices offer the advantage of continuous display of data—which can be used to rapidly detect unanticipated changes in level of conscious—such as accidental cessation of propofol infusion.[67] However, validation studies of these objective tools against sedation scales and other parameters has yielded inconsistent results.[4,67,121] A particularly challenging problem has been filtering out electromyographic signals generated by activity of muscles of the head that lie between the brain and the EEG electrodes.[122] Additionally, demonstration of added value to justify widespread use of this expensive monitoring technology when compared to routine sedation scale monitoring has been lacking in RCTs of ICU patients. Accordingly, the use of objective measures of brain function to assess the depth of sedation in noncomatose adult ICU patients who are not receiving NMBA is not recommended in the 2013 SCCM guidelines.[4] There are unique clinical circumstances for which objective monitoring may be superior to routine clinical monitoring, including patients who are receiving NMBAs and to guide titration of anticonvulsant medications to achieve burst suppression.[4]

Sedative Drug Therapy

Sedative medications are widely used in the ICU setting and although various agents can be administered by other routes, most are given by the IV route—either by continuous infusion or intermittent bolus. Inhalational agents, such as sevoflurane, can provide effective sedation and can improve oxygenation, but have significant logistical barriers for widespread use.[123] Historically, benzodiazepines formed the cornerstone of ICU sedation; however, clinical trial results and meta-analyses suggest that nonbenzodiazepines such as propofol and dexmedetomidine are associated with better results such as reduced delirium and shorter ventilator time.[4]

Propofol is perhaps the most widely used agent administered for continuous IV sedation in the United States.[124] Propofol binds to gamma-aminobutyric acid (GABA) A receptors as well glycine, nicotinic, and muscarinic receptors, producing effects similar to benzodiazepines.[4,125] Like benzodiazepines, propofol has no analgesic effects. Propofol is highly lipid soluble, quickly crosses the blood-brain barrier, and rapidly redistributes into peripheral tissues. These features result in rapid onset and offset of action (Table 20.7). However, prolonged administration can result in tissue saturation that can ultimately produce delayed offset of action. Similar to benzodiazepines, propofol commonly causes respiratory depression as well as systemic hypotension. Because propofol is dissolved in a lipid emulsion, higher rates of propofol infusion can produce hypertriglyceridemia and acute pancreatitis. Each milliliter of propofol solution contains 1.1 kcal of nutrition; thus an infusion rate of about 40 mL/h results in more than 1000 kcal of nutrition in 24 hours. Propofol infusion syndrome is an uncommon complication that is typically associated with prolonged infusion of high dose propofol (i.e., >70 μg/kg per minute), although cases are reported at lower infusion rates or more brief administration. Propofol infusion syndrome is characterized by metabolic acidosis, hypotension, cardiac arrhythmias, hypertriglyceridemia, and less commonly, with acute kidney injury, rhabdomyolysis, liver

TABLE 20.7 Common Sedative Medications

Drug	Metabolism	Onset/Duration	Dosing	Titration	Advantages	Disadvantages
Lorazepam	Conjugation to inactive metabolite	5–20 min/6–8 h (duration prolonged in elderly/cirrhosis/ESRD to 48–72 h)	Bolus: 2–4 mg IV push MD: 2–6 mg IV/PO every 4–6 h (preferred); infusion 0.25–20 mg/h	Infusion: Increase/decrease in increments of 0.5–2 mg every 10–60 min to attain goal RASS	Long half-life allows for intermittent dosing, less accumulation with renal/hepatic dysfunction	Propylene glycol toxicity in patients with renal failure; accumulation common with continuous infusion
Midazolam	Cytochrome P450 3A4; active metabolite renally excreted	5–10 min/1–4 h (accumulates in ESRD/CHF/liver failure)	Bolus: 2–4 g IV push MD: 0.5–25 mg/h	Increase/decrease in increments of 1–2 mg every 5–60 min to attain goal RASS	Short-acting if preserved organ function or with bolus dosing; fast onset	CYP 3A4 inhibitors may increase effect; accumulates with both renal and hepatic dysfunction; distributes to adipose tissue
Propofol	Conjugation	30–50 sec/3–10 min	MD: 2.5–105 μg/kg per minute	Increase/decrease in increments of 2.5–15 μg/kg per minute every 1–15 min to attain goal RASS	Short-acting; less delirium than with benzodiazepines	Hypotension; increased triglycerides; pancreatitis; propofol-related infusion syndrome; zinc depletion (brand name only)
Dexmedetomidine	Hepatic via cytochrome P450 and glucuronidation	Immediate onset only when bolus is given; ~3 h to see full effect if bolus omitted/6 min (longer in liver failure)	Bolus: 0.5–1 μg/kg, *rarely given* owing to hypotension/bradycardia MD: 0.2–1.5 μg/kg per hour	Increase by 0.1 μg/kg per hour no more often than every 30 min. May titrate to effect (goal RASS) OR until HR decreases by 10–20 bpm. Full effect will take ~3 h to see. If patient becomes hypotensive or bradycardic (HR <55 bpm), contact MD and stop infusion	Associated with less delirium than other agents; short-acting; little to no respiratory depression	Hypotension (especially with bolus dose and in under–fluid-resuscitated patients); bradycardia

bpm, Beats/min; *CHF*, congestive heart failure; *CYP*, cytochrome P450; *ESRD*, end-stage renal disease; *HR*, heart rate; *IV*, intravenous; *MD*, physician; *PO*, oral; *RASS*, Richmond Agitation-Sedation Scale.

dysfunction, and hyperkalemia.[4,126,127] In a meta-analysis of 16 RCTs that compared propofol with alternative agents for moderate- to long-duration sedation (i.e., >2 days), propofol was associated with shorter duration of mechanical ventilation and shorter ICU LOS.[128]

Dexmedetomidine is a selective α_2-receptor agonist with sedative properties similar to benzodiazepines and propofol, but has a number of unique features. In contrast to other sedatives, dexmedetomidine has analgesic properties and can be opioid-sparing; is sympatholytic, potentially producing prominent bradycardia as well as hypotension at higher doses; is associated with a more alert state relative to anxiolytic properties; and has minimal effect on respiratory drive.[129,130] It does not bind GABA receptors. Selected pharmacokinetic and clinical characteristics are displayed in Table 20.7. The most common AEs are hypotension and bradycardia. Hypotension can be particularly prominent when a loading dose is used—although hypertension can also occur. In a meta-analysis of 24 RCTs comparing dexmedetomidine with alternative agents, ICU LOS was shorter with dexmedetomidine, whereas duration of mechanical ventilation was not significantly different.[131] Clinical trial results suggest that when compared directly with midazolam, dexmedetomidine may be associated with lower prevalence of delirium.[132] The 2013 SCCM guidelines suggest that dexmedetomidine may be preferred over benzodiazepines in mechanically ventilated patients who have delirium and require continuous IV infusion of sedative medications.[4]

Benzodiazepines activate GABA A receptors, producing anxiolytic, amnestic, sedating, and hypnotic effects.[4,133] Benzodiazepines cause respiratory depression and systemic hypotension—problems that are particularly prominent in the elderly. Although diazepam, midazolam, and lorazepam have been used for ICU sedation over the years, diazepam is now used infrequently. Key pharmacokinetic and clinical features of midazolam and lorazepam are displayed in Table 20.7. Delayed offset of action is relatively common with these drugs for a variety of reasons, including tissue saturation after prolonged administration, impaired metabolism owing to hepatic dysfunction, and in the case of midazolam, accumulation of active renally cleared metabolities.[6,133,134] Continuous infusion of lorazepam can lead to accumulation of the diluent vehicle, propylene glycol, causing toxicity that is characterized by metabolic acidosis and acute kidney injury, and accompanied by development of an increased osmolal gap.[135,136]

Management of Sedation

Sedative drug therapy is an important component of sedation and analgesia management as discussed earlier and outlined in Box 20.2. Careful selection and titration of sedative drugs is critical to achieve optimal patient comfort while avoiding the adverse impact of excessive or unnecessarily prolonged sedation. The use of structured approaches to sedation and analgesia via algorithms and protocols has achieved a prominent place in ICU practice. There are several common themes. One theme is to tailor the sedation to the specific patient, including medication selection based on sedation goals (such as rapid arousal), avoidance of side effects (such as hypotension), and consideration of elimination issues (such as avoiding midazolam in a patient with impaired renal function).

Although all of the sedative drugs listed in Table 20.7 have a role in ICU sedation management, emerging evidence appears to favor using propofol or dexmedetomidine in preference to benzodiazepines in patients for whom continuous infusion sedation is needed—as suggested in the 2013 guidelines.[4] A meta-analysis limited to moderate- or high-quality RCTs demonstrated slightly longer ICU LOS with benzodiazepines compared with propofol or dexmedetomidine.[4] Several studies deserve additional comment. A multicenter RCT comparing dexmedetomidine to midazolam by Riker and colleagues demonstrated that dexmedetomidine was associated with a shorter time to extubation, lower prevalence of delirium, and fewer infections but no difference in ICU LOS, mortality, or sedation quality.[132] Dexmedetomidine was less potent than midazolam and was associated with more bradycardia but less hypertension.[132] Jakob and coworkers subsequently reported two phase III multicenter RCTs that compared dexmedetomidine with midazolam and propofol.[137] Patients randomly assigned to receive dexmedetomidine had a shorter duration of mechanical ventilation than those who received midazolam, but not those who received propofol. Patient interaction (communication, arousability, cooperation) was better with dexmedetomidine than with either other agent, but hypotension and bradycardia were more common.

Prospective studies have identified additional unique patient circumstances in which dexmedetomidine may be advantageous. For example, use of dexmedetomidine in patients with alcohol withdrawal syndrome is associated with reduced benzodiazepine and haloperidol administration as well as better sedation quality and patient communication, although bradycardia was common.[138,139] Similarly, adding dexmedetomidine to the management of patients with agitated delirium can enhance the quality of sedation and reduce the duration of mechanical ventilation and ICU stay.[140,141] Finally, compared with propofol, dexmedetomidine has been linked to reduced delirium and reduced likelihood of development of atrial fibrillation after cardiac surgery.[142,143]

A second major theme is to focus first on analgesia, as discussed. The 2013 guidelines suggest that analgesia-first sedation be used in mechanically ventilated adult ICU patients.[4] Asking first about pain, before the patient has been sedated and cognitively impaired, is advantageous. Additionally, several RCTs have demonstrated analgesia-based sedation to be associated with shorter duration of mechanical ventilation compared with hypnotic-based sedation.[144–146] Finally, Strom et al. randomized assigned mechanically ventilated adult ICU patients to bolus morphine (analgesia-based, limited sedation) versus morphine plus propofol for the first 48 hours, then midazolam (sedation + analgesia) and found shorter duration of mechanical ventilation and ICU LOS but threefold more agitation when sedative drugs were minimized.[15]

A third major theme is to strive for a light level of consciousness and to avoid accumulation of medications and their active metabolites, thus reducing the likelihood of delayed awakening. This approach is strongly recommended in the 2013 guidelines,[4] based in part on studies like those of Strom et al.[15] The underlying rationale for this approach arises from the observation by Kollef and colleagues that use of continuous IV sedation and analgesia is associated with delayed recovery from respiratory failure and longer LOS.[12] Although a variety of sedation management strategies have been demonstrated to shorten the duration of mechanical ventilation, the most robust data support the use of a sedation protocol or the implementation of daily interruption of sedation.[4,17] In an early RCT, Brook et al. found the use of a nurse-implemented protocol that emphasized intermittent therapy to be associated with shorter duration of mechanical ventilation, reduced ICU and hospital LOS, and fewer tracheostomies compared with usual management.[13]

The following year, Kress and colleagues showed in an RCT that daily interruption of IV sedation (DIS) or a spontaneous

awakening trial until the patient was alert or agitated then restarting the medications at 50% of the original dose was accompanied by more rapid recovery from respiratory failure, as well as performance of fewer tests for unexplained altered mental status.[14] Interestingly, not all of the benefit could be attributable to reduced accumulation of medications or active metabolites because the total propofol dosage was similar between groups although significantly less midazolam was used with daily interruption.[14] This prompted speculation that the DIS might also permit earlier identification of sufficient respiratory reserve for ventilator weaning (i.e., "wake up and breathe").[148] Girard and colleagues subsequently demonstrated that the strategy of combining DIS with performance of a spontaneous breathing trial (SBT) led to faster recovery from respiratory failure as well as reduced all-cause 1-year mortality compared with SBT alone.[149] Abrupt withdrawal of sedative (and sometimes analgesic) medications is accompanied by severalfold increases in circulating catecholamines as well as tachycardia and hypertension.[44] Experts have expressed concern that this unmasked stress response might be associated with cardiac ischemia.[150] In a prospective study, DIS was not accompanied by electrocardiographic or cardiac enzyme evidence of myocardial ischemia in at-risk patients.[44] Questions have also been raised as to the potential impact of this abrupt withdrawal of medications designed to provide comfort on downstream neuropsychological disturbances such as posttraumatic stress disorder (PTSD).[150] An additional study by Kress and colleagues demonstrated no increase in subsequent posttraumatic stress disorder and, actually, trends for better neuropsychological health months after daily interruption[151]—perhaps as a result of the added opportunities to establish concrete memories during awakening.[152]

There are populations for whom complete cessation of IV sedatives and analgesics is probably unwise. Girard et al. incorporated a safety screen into their protocol and avoid performing DIS in patients (1) receiving sedative infusion for active seizures or alcohol withdrawal, (2) receiving escalating doses for ongoing agitation, (3) receiving NMBAs, (4) having evidence of myocardial ischemia within the past 24 hours, or (5) having elevated ICP.[138] It may be that patients with alcoholism are at particular risk for poor tolerance of daily interruption because patients randomly assigned to this intervention had worse outcomes compared with a protocol approach in an RCT conducted in an ICU with a high prevalence of patients with alcohol use disorders.[153] In a multicenter RCT major outcomes were identical for patients randomly assigned to protocolized sedation versus protocolized sedation plus DIS.[154] Patients randomly assigned to DIS had more doses and higher total amount of midazolam and fentanyl and corresponding greater nursing workload.

A variety of other structured approaches have been examined in prospective trials, although many have used a less robust two-phase approach. Protocols that use an evidence-based nurse-implemented algorithm that seeks to minimize medication doses have been linked to shorter duration of mechanical ventilation,[155–160] shorter ICU and hospital LOS,[156,159,160] lower direct drug costs,[156,158] less opioid medication,[160] less medication-induced coma,[160] and lower 30-day morality.[160] These interventions appear to be less effective in Australian ICUs, perhaps as a result of higher nurse:patient ratios.[161,162] Other algorithms apply active pharmacist input[163] or focus on pain and agitation.[118] Carson and colleagues found continuous infusion propofol with DIS to be superior to intermittent lorazepam.[164]

In summary, a variety of structured approaches to sedation management are effective for speeding recovery from respiratory failure and critical illness. Practical considerations for establishing a sedation protocol include multidisciplinary development, integrating published algorithms into the local environment, and sustaining a durable approach despite the challenges of insufficient time and resources.[17] Finally, emphasis on protocolized light sedation brings additional opportunities such as linking to SBTs[149] and to early mobilization,[165] with the importance of using safety screens to identify appropriate clinical scenarios in which lightening of sedation is appropriate and considering that unplanned extubation is more common with lighter sedation.[165a] Sedative and opioid dosing should be scrutinized as they tend to be higher at night and such excessive dosing is associated with delayed extubation.[166]

• BOX 20.4 ABCDEF Bundle

- **A** Assess, prevent, and manage pain
- **B** Both spontaneous awakening trials and spontaneous breathing trials
- **C** Choice of analgesia and sedation
- **D** Delirium: assess, prevent, and manage
- **E** Early mobility and exercise
- **F** Family engagement and empowerment

The 2013 SCCM guidelines recommend using a multidisciplinary ICU team approach with provider education, preprinted protocols and order sets, and ICU rounds checklist to facilitate pain, agitation, and delirium management guidelines and protocols.[4] Much work has been done to adapt the recommendation from the 2013 guidelines into tools to promote implementation of pain, agitation, and delirium guidelines. A robust approach is the "ABCDEF bundle."[167] This bundle embraces the concept of fully integrating management of pain, agitation, and delirium into the comprehensive care of the patient and family with each letter representing to one component of best practice in critical care as displayed in Box 20.4. As discussed earlier, this strategy begins with (A) managing pain, (B) stressing linkage of the awakening the patient to providing the opportunity for the patient to demonstrate readiness to breath independently, (C) emphasizing optimal selection of medications for analgesia and sedation, (D) promoting effective prevention and/or management of delirium, (E) highlighting mobility and exercise for the patient, and (F) circling back to family support for the patient. Application of the ABCDEF bundle can speed recovery from critical illness and respiratory failure, reduce incidence of delirium, shorten LOS, and enhance quality of life.[167] Some approaches that can enhance the successful implementation of sedation-focused bundles include proactive pharmacist involvement, use of daily rounds checklists, high-quality order sets, and process control methodology.[168–172]

Neuromuscular Blocking Agents

In contrast to analgesic and sedative medications, NMBAs are administered relatively infrequently in the management of mechanically ventilated ICU patients. In an international study of mechanically ventilated patients with ARDS, 22% of patients received NMBAs, although the rate was higher at 38% of patients with severe ARDS.[173] The most common indication for NMBA is to facilitate mechanical ventilation in particularly challenging scenarios such as ARDS or refractory status asthmaticus. NMBAs can enhance oxygenation, reduce the risk of barotrauma, and improve synchronization of the patient and ventilator.[28,174] There are additional data that pulmonary and systemic inflammation may be reduced, although the mechanism(s) are not established.[175] Indications for

use of NMBAs include facilitation of mechanical ventilation, control of ICP, management of status epilepticus, reduction of oxygen consumption from muscle rigidity or shivering, prevention of lactic acidosis in conditions such as tetanus or neuroleptic malignant syndrome, and empirically in patients with severe ARDS.

Generally lacking robust RCTs, it is noteworthy that the most recent published guidelines assigned either a weak recommendation (ARDS) or make no recommendation for most of the indications just mentioned.[28] Most use of NMBAs is driven by improving control of a particular problem such as patient-ventilator asynchrony or elevated ICP that persists despite use of less invasive measures.[28,29] To date, the results of three RCTs and meta-analyses of these studies support the use of cisatracurium for patients with ARDS with a partial pressure of arterial oxygen:fraction of inspired oxygen (PaO_2/FIO_2) ratio less than 150 mm Hg, as there is an association of neuromuscular blockade infusion for 48 hours with lower 90-day, 28-day, and ICU mortality and barotrauma with no difference in ICU-acquired weakness.[28,30,174–176] Post hoc analysis of the largest study revealed that the benefit appeared to be confined to patients with PaO_2/FIO_2 less than 120 mm Hg.[30] A confirmatory multicenter study of North American patients is under way.

Comparison of Neuromuscular Blocking Agents (Table 20.8)

The neuromuscular junction consists of a prejunctional motor nerve ending separated from a postjunctional membrane—or motor end plate—of skeletal muscle by a synaptic cleft.[177] Acetylcholine (ACh) is released from vesicles in the prejunctional motor ending and bind nicotinic cholinergic receptors of the motor end plate, producing a change in membrane potential as a result of influx of sodium and efflux of potassium. Calcium is released from the sarcoplasmic reticulum, producing muscle action potential. Depolarizing NMBAs such as succinylcholine bind the receptors and cause the ion channel to remain open, producing depolarization and potentially causing sufficient potassium efflux to produce hyperkalemia. Additional depolarizations cannot occur until the agent diffuses from the receptors. Succinylcholine is the prototypical paralytic for rapid-sequence intubation owing to its rapid onset and short duration of action.[178] However, it can precipitate malignant hypertension and can cause hyperkalemia, which can lead to fatal arrhythmias.[179] The cause of this adverse event is thought to be upregulation of ACh receptors along the skeletal muscle membrane. Stimulation of these additional receptors by succinylcholine results in potassium efflux, leading to hyperkalemia. Hence, caution should be used when succinylcholine is considered for patients at risk for upregulation of ACh receptors such as upper or lower motor denervation, chemical denervation (by muscle relaxants, drugs, or toxins), immobilization, infection, direct muscle trauma, muscle tumor, muscle inflammation, and/or burn injury. Furthermore, succinylcholine should be avoided in patients with renal dysfunction, as hyperkalemia is potentiated in this population. Additionally, succinylcholine has been associated with increases in intracranial and intraocular pressure and should be used with caution in patients with acute ocular or traumatic brain injury.[180]

The nondepolarizing agents are bulky molecules with ACh-like moieties that bind the ACh receptors without ion flow or depolarization. Broadly, the nondepolarizing NMBAs are divided into two structural classes: aminosteroidal and benzylisoquinolinium agents. The aminosteroidal NMBAs incorporate an ACh-like structure onto a steroid backbone.[181] Much like other steroidal drugs, elimination of the aminosteroidal agents is organ dependent. Pancuronium, the first aminosteroidal NMBA, antagonizes not only nicotinic ACh receptors, but also muscarinic receptors.[182] This results in vagal blockade and tachycardia, making it less ideal for patients with significant cardiac disease.[28,29] Compared with other aminosteroidal NMBAs, pancuronium has a long half-life, which allows for sustained neuromuscular blockade to be achieved with intermittent bolus dosing.[28] Because of its long half-life, organ-dependent metabolism, and production of active metabolites, pancuronium has a high propensity to accumulate in critically ill patients. Newer aminosteroidal NMBAs, such as vecuronium and rocuronium, offer advantages over pancuronium as they do not antagonize muscarinic receptors. Vecuronium is an intermediate-acting aminosteroidal NMBA with both renal and hepatic elimination. It offers utility both for procedural and sustained paralysis, but like pancuronium, can accumulate in patients with organ dysfunction. Rocuronium has the fastest onset and shortest duration of action of the aminosteroidal NMBAs, making it ideal for rapid-sequence intubation in circumstances when succinylcholine is contraindicated. Like all aminosteroidal NMBAs, it exhibits organ-dependent clearance; however, when used as intermittently for procedural paralysis, this is rarely of clinical significance.

In contrast to the aminosteroidal NMBAs, benzylisoquinolinium agents are nonsteroidal agents that are degraded by plasma esterase and Hofmann degradation.[181–182] Atracurium was the first benzylisoquinolinium NMBA and was advantageous in that it was an intermediate-acting paralytic with organ-independent clearance. However, atracurium causes significant histamine release and thus must be used with caution in patients with hypotension and/or shock. Additionally, patients with organ dysfunction are at increased risk of seizures when atracurium is used for sustained paralysis owing to accumulation of a toxic metabolite, laudanosine.[29] Cisatracurium is the cis-cis isomer of atracurium and represents approximately 15% of the atracurium conformation.[181] Like atracurium, cisatracurium undergoes clearance via plasma esterase and Hofmann degradation but is devoid of histamine release and toxic metabolites.

Monitoring

Monitoring of the patient during chemical paralysis is performed to ensure safety and effectiveness of the intervention. Goals of monitoring include achieving the targeted depth of paralysis to accomplish therapeutic goals while reducing the likelihood of undesired prolonged paralysis or acute quadriplegic myopathy (AQM), and also avoiding other potential complications. Different targets for neuromuscular blockade may vary from merely reduced spontaneous movement or better synchronization of spontaneous breathing with mechanical ventilation, to apnea for fully passive ventilation or complete cessation of all skeletal muscle activity. Accordingly, observation of limb and respiratory muscle activity as well as review of graphic display of ventilator data should be performed to confirm the therapeutic target is reached. Testing of deep tendon reflexes may be helpful as they disappear as 100% blockade is reached. Monitoring the depth and duration of paralysis is important to optimize neuromuscular blockade for each individual patient and to avoid complications of therapy.[28,29,177,183] Such monitoring typically includes clinical evaluation as well as an objective measure of the extent of blockade using peripheral nerve stimulation (PNS) testing by evaluating the response to "train-of-four" (TOF) stimulation. In TOF testing, four equal brief electrical charges are delivered every 0.5 seconds from a nerve stimulator device attached to leads placed on the skin overlying a superficial

TABLE 20.8 Properties of Neuromuscular Blocking Agents

Property	Atracurium	Cisatracurium	Pancuronium	Rocuronium	Succinylcholine	Vecuronium
Mechanism of action	Nondepolarizing	Nondepolarizing	Nondepolarizing	Nondepolarizing	Depolarizing	Nondepolarizing
Class	Benzylisoquinolinium agent	Benzylisoquinolinium agent	Aminosteroidal agent	Aminosteroidal agent	Acetylcholine-like	Aminosteroidal agent
Onset	3–5 min	2–3 min	2–3 min	1–2 min	1–1.5 min	3–4 min
Duration	25–35 min	45–60 min	90–100 min	30 min	5–10 min	35–45 min
Renal elimination	<5%	<20% by renal and hepatic pathways combined	60%–80%	30%	<10%	10%–20%
Hepatic elimination	—	<20% by renal and hepatic pathways combined	15%–40%	—	—	20%–30%
Biliary excretion	—	—	5%–10%	50%	—	40%–75%
Hofmann elimination and ester hydrolysis	Yes	Yes	No	No	—	No
Plasma cholinesterase	No	No	No	No	Yes	No
Active metabolites	None (toxic metabolite laudanosine)	None	3–OH and 17–OH pancuronium	None	Succinylmonocholine (clinically insignificant depolarizing muscle relaxant properties)	3-Desacetylvecuronium
Bolus dosing	0.4–0.5 mg/kg	0.1–0.2 mg/kg	0.02–0.1 mg/kg	0.6–1 mg/kg	0.3–1.5 mg/kg	0.08–0.1 mg/kg
Continuous dosing	5–20 μg/kg/min	3 μg/kg per minute (initial: titrated to effect) vs. 37.5 mg/h (fixed dose in ARDS)	0.8–1.7 μg/kg per minute	8–12 μg/kg per minute	0.6–6 mg/kg per hour (not routinely recommended)	0.8–1.7 μg/kg per minute
Histamine release	Yes (dose-dependent)	No	No	No	Yes	No
Vagal blockade tachycardia	No	No	Yes	At higher doses	None (actually can cause bradycardia from vagal stimulation)	No
Prolonged blockade	Rare	Rare	Yes	No	Yes (in patients with reduced plasma cholinesterase activity)	Yes

ARDS, Acute respiratory distress syndrome.
For continuous dosing, use consistent weight such as ideal or adjusted body weight for dosing paralytic in obese patients.

nerve that innervates an easily observed muscle. The most common placement is over the ulnar nerve with observation of contraction of the adductor pollicis muscle, or over the facial nerve with observation of contraction of the orbicularis occuli muscle. It is estimated that if less than 75% of receptors are blocked, the four muscular contractions are equal in intensity and that once more than 90% of receptors are blocked no contractions occur. A common safety goal is for titration of NMBA so that one to three muscle contractions are present, thus potentially avoiding excessive dosing. It is worth considering, however, that clinical effectiveness (such as patient-ventilator synchrony) is sometimes achieved while TOF reveals all four contractions. In contrast, to achieve apnea or complete cessation of muscular activity, TOF of zero may be necessary. In this circumstance, periodically decreasing the NMBA infusion rate until TOF is 1 or above may be necessary to avoid excessive dosing.

Despite the intuitive value of monitoring the depth of NMB, clinical trials that compare PNS monitoring to clinical monitoring alone have not consistently demonstrated added value. In one RCT, Rudis and coworkers demonstrated more rapid recovery to 4/4 TOF contractions and to spontaneous breathing as well as fewer episodes of delayed recovery when vecuronium infusion was titrated to achieve 1/4 TOF contractions compared to patients with clinical monitoring alone.[184] Patients with impaired renal function had the slowest recovery. In contrast, PNS monitoring did not lead to better outcomes in prospective trials of patients who received atracurium [185] or cisatracurium.[186] Further, intentional dosing of cisatracurium to achieve TOF of zero only marginally prolonged the recovery time.[187] Finally, no PNS monitoring was performed in the 2010 placebo-controlled RCT in which 178 patients received a 48-hr cisatracurium infusion and there was no difference in the rate of ICU paresis compared to the placebo group.[30] Unfortunately, maintenance of TOF in excess of 0 does not guarantee AQM will not occur. Most reported cases developed despite documented appropriate TOF results. Accordingly, the 2016 guidelines state that PNS monitoring with TOF may be useful for monitoring the depth of NMB, but only if it is incorporated with a clinical patient assessment (weak recommendation, very low–quality of evidence).[28] Monitoring of patients who are receiving NMBAs should also address prevention and/or early detection of VTE, pressure ulcers, corneal ulcers, patient awareness, and inadequately controlled pain and anxiety.[28]

Complications of Neuromuscular Blocking Agents

The primary safety concerns with NMBAs relate to prolonged paralysis owing to persistent drug effect or from AQM. Both circumstances result in significant weakness and are considerations in the broad differential diagnosis of weakness in the ICU patient. Causes of weakness range widely from severe electrolyte disturbances like hypermagnesemia or hypophosphatemia to critical illness polyneuropathy, steroid myopathy, or Guillain-Barré syndrome. A variety of factors can increase the risk for prolonged recovery from NMBA, including organ dysfunction and resulting impaired clearance of the parent compound, accumulation of active metabolites, drug-drug interactions, and other medical conditions. Drugs that potentiate or antagonize the actions of nondepolarizing NMBAs are listed in Box 20.5. There is also considerable variability in duration of effect among NMBAs. The aminosteroids are eliminated by a combination of renal clearance and hepatic metabolism to a number of compounds, some of which are active and are eliminated in the urine. Accordingly, dysfunction of liver and/or kidneys is associated with prolonged paralysis.[29,188] Resolution of paralysis is not predictable with vecuronium, particularly with prolonged infusion.[188,189] This contrasts sharply with the benzylisoquinoliniums with recovery times of about 1 hour, even despite prolonged infusion and with higher doses.[187] Perhaps most instructive is a prospective head-to-head comparison of vecuronium and cisatracurium in ICU patients in which average recovery time was fivefold longer with vecuronium.[190] Close monitoring of depth of sedation using TOF PNS appears to reduce the incidence of prolonged paralysis with vecuronium[184] but is of less certain value with atracurium or cisatracurium[185,186]

AQM is a potentially devastating form of NMBA-related weakness because the muscle weakness can be severe and quite protracted.[28] AQM is characterized by weakness of the limb and trunk muscles with sparing of the extraocular muscles as well as preserved sensory function and cognition. Understanding of the mechanisms underlying AQM has evolved from suspicion that myonecrosis alone was responsible to that of altered muscle membrane properties with loss of motor protein myosin and myosin-associated thick filament proteins. Work by Larsson and associates has demonstrated that a combination of myofibrillar protein degradation plus downregulation of protein synthesis at the transcriptional level is prominent.[191] Key predisposing factors for intensive care–acquired weakness appear to be functional denervation—such as from NMBAs and corticosteroids. The argument has been made that prolonged deep sedation may be another source of immobilization. Additional risk factors for

• BOX 20.5 Drugs That Potentiate or Antagonize the Actions of Nondepolarizing Neuromuscular Blocking Agents

Drugs That Potentiate the Action of Nondepolarizing NMBAs

Local anesthetics
Lidocaine
Antimicrobials (aminoglycosides, polymyxin B, clindamycin, tetracycline, vancomycin, amphotericin B, colistin)
Antiarrhythmics (procainamide, quinidine)
Magnesium
Calcium channel blockers
β-Adrenergic blockers
Immunosuppressive agents (cyclophosphamide, cyclosporine)
Dantrolene
Diuretics (furosemide, bumetanide, ethacrynic acid)
Lithium carbonate
Corticosteroids
Inhaled anesthetics (enflurane, halothane, isoflurane, methoxyflurane, nitrous oxide)
Acetylcholinesterase inhibitors

Drugs That Antagonize the Actions of Nondepolarizing NMBAs

Phenytoin
Carbamazepine
Theophylline
Ranitidine

NMBA, *Nondepolarizing neuromuscular blocking agents.*
Modified from Murray MJ, DeBlock H, Erstad, B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med. *2016;44:2079–2103; and Warr J, Thiboutot Z, Rose L, et al. Current therapeutic uses, pharmacology, and clinical considerations of neuromuscular blocking agents for critically ill adults.* Ann Pharmacother. *2011;45:1116–1126.*

ICU-acquired polyneuropathy and myopathy include sepsis and other forms of systemic inflammation, hyperglycemia, malnutrition, and prolonged immobility. Although both aminosteroid and benzylisoquinolinium agents have been linked to AQM in case reports, it is noteworthy that in the relatively limited prospective clinical trial literature of NMBs in ICU patients, AQM is described in about 5% of patients who received vecuronium but none of the more than 200 patients who received atracurium or cisatracurium infusions.[183] Further, in the largest multicenter RCT of cisatracurium versus placebo, there was no difference in the incidence of ICU-acquired weakness.[30] Finally, some experts consider the causality of NMBAs—particularly short-duration NMBAs—for producing ICU-acquired weakness to be far from certain.[31] Standard precautions to reduce the likelihood of NMBA-associated weakness include a preference for use of cisatracurium, limiting duration of NMBA infusion to less than 48 hours if possible, performing periodic interruption of infusion, and ongoing clinical evaluation.[28,192,193]

Summary and Conclusions

The use of analgesic and sedative medications is the ICU setting is widespread and although often viewed as a component of "supportive care" of critically ill patients, clearly can affect major outcomes. Accordingly, adopting a thoughtful, structured, and multidisciplinary approach to managing analgesia and sedation is important and centers around reasoned medication selection, close monitoring, and applying strategies to use the lowest effective dose. Similarly, NMBA administration can be of critical importance in managing selected clinical situations and should be guided by monitoring and limiting use to the shortest duration possible.

Key Points

- A combination of nonpharmacologic and pharmacologic interventions can be useful to enhance patient comfort and reduce the distress associated with invasive procedures, mechanical ventilation, postoperative pain, and sleep deprivation common to the ICU experience.
- Adopting a patient-focused approach to managing sedation and analgesia that strives to minimize the depth and duration of reduced consciousness is associated with better outcomes.
- Development of delirium in the ICU is associated with worse outcomes, including impaired cognitive function after discharge.
- Agitated behavior is a common occurrence associated with adverse consequences, including self-removal of critical tubes and lines and excessive adrenergic stress response.
- Identification of delirium or agitation should prompt a search for predisposing and precipitating medical conditions and medications.
- Self-reporting using standardized tools is the best method to detect and quantify pain; however, observation of characteristic behaviors can be helpful in the patient who is unable to self-report.
- Routine use of a validated sedation-agitation scale such as the RASS or SAS promotes better communication, more precise sedative drug titration, and timely detection and grading of agitation.
- Use of nonbenzodiazepines is preferred to benzodiazepines when continuous infusion sedation is required.
- Targeting a more alert state for mechanically ventilated ICU patients is associated with better outcomes, including shorter duration of mechanical ventilation, fewer tests, and shorter ICU LOS.
- Linking management of sedation and analgesia, including interruption of sedation, with SBTs on mechanical ventilation, delirium prevention, and early mobility improves patient outcomes.
- NMBAs, particularly cis-atracurium, can be of value to facilitate mechanical ventilation in severe ARDS or status asthmaticus.
- Safe and effective use of NMBAs requires prevention of undetected pain and awareness in the paralyzed patient, prevention of adverse consequences of paralysis such as corneal damage or nerve injury from inappropriate positioning, prophylaxis against deep venous thrombosis, and clinical monitoring.

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Review Questions

1. Dexmedetomedine is associated with which one of the following adverse effects?
a. Hypertriglyceridemia
b. Bradycardia
c. Metabolic acidosis
d. Prolonged drug effect in patients with renal failure
Answer: b. Dexmedetomidine is an α_1-agonist sedative with unique characteristics of limited suppression of respiratory drive, reduced rates of delirium, and modest analgesia. The most common adverse effect is bradycardia and it can produce hypotension. Propofol is formulated in a lipid vehicle for administration and can be associated with hypertriglyceridemia when given at higher doses. The vehicle for delivery of lorazepam includes several glycols, which can lead to metabolic acidosis, impaired renal function, and increased osmolar gap. Midazolam has active metabolites that can accumulate in patients with impaired renal function, resulting in prolonged drug effect.

2. Which of the following opioid analgesics is associated with the uncommon complication of chest wall rigidity?
a. Fentanyl
b. Morphine sulfate
c. Meperidine
d. Hydromorphone
Answer: a. Fentanyl has been associated with chest wall rigidity—an uncommon adverse effect that can produce impaired ventilation. Morphine sulfate is associated with histamine release, which can produce hypotension or bronchospasm and delayed recovery as active metabolites can accumulate in patients with renal failure. Meperidine has been linked to neuroexcitatory complications including seizures and its use in critically ill patients is discouraged. Hydromorphone is a potent opioid analgesic not associated with chest wall rigidity.

3. Which of the following statements regarding train-of-four (TOF) peripheral nerve testing during neuromuscular blockade is true?
a. Responses differ for steroid nucleus agents (i.e., vecuronium) versus benzoquinolinium agents (i.e., cisatracurium).
b. Absence of TOF response always means there is an overdose of the neuromuscular blocking agent.
c. Presence of two of four muscle twitches during TOF testing signifies blockade of about 50% of receptors.
d. TOF testing should be paired with clinical evaluation.
Answer: d. TOF peripheral nerve stimulation is used to gauge the depth of paralysis with neuromuscular blocking agents (NMBAs) of all classes administered by continuous infusion to mechanically ventilated patients. A series of four brief electrical stimuli is applied to a peripheral nerve (typically ulnar or facial nerve) and the contractile response of the innervated muscle is observed. Presence of one to four muscle twitches indicates blockade of more than 75% of receptors. Although the absence of all twitches may signify an excessive dose of NMBA, it may also be the result of inadequate stimulation of the nerve owing to development of tissue edema or faulty positioning of the nerve stimulator leads. In all cases, TOF testing should be paired with clinical evaluation, including assessment of breathing or other movement.

4. What does the C of the ABCDEF bundle stand for?
a. Circulatory assessment
b. Comfort
c. Choice of analgesia and sedation
d. Confusion rating scale
Answer: c. The ABCDEF bundle provides a structure for managing pain, sedation, delirium, mechanical ventilation, exercise, and family engagement as follows: A = assess, prevent, and manage pain; B = both spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs); C = choice of analgesia and sedation; D = delirium: assess, prevent, and manage; E = early mobility and exercise; F = family engagement and empowerment.

5. Which of the following statements about cisatracurium is correct?
a. Metabolism is independent of end-organ function.
b. It is associated with a higher incidence of prolonged residual paralysis compared with vecuronium.
c. It may be associated with clinically significant histamine release.
d. Onset of action after injection occurs in 20 to 30 seconds.
Answer: a. Cisatracurium is a benzoquinolinium neuromuscular blocking agent that is metabolized by Hofmann degradation—an enzymatic process that is not dependent on hepatic metabolism or renal clearance. Onset of action is within 2 to 3 minutes. In contrast to its related compound atracurium, cisatracurium it is not associated with histamine release. When compared with vecuronium it has a shorter and more reliable duration of residual effect, particularly in patients with renal or liver disease.

21

The Effect of Critical Illness on Pharmacokinetics and Pharmacodynamics

JUDITH JACOBI AND QUINN A. CZOSNOWSKI

CHAPTER OUTLINE

Physiologic Changes in Critical Illness
General Pharmacokinetic Principles
- Absorption
- Distribution
- Clearance
- Half-Life

Pharmacodynamics
- β-Lactams
- Aminoglycosides
- Vancomycin

Dosing Considerations in Select Critical Care Patients
- Renal Disease
- Hepatic Disease
- Obese Patients
- Pregnancy
- Burn Injury
- Hypothermia

Pharmacogenetics
Principles of Therapeutic Drug Monitoring
Conclusion

Critically ill patients are closely monitored and procedures are performed, but supportive care and treatment is primarily with medications. To maximize effectiveness and minimize adverse effects, dosing must be optimized for each patient, which requires an understanding of typical pharmacokinetic changes. Individualized dosing regimens, based on expected concentrations and potential changes over time, are needed. The science of pharmacokinetics (PK) describes what the body does to drugs: absorption, distribution, metabolism, and excretion. However, understanding PK alone is not sufficient to design optimal dosing regimens. Other important questions remain: What concentration is needed to produce the desired effect? What concentration has the potential to produce toxicity? These questions are answered by the science of pharmacodynamics (PD), the study of what drugs do to the body, ideally at a receptor level. Understanding PD allows the clinician to relate specific serum concentrations to pharmacologic effects. The use of both pharmacokinetic and pharmacodynamic principles enables the clinician to maximize therapeutic efficacy while minimizing toxicity.

Complexity around drug dosing is typical for critically ill patients. The majority of pharmacokinetic and pharmacodynamic information available has been obtained from studies in healthy volunteers and other non–critically ill populations. Critically ill patients differ from those often studied because they frequently experience hepatic and renal dysfunction, receive aggressive fluid resuscitation, and require vasoactive medications to maintain adequate organ perfusion. These physiologic alterations can dramatically alter dose response and vary greatly from patient to patient and even from day to day in the same patient. In addition, patients also frequently have significant comorbid conditions, such as chronic kidney disease, cirrhosis, and heart failure, that affect dose response. Interventions such as renal replacement therapies and extracorporeal circulation can further influence drug effect and behavior.

Physiologic Changes in Critical Illness

The third international consensus conference on definitions of sepsis recommended the de-emphasis of the systemic inflammatory response syndrome (SIRS) and the abandonment of a special characterization of the group of infected patients with SIRS but no organ dysfunction.[1] However, we believe the use of SIRS to describe the systemic perturbation that often occurs in the presence of acute body insult is important to the understanding of how drug therapy is influenced in conditions associated with SIRS, especially when it is profound. SIRS is present to some degree in nearly all critically ill patients. Common insults, such as sepsis, trauma, surgery, the acute respiratory distress syndrome (ARDS), and pancreatitis, all produce SIRS. Before adequate fluid resuscitation patients may have low intravascular volume, inadequate preload, and low cardiac output. As a result, blood flow to organs such as the liver and kidneys can be compromised, leading to decreased drug clearance with associated serum and tissue drug accumulation. This physiology is commonly seen in patients admitted with sepsis when adequate resuscitation has not yet occurred. Fluid resuscitation restores preload and increases cardiac output. Because of increased

heart rate and low systemic vascular resistance, patients with resuscitated SIRS or sepsis frequently have hyperdynamic physiology in which organ blood flow can be higher than normal.[2] Sepsis also frequently leads to organ dysfunction including acute liver and kidney injury. Careful assessment of renal and hepatic clearance is required and must be combined with prudent judgment of the risk-benefit ratio of each individual drug. Clinicians may err on the aggressive side of dosing decisions for drugs with a wide therapeutic index such as the β-lactam antibiotics. Conversely, the risk-benefit ratio may support more conservative dosing decisions for drugs that have serious dose-related toxicity such as antiarrhythmic agents and anticoagulants.

The amount of fluid resuscitation required to maintain intravascular volume in patients with SIRS can be significant. Positive fluid balance may also occur in postsurgical patients, trauma patients, and patients with ARDS, among others. These changes in fluid balance combined with the capillary leak produced by SIRS can have significant effects on the distribution and dilution of hydrophilic drugs. In addition to changes in organ blood flow and volume status, critically ill patients also have altered serum protein concentrations, which can have important effects on drugs that are highly protein bound. The two most important serum proteins that contribute to drug binding are albumin, which binds mostly to acidic drugs, and α_1-acid glycoprotein (AGP), which binds mostly to basic drugs. A variety of factors contribute to altered serum protein concentration, including malnutrition, hemodilution, and the acute-phase response. Interestingly, the acute-phase response has a discordant effect on these proteins: albumin decreases whereas AGP increases.[3]

General Pharmacokinetic Principles

The PK profile of a drug is a mathematical model that describes the determinants of drug exposure. A complete model provides quantitative estimates of drug absorption, distribution, metabolism, and excretion after single doses, in addition to the extent of serum and tissue accumulation after multiple doses. The definition of common PK terms can be found in Table 21.1. The illustration in Fig. 21.1 depicts the concentration-time curve for a single intravenous (IV) dose of tobramycin. The curve allows for estimation of the maximum concentration achieved and the time course of drug elimination. If dosing is repeated before elimination is complete, accumulation occurs and will continue until the system reaches "steady state," at which time the rate of administration is in equilibrium with the rate of elimination (Fig. 21.2). Understanding the basic concepts of PK and PD is essential to providing safe and effective drug therapy. However, the physiologic derangements found in critically ill patients can significantly alter PK/PD relationships, which can lead to both exaggerated and diminished pharmacologic response with standard dosing regimens. Consequently, the intensive care unit clinician must integrate a thorough understanding of critical illness physiology with PK/PD principles to provide appropriate drug therapy. A summary of these changes can be found in Table 21.2.

Absorption

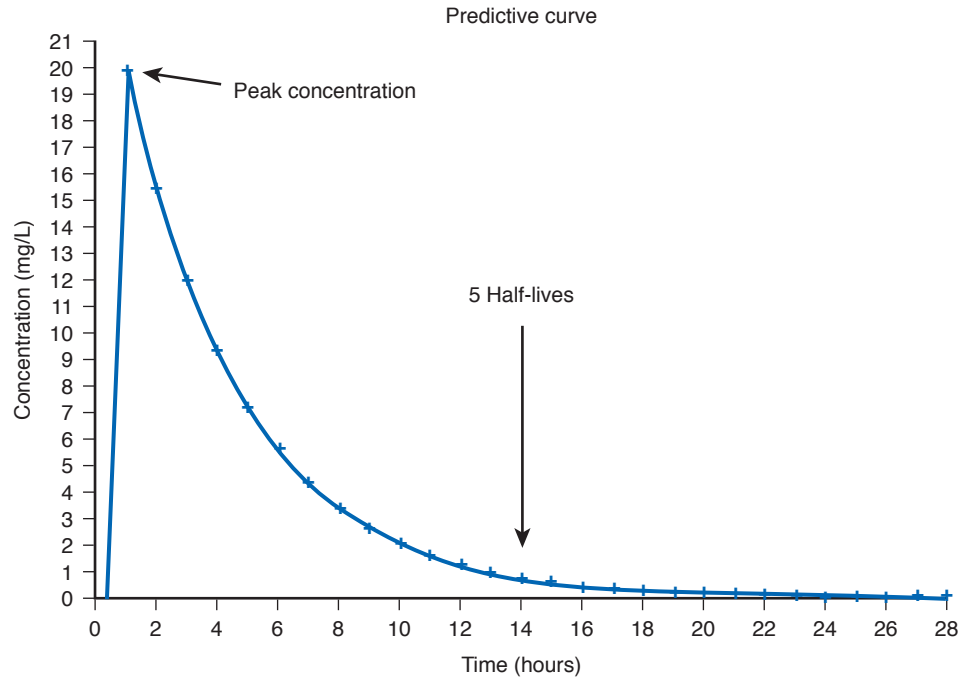
The first step in modeling exposure is to quantify the relationship between drug dosage administered and the amount of drug that reaches the systemic circulation. This relationship is known as the drug's bioavailability. IV administration provides 100% bioavailability, whereas this value can be considerably less for other routes. The oral route is the most common for the general population and remains useful in many critically ill patients. Bioavailability through oral administration is usually less than 100% and is a function of two main factors: (1) absorption, which is the intrinsic ability of the drug to cross the gastrointestinal (GI) tract, and (2) presystemic metabolism, also known as the first-pass effect, which

TABLE 21.1 Basic Pharmacokinetic Parameters

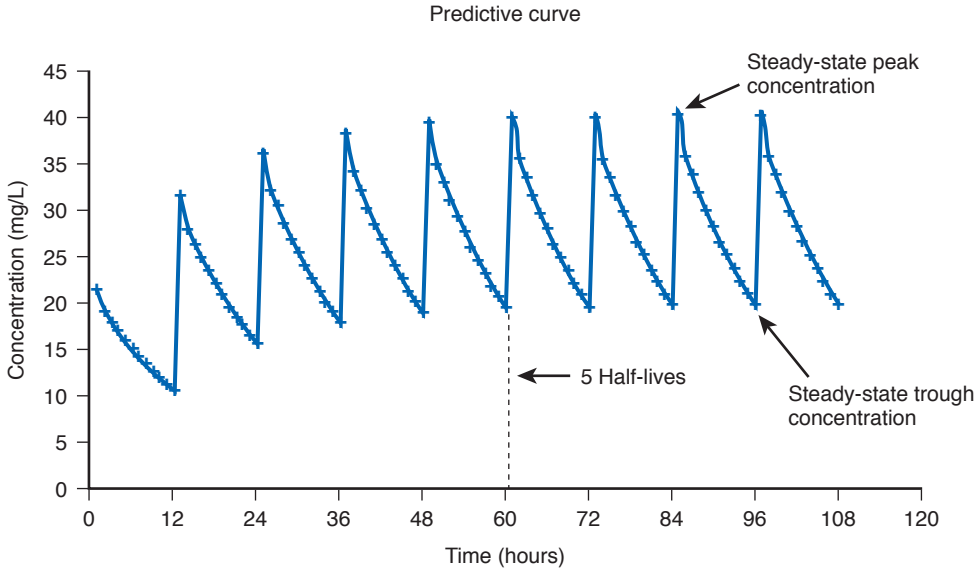
Parameter	Definition	Notes
Volume of distribution (Vd)	$Vd = \frac{\text{Dose (mg)}}{\text{Peak concentration (mg/L)}}$	Size of distribution compartment Quantifies the degree to which drug distributes into tissue
Area under the concentration time curve (AUC)	$AUC = \frac{\text{Dose (mg/h)}}{\text{Cl (L/h)}}$	Total drug exposure produced by administered dose
Clearance (Cl)	$Cl = \frac{\text{Dose (mg/h)}}{\text{AUC (mg/L per hour)}}$	Volume of blood cleared of drug per unit time
Elimination rate constant (Ke)	$Ke = \frac{Cl\ (L/h)}{Vd\ (L)}$	The rate of drug elimination from the body per unit of time. Relates clearance (liters cleared/hour) and Vd (volume to be cleared). This value is inversely related to drug half-life.

Bioavailability (F)	$F = \frac{AUC_{po}/dose_{po}}{AUC_{IV}/dose_{IV}}$	Percentage of dose that reaches systemic circulation
		Varies by route:
		• Intravenous (100%)
		• Variable (0%–100%)
		  • Oral
		  • Subcutaneous
		  • Transdermal
		Value expressed as a percentage of exposure relative to IV administration

Cl, Clearance; *IV*, intravenous; *po*, oral.



• **Fig. 21.1** Concentration versus time curve following a single 200-mg intravenous dose of tobramcyin in a 50-kg female. Note: Peak concentration determined by volume of distribution (Vd) and the size of dose given. The time course of elimination is determined by clearance and Vd. Approximately 90% of dose is eliminated after 5 half-lives.



• **Fig. 21.2** Concentration versus time curve demonstrating accumulation after repeated dosing of 750 mg vancomycin every 12 hours in a 50-kg patient. Note: Dosing regimens are based on steady-state concentrations. Therapeutic drug monitoring should be conducted when regimens have reached steady state, which occurs after 5 to 7 half-lives.

occurs primarily in the liver, and to a lesser extent in the intestinal lumen. Drugs that undergo extensive hepatic metabolism may have large first-pass effects and thus low bioavailability compared with IV administration. Similarly, drugs that are poorly absorbed will have low bioavailability.

Factors that determine absorption from the GI tract include drug characteristics, such as lipid solubility, ionization, and molecular size, in addition to physiologic factors, such as gastric emptying rate, intestinal blood flow, motility, gastric and intestinal pH, gut wall permeability, and whether the dose is administered during the fasted or fed state. Most drugs are orally absorbed through passive diffusion, although carrier-mediated absorption can also be important. The most important sites of absorption are the upper and lower segments of the small intestine.[4] The stomach regulates absorption through gastric emptying but is not an important site for absorption. Similarly, little drug absorption occurs in the colon,

TABLE 21.2 Pharmacokinetic Changes During Critical Illness

Parameter	Relevant Critical Illness Physiology	Effect on Pharmacokinetics
Absorption	Reduced mesenteric and subcutaneous blood flow during shock Delayed gastric emptying Reduced GI motility	Reduced peak concentration and AUC Delayed onset of effect Variable
Distribution	Capillary leak and fluid resuscitation Reduced albumin concentration Increased AGP concentration Decreased tissue binding	Increased Vd for hydrophilic drugs Increased Vd for drugs highly bound to albumin Decreased Vd for drugs highly bound to AGP Decreased Vd
Clearance	SIRS response increases blood flow to liver and kidneys Acute kidney injury and acute liver injury Reduced albumin concentration Increased AGP concentration	Increased drug clearance Decreased drug clearance Increased drug clearance for acidic drugs highly bound to albumin Decreased clearance for basic drugs highly bound to AGP

AGP, α_1-Acid glycoprotein; *AUC*, area under the concentration-time curve; *GI*, gastrointestinal; *SIRS*, systemic inflammatory response syndrome; *Vd*, volume of distribution.

with the exception of extended-release products. Drugs with low oral bioavailability will require larger doses administered orally to produce equivalent exposure to that obtained from IV administration. Some drugs (e.g., vancomycin) have such poor bioavailability after oral administration that they cannot be used to treat the same disease processes as the IV formulations. Bioavailability is an important consideration when converting between oral and IV routes. For example, converting amiodarone IV at 0.5 mg/min (720 mg/24 h) to an equivalent oral dose would require approximately 1440 mg/24 h, considering the average 50% (35%–65%) bioavailability.[5] Other routes of administration include subcutaneous or intramuscular injection, transdermal or buccal absorption, and inhalation. Many drugs available as IV preparations are amenable to subcutaneous and intramuscular administration. Drugs with adequate lipid solubility may be available for transdermal or buccal administration, including nitroglycerin, fentanyl, and tacrolimus.

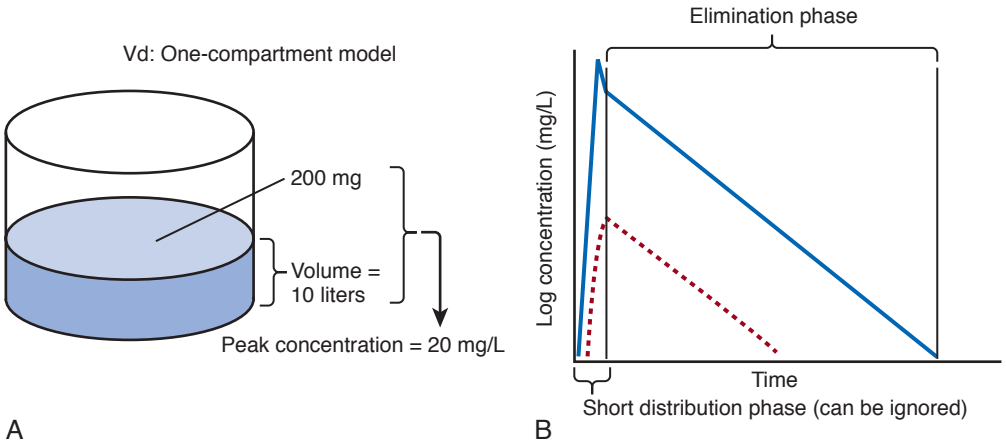
Although oral administration is useful in critically ill patients, the route may not always be appropriate. Physiologic changes, such as decreased mesenteric blood flow, altered intestinal motility, gastric acid suppression, and gut wall edema, can alter the rate and extent of absorption.[6] The hemodynamic response to hypotension involves shunting blood flow away from mesenteric circulation, substantially limiting a drug's access to the systemic circulation.[7] Hepatic blood flow may be preserved in the short term owing to the "hepatic buffer" response but is often decreased with prolonged states of low systemic perfusion.[8] Low hepatic blood flow will limit hepatic metabolism and result in increased bioavailability of drugs with a large first-pass effect. The net effect of these derangements can be highly unpredictable but often leads to diminished bioavailability. Slow gastric emptying, which occurs in 50% to 60% of critically ill patients, delays the onset of absorption and often results in lower peak serum concentrations.[9–11] Impaired small intestine motility also slows the rate of absorption. However, because residence time in the GI tract will be longer, bioavailability may actually increase for poorly absorbable drugs such as furosemide and ampicillin.[12] Carrier-mediated absorption may be limited independent of changes in motility or blood flow as a result of dysfunctional membrane transporters.

There are limited data describing the effectiveness of oral administration in critically ill patients. Some studies, conducted in patients tolerating enteral feeding, show absorption to be adequate for drugs with normally high bioavailability such as fluconazole and ciprofloxacin.[13,14] However, other studies show unpredictable and sometimes inadequate absorption.[15] Given this variability and the absence of a useful parameter to monitor GI function at the bedside, the IV route is preferred in patients with hemodynamic instability. The oral route should be reserved for patients who are clinically stable and tolerating enteral feeding. When transitioning medications from IV to oral, it is helpful to begin with agents that have easily measurable effects, such as cardiovascular agents. Very little research has been done on the absorption of medications after delivery via jejunal feeding tubes. Although sustained-release products cannot be crushed, others with special coatings may be successfully delivered beyond gastric acid. Some medications, such as rivaroxaban, may not be well absorbed if delivered beyond the stomach, with a 29% decrease in area under the concentration-time curve and 56% decrease in the maximum concentration when delivered to the proximal small intestine, and may be lower if delivered to the distal small intestine.[16]

Subcutaneous absorption is dependent on the characteristics of the drug, volume administered, and perfusion of the tissue. Special formulations like glargine insulin are delivered as soluble microcrystals in acid solution that covert into aggregates of insulin hexamers at physiologic pH. These hexamers slowly dissociate into monomers that are then physiologically active and are slowly absorbed. However, patients receiving vasopressors or those with subcutaneous edema may not absorb drugs well from the subcutaneous space, as demonstrated with low–molecular-weight heparins.[17,18] Peak anti–factor Xa levels of these agents are significantly reduced in patients receiving vasopressors.[17,19] Although these data are provocative, the clinical importance of low anti–factor Xa levels is unclear regarding the risk of thrombosis.[20,21]

Distribution

After reaching the systemic circulation an administered dose then distributes throughout the body to produce a peak concentration. The relationship between the dose administered and the peak concentration observed is termed the *volume of distribution* (Vd). The Vd estimates the size of the compartment into which the drug distributes. Although it is not a measurable space, it



• **Fig. 21.3** One-compartment model of drug distribution when drug rapidly distributes between plasma and tissue. A, Volume of distribution *(Vd)* defines the relationship between dose and peak concentration. B, Concentration versus time curve for one-compartment model on a logarithmic scale. The *solid line* represents serum concentration. The *dashed line* represents tissue concentration. Note that tissue concentrations increase during the distribution phase. Because target receptors are frequently within tissues, the time course of the dashed line determines the onset and duration of effect.

rather mathematically reflects the net effect of multiple fluid and tissue spaces. Total plasma volume in the average adult is 3 to 4 L but may be larger in critically ill patients, although the Vd for most drugs is much greater than this value. The discrepancy between plasma volume and a drug's Vd depends on the extent that drugs concentrate in various tissues. The main determinants of Vd are the lipid solubility, degree of protein binding, and extent of tissue binding. High lipid solubility increases Vd through improved passage across cell membranes. Avid tissue binding also increases Vd as this concentrates drug outside the vascular space. Conversely, because only unbound drug can cross cell membranes and bind to tissue, high serum protein binding decreases Vd, concentrating drug in the vascular space.

The simplest conceptualization of Vd is to view the body as a bucket—one large compartment where drug rapidly equilibrates between plasma and tissue and has uniform distribution (Fig. 21.3A). The one-compartment assumption is useful for drugs with small to intermediate Vd, such as aminoglycoside or many cephalosporin antibiotics, because these hydrophilic drugs have a short distribution phase owing to their limited tissue penetration. Drugs with large Vds, such as fentanyl and amiodarone, require longer periods of time to achieve equilibrium between serum and tissue and thus have a prolonged distribution phase. As a result, the one-compartment assumption fails to accurately describe Vd drugs with large Vds. An alternative is to view the body as multiple compartments: a central compartment composed of blood, extracellular fluid, and highly perfused tissues; and one or more peripheral compartments composed of tissue beds with lower perfusion and higher drug binding affinity (Fig. 21.4A). The number of peripheral compartments is determined by the differential distribution rate in each tissue. Two-compartment models adequately describe most drugs with large Vds; however, a three-compartment model can be useful for agents that act in the central nervous system because of slower distribution as a result of the blood-brain barrier.

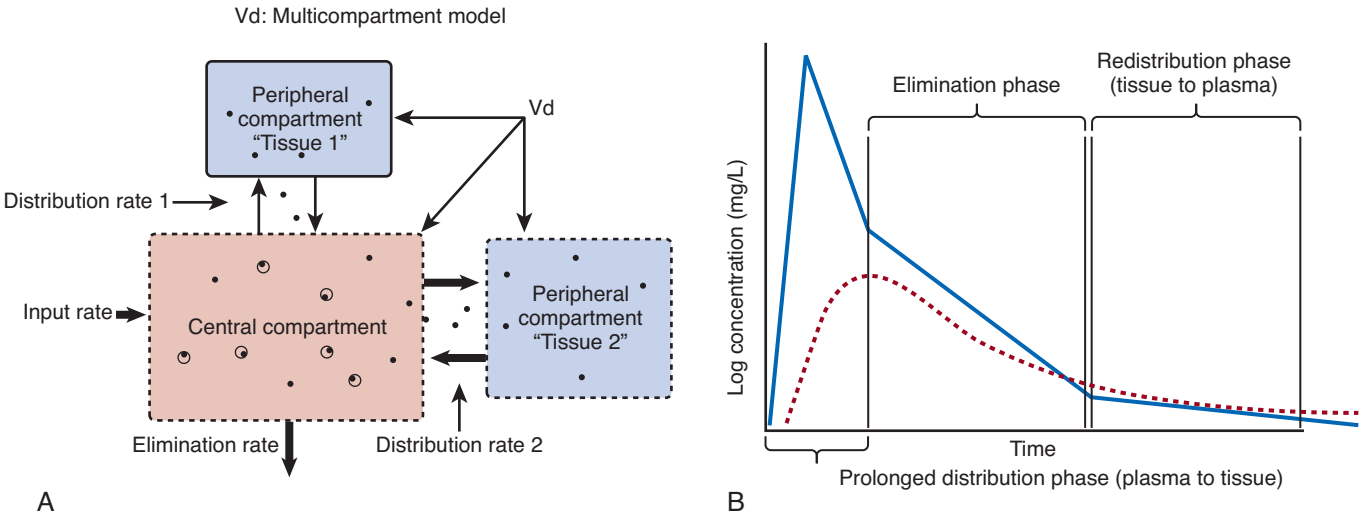
An increase in the Vd of hydrophilic drugs is predictable in critically ill patients with expanded body water, proportionately reducing the peak concentration of the initial dose. Loading doses of most antimicrobials should be considered during and after volume resuscitation to compensate for this dilutional effect.

As previously discussed, changes in protein concentrations—such as reduced albumin and elevated AGP—may affect the degree of drug binding. The levels of AGP are not static after an acute injury or illness, making assessment of free (non–protein-bound) drug more challenging.[22] Lidocaine is the primary agent studied for the impact of AGP changes, but phenytoin is also slightly bound to this protein, and changes in AGP may alter total protein binding, although formulas to predict free phenytoin levels typically consider only albumin concentration; thus direct measurement of the free level is recommended when possible.[23]

Other physiologic changes such as the extremes of weight also make prediction of Vd difficult, as obese patients have varying ratios of muscle and fat, as discussed later.

Clearance

Drug elimination begins immediately upon entry into the body and can be divided into two main components: metabolism and excretion. Metabolism occurs mainly in the liver via enzymatic degradation, although it occurs to lesser extents in other tissues, such as the kidney, lung, small intestine, and skin. Enzymes found in the serum also metabolize drugs, such as remifentanil elimination via nonspecific plasma and tissue esterases. Nonenzymatic metabolism also occurs in the serum, as is the case for cisatracurium, which undergoes spontaneous degradation in the serum through ester hydrolysis. Excretion occurs primarily in the kidney, bile, and feces. Some drugs are eliminated predominantly by a single mechanism. For example, more than 95% of elimination for the aminoglycoside antibiotics occurs through excretion in the kidneys. Other drugs, such as ceftriaxone, are removed through multiple pathways (renal and biliary elimination). Regardless of pathway, the degree of protein binding exhibited by a drug is an important determinant of elimination rate, as only unbound drug can be eliminated from the serum. A reduction in albumin binding is expected to increase the percentage of unbound drug or free fraction, although the free concentration may not increase to the extent predicted if more unbound drug is eliminated. Ceftriaxone is normally 85% to 95% protein bound, but as protein concentrations fall in critical illness, the Vd may increase by 90% and clearance



• **Fig. 21.4** Multicompartment model of drug distribution when drug requires a longer period of time to achieve equilibrium between plasma and tissue. A, Depiction of a multicompartment model of volume of distribution *(Vd)*. Drug enters the central compartment (serum) and then distributes into peripheral compartments (tissues). Total drug Vd is the sum of the individual compartments. Drug must then distribute back into serum to be eliminated. *Open circles* represent serum protein molecules. *Solid circles* represent drug molecules. B, Concentration versus time curve for one-compartment model on a logarithmic scale. The *solid line* represents serum concentration. The *dashed line* represents tissue concentration. Note that tissue concentrations increase during the distribution phase. Drugs with large Vds require prolonged distribution phases to saturate the peripheral compartments. The large Vd also results in a prolonged redistribution phase, which prolongs drug half-life.

by 100%, leading to suggestions of more frequent dosing or continuous infusion to maintain effective concentrations.[24,25]

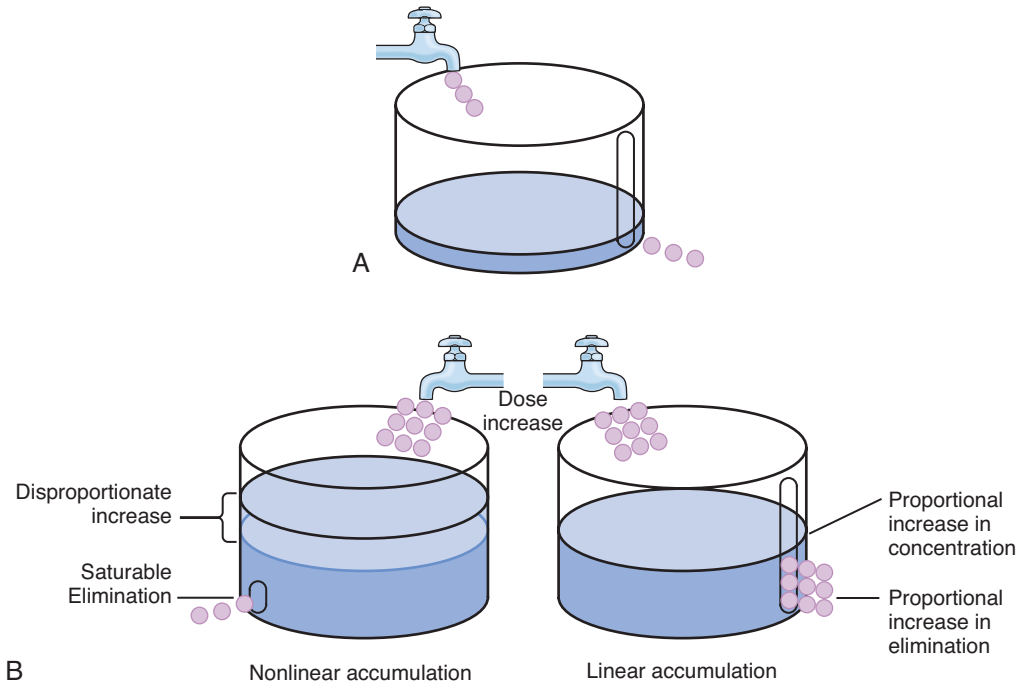
The rate of drug removal via all routes is termed clearance (Cl), which is expressed as the volume of plasma cleared per unit of time. This value is assumed to be constant for most drugs when organ function is stable. If the *volume cleared per unit of time is constant,* it then holds that the *amount of drug cleared per unit of time* must change in proportion to serum concentration. Rapid administration and a high concentration increase the amount of drug removed. The amount of drug removed per unit of time is called the elimination rate (ke). In contrast, a reduction in serum concentration, owing to expansion of the Vd, reduces the amount of drug removed and reduces the ke. Mathematically, ke is inversely related to the half-life. Serum and tissue concentrations accumulate until the ke is in equilibrium with the rate of administration, at which time the system is said to be at "steady state" (Figs. 21.2 and 21.5). Accumulation follows a linear pattern for most drugs, meaning that increases in dose are always matched by proportional increases in elimination, thus producing proportional changes in serum concentration (Fig. 21.5). Drugs that follow this pattern of accumulation are said to have first-order kinetics.

However, some drugs exhibit saturable elimination. These drugs follow linear accumulation until a saturation point is reached. Once elimination is saturated, small changes in dose can produce substantial increases in concentration (see Fig. 21.5). Drugs that follow this pattern of accumulation have zero-order kinetics. Examples of drugs with saturable elimination are phenytoin, high-dose heparin, propranolol, and verapamil.

Renal elimination of drugs is an important clearance mechanism. Glomerular filtration rate (GFR) is measured or estimated to predict elimination of drugs undergoing filtration, but is less accurate for drugs with substantial tubular secretion. Methods to estimate or measure GFR are discussed in detail later. Although most of the research has focused on reduced renal function, it is now recognized that a subset of critically ill patients may experience augmented renal clearance (ARC), exceeding what may have been taught as the "maximum" Cl through higher GFR and renal tubular anion secretion.[26,27] This ARC is defined as creatinine clearance (CrCl) greater than 130 mL/min (range >120 to >150 mL/min) and has been described in patients younger than 50 years of age, male sex, higher diastolic blood pressure, and fewer acute comorbidities over the first week of care.[28] Populations at risk include those with major trauma, traumatic brain injury (TBI) or subarachnoid hemorrhage, or central nervous system infection. Patients with ARC are at risk for treatment failure if doses are not increased. Urine collection for measured CrCl is needed to identify these patients and should be considered for younger patients and those with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)-estimated CrCl >108 mL/min.[29]

The liver serves as the primary site for drug metabolism, and therefore drug dosing is an important consideration in any patient with hepatic disease. Hepatic drug clearance (CL_H) is an extremely complex process, dependent on hepatic blood flow and the hepatic extraction ratio. The hepatic extraction ratio depends on hepatic flow, intrinsic clearance of unbound drug (CL_{int}), and the fraction of unbound drug in blood.[30]

Drugs can be categorized as either high– or low–extraction ratio drugs. Elimination of high–extraction ratio drugs is dictated by hepatic blood flow and is less sensitive to changes in drug protein binding or enzyme activity. With oral administration, high–extraction ratio drugs (>70% extracted) undergo extensive presystemic metabolism, commonly referred to as the hepatic first-pass effect. This results in significantly lower bioavailability and serum drug concentrations. Patients with reduced hepatic



• **Fig. 21.5** Pharmacokinetic principle of linear and nonlinear drug elimination. A, Faucet and bucket representation of drug elimination. The faucet represents drug input rate. The channel in the side of the bucket represents drug elimination pathways. At steady state drug input is in equilibrium with drug elimination. B, The effect of a dose increase. On the right is an example of first-order kinetics. The channel allows for elimination to increase in proportion to the dose increase, producing proportional changes in drug level. On the left is an example of zero-order kinetics, in which elimination is constant after the saturation point. Here the elimination channel is saturated at low input rates, producing a disproportionate increase in drug level.

blood flow have less first-pass effect, leading to higher serum concentrations. This effect is most pronounced in drugs that normally have low bioavailability after oral administration. Agents such as lidocaine, morphine, verapamil, propranolol, propofol, and nitroglycerin illustrate flow dependence, and poor cardiac output will contribute to rapid accumulation of serum concentrations unless doses are adjusted. Hyperdynamic flow rates in sepsis or stimulated by catecholamines could increase the rate of drug elimination of high–extraction ratio drugs.

Low–extraction ratio drugs are more sensitive to changes in drug protein binding and enzyme activity and are affected to a lesser degree by changes in blood flow. Plasma protein binding of drugs is lower in critically ill patients and those with hepatic disease owing to decreased albumin production and accumulation of endogenous compounds that inhibit protein binding (e.g., uremia or hyperbilirubinemia). As discussed previously, this decrease in protein binding can increase free/unbound drug levels and may increase the risk of adverse effects.

Intrinsic hepatic clearance is the ability of the liver to clear unbound drug from the blood. It is highly dependent on the activity of metabolic enzymes and hepatic transporters. The two phases of hepatic metabolism are phase I (i.e., hydrolysis, oxidation, reduction) and phase II (i.e., acetylation, glucuronidation, sulfation). The cytochrome P450 (CYP) family of enzymes is responsible for approximately 75% of drug metabolism and the phase I reactions.[31] Drugs are converted to a more soluble salt form and in some cases to the active moiety or active metabolites. For example, midazolam oxidative metabolism produces several metabolites, including α_1-hydroxymidazolam, a renally eliminated active, sedating moiety.[32]

The activity of phase I enzymes is dependent on genetic predisposition, drug interactions (inhibition or induction), body temperature, and hepatic injury. Phase I metabolism is very dependent on oxygen and is sensitive to reduced oxygen delivery, such as shunting, sinusoidal capillarization, and reduced liver perfusion.[33] The changes are not homogenous across CYP 450 isoenzymes after a hypoxemic insult.

Phase II metabolism converts the parent drug to an inactive salt form that is renally eliminated (e.g., lorazepam, valproic acid). These conjugation reactions were historically thought to be spared in patients with liver disease, but recent data suggest that impairment in patients with advanced cirrhosis as well.[30] A unique interaction involving phase II metabolism is the most plausible explanation of the dramatic reduction in valproic acid concentrations with concurrent carbapenem (doripenem, ertapenem, imipenem, meropenem) administration.[34,35] The interaction occurs without regard to route of valproic acid administration and cannot be easily overcome with an increase in valproate dose, resulting in seizures or loss of control of mania. This combination should be avoided. Demonstration that meropenem accelerates the glucuronidation of valproic acid glucuronide and further inhibits the hydrolysis or deconjugation back to the parent compound is the leading explanation for this interaction.[35] The valproic acid glucuronide is rapidly eliminated via renal routes. It is unknown if other interactions can alter phase II homeostasis in a similar manner.

Half-Life

Once clearance is known the clinician can estimate the time needed for a given dose to be eliminated. Elimination time is commonly

expressed in terms of half-life ($t_{1/2}$), the time required for the amount of drug to decrease by 50%. Half-life is calculated from the elimination rate constant:

$$\text{ke (per hour)} = \frac{\text{Cl (L/h)}}{\text{Vd (L)}};$$

ke can be further transformed into half-life:

$$t_{1/2}\text{(hours)} = \frac{0.693}{\text{ke}}$$

For any system that follows exponential decay, half-life can be used to estimate the amount of elimination that has occurred; after 5 half-lives more than 90% is eliminated. Elimination approaches 100% after 7 half-lives. The time required for a dosing regimen to reach steady state is also an exponential function and thus can be estimated using half-life. This same "5-7" rule of thumb is useful at the bedside. Dosing regimens approach maximal effects after 5 to 7 half-lives. Similarly, drug effects are usually completely dissipated after 5 to 7 half-lives. Using this rule, it can be predicted that drugs with long half-lives may take several days to produce target effects. Lorazepam via continuous infusion is a classic example owing to its prolonged half-life.[36] This is less than ideal in the critically ill population when effective treatment is needed rapidly. As a result, loading doses are frequently used to hasten the time to achieve the goal concentration.

It is important to note that the time needed to eliminate a given dose is dependent not only on the clearance rate, but also on the drug's Vd. It is intuitive that half-life is affected by changes in elimination pathways (e.g., renal failure). However, changes in Vd can have equally important effects on half-life. For example, expanded Vd after resuscitation prolongs the half-life of aminoglycosides, without a change in clearance, as illustrated in the previous equations. Failure to account for Vd expansion can lead to drug accumulation independent of changes in drug clearance.

Modeling the Concentration-Time Curve

When estimations of bioavailability, Vd, and clearance are available, the concentration-time curve can be modeled. As discussed earlier, the one-compartment model is useful for hydrophilic drugs with small Vd, such as aminoglycosides. Fig. 21.3B depicts the serum concentration-time curve of a one-compartment model drug after intermittent IV administration plotted on a logarithmic scale. The initial peak concentration can be estimated from dose and Vd. The peak is followed by a short distribution (α) phase, during which time drug is removed from the plasma through distribution to tissue in addition to clearance. After distribution is complete, the curve is defined by a second phase (β) when drug is removed from plasma via clearance. The time course of this phase can be estimated using half-life. The transition from distribution to elimination phase occurs at an inflection in the slope of the concentration curve. This is known as a biexponential pattern of decay. Because the distribution phase is often short (usually 15–30 minutes) it can usually be ignored when performing calculations.

Conversely, drugs with large Vds are more accurately represented using a two-compartment model (see Fig. 21.4B). The important difference between one-compartment and two-compartment models is the significance of the distribution phase, which is much longer for drugs following a two-compartment model. Concentration sampling before completion of the distribution phase can lead to dosing errors through calculation of an inappropriately rapid ke. A third phase is also evident near the end of the curve (γ), at the end of therapy, or with a long dosing interval. This redistribution phase is a result of slow release of drug from the tissues back into the serum. This slow tissue release, known as the "context-sensitive half-life," is responsible for the prolonged duration of pharmacologic effect seen after continuous infusions of highly lipophilic drugs such as fentanyl, midazolam, and propofol.

Pharmacodynamics

PD parameters provide an additional perspective on drug dosing by focusing on important clinical endpoints, such as bactericidal efficiency or ability to achieve the desired clinical response to a sedative. Although PD concepts are important for all dosing decisions, PD parameters have been best defined for antibiotics in part because the effect of interest (bacterial killing) can be readily measured through in vitro and in vivo studies. Therefore the PD portion of this chapter focuses on antibiotics. However, the basic concepts can be applied to all drugs. Minimum inhibitory concentration (MIC) was the first PD parameter to show utility in predicting the effectiveness of antibiotic regimens. The MIC of an antibiotic is the lowest tested concentration needed to inhibit bacterial growth in vitro. There are at least three patterns relating drug effect to MIC: concentration-dependent or time-dependent killing, and a combined endpoint relating area under the concentration-time curve (AUC) to the MIC. In concentration-dependent killing, the ability to achieve a peak concentration many times greater than the MIC determines effectiveness. Aminglycosides achieve maximal bacterial killing with a peak concentration at or above 8 to 10 times the MIC and quinolones similarly exhibit concentration dependence (peak:MIC). High peak concentrations may also increase tissue penetration of intracellular-active agents. However, the maximal dose is often limited by potential adverse effects. In contrast, the time-dependent agents, such as β-lactams, are most effective when the concentration exceeds the MIC for a large portion of the dosing interval (time [T] > MIC). These antibiotics reduce the formation of bacterial cell walls via inhibition of penicillin-binding protein. This protein is located on the bacterial cell surface, and effective drug binding occurs at low drug concentrations. In fact, in vitro analyses have shown that nearly all available penicillin-binding protein targets become saturated at concentrations that are four to five times the bacteria's MIC.[37] Effectiveness of the third group of antimicrobials, including vancomycin, requires consideration of total antibiotic exposure, measured as a ratio of AUC to the MIC (AUC:MIC). Effectiveness measures for antimicrobials are illustrated in Fig. 21.6.

It is important to note that most PD analysis is based on total drug concentrations in the serum. However, only free drug concentrations reach the site of action and cause bacterial killing. High protein binding or a large Vd predicts poor tissue penetration and potential treatment failure, despite high serum concentrations, such as daptomycin for pneumonia. Tissue level analysis may offer better prediction of effectiveness but availability is limited in clinical practice.

Dosing regimens should be designed to optimize achievement of the desired PD endpoint for the majority of patients, accounting for inherent PK differences. This is termed the target attainment. Dosing regimens for optimal target attainment in critically ill patients are often different from those listed in approved drug labeling, obligating clinicians to individualize drug dosing.

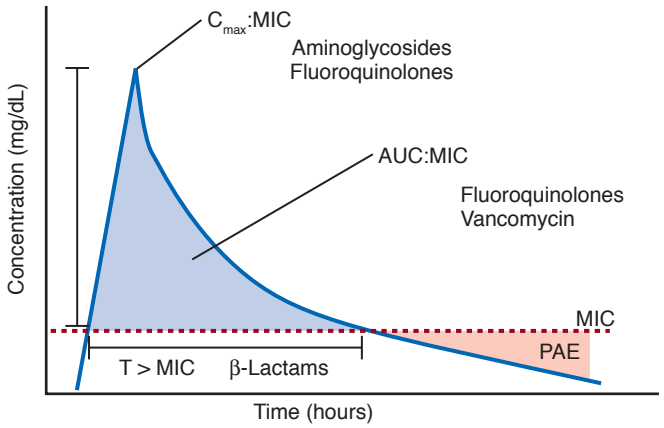
β-Lactams

The T > MIC endpoint for target attainment varies within the β-lactam class. Cephalosporins require the highest T > MIC (50%–70%), followed by the penicillins (30%–50%) and the carbapenems (20%–40%) to effect optimal bacterial killing.[38,39] The importance of T > MIC has gained significant attention with increasing bacterial resistance (higher MIC). Resistant bacteria have higher MICs, making it more difficult to achieve adequate T > MIC (Fig. 21.7). Studies conducted in critically ill patients have shown that using standard β-lactam dosing regimens, developed for non–critically ill patients, may produce unacceptably low serum concentrations, resulting in inadequate T > MIC.[40,41] Various strategies may address these deficiencies by increasing time above MIC, including loading doses, larger or more frequent maintenance doses, prolonged infusions, or continuous infusion.[42] Continuous-infusion β-lactam regimens may be the most appealing in theory, but they are less practical when considering limited stability in solution, need for dedicated IV sites owing to incompatibility, and less clinical outcome data.[43,44]

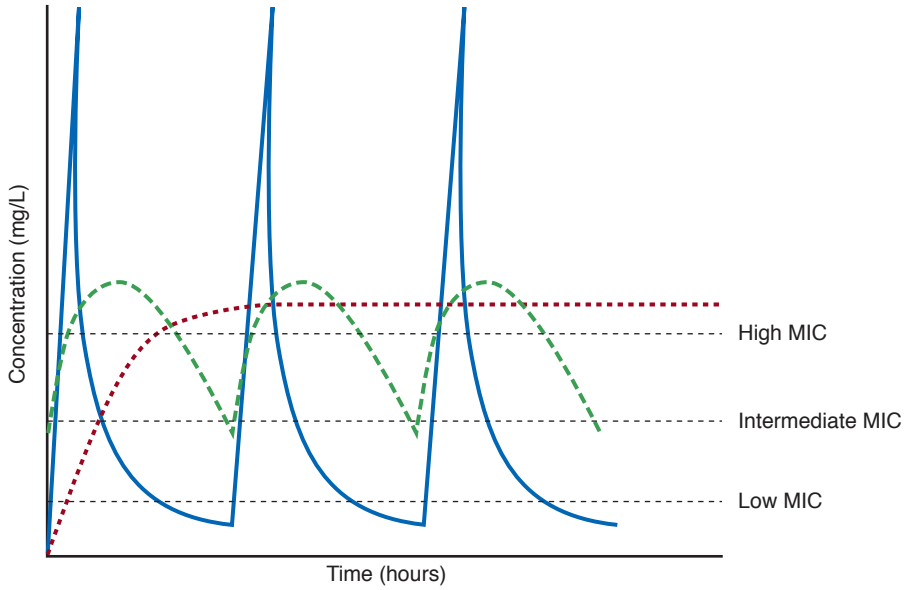
There is also a theoretical concern for selection of resistant subpopulations. Mathematical modeling of bacterial growth dynamics suggests that a constant rate of bacterial killing creates more opportunity for generating resistant mutants than does a fluctuating kill rate.[41,45] A concentration above the inhibitory threshold but below the bactericidal concentration of these strains has been coined the mutant selective window.[45] A concentration that kills these bacteria has been coined the mutant protection concentration. An in vitro model of ceftazidime via continuous infusion, with maintenance of steady-state serum concentrations slightly above the bacteria's MIC resulted in the emergence of resistant bacteria subpopulations.[46]

The use of prolonged infusions of β-lactam antimicrobials over 3 to 4 hours has become common as a mechanism to maximize T > MIC with the same or lower total daily dose, while minimizing some of the challenges with continuous infusions. Extending the infusion duration, without a dose increase changes the shape of the concentration-time curve to promote longer T > MIC, as seen in Fig. 21.7. Effectiveness of this strategy has been demonstrated with improved target attainment and improved clinical outcomes, including reduced mortality in critically ill patients.[43,44,47,48] With either continuous or prolonged infusions, loading doses are advocated for critically ill patients with an expanded Vd to achieve target concentrations more rapidly.[49]

Larger doses at a typical interval or high total daily doses may improve target attainment, but they also increase the risk of adverse effects, illustrated by the reports of seizures and neurotoxicity when doses of cefepime or meropenem are not appropriately adjusted for reduced CrCl.[50,51]



• **Fig. 21.6** Pharmacokinetic and pharmacodynamic parameters on a concentration versus time curve. This figure depicts how drug concentration relates to bactericidal effect for various antimicrobial agents. *AUC,* Area under the concentration-time curve; *MIC,* minimum inhibitory concentration; *PAE,* postantibiotic effect; *T,* time.



• **Fig. 21.7** Impact of increasing minimum inhibitory concentration on ability to achieve pharmacodynamic goals and impact of differing dosing regimens. The *solid lines* represent standard, short infusion administration. The *green dashed line* represents extended infusion administration. The *red dashed line* represents continuous infusion. *MIC,* Minimum inhibitory concentration.

Aminoglycosides

Aminoglycosides are broad-spectrum gram-negative antimicrobial agents that have been in clinical use since the 1960s, but they are increasingly used for resistant pathogens and as a potentially synergistic agent with other broad-spectrum agents for patients with septic shock.[52] Historical dosing strategies used low doses given every 8 hours and proved to be suboptimal with high rates of nephrotoxicity and inadequate clinical response compared with other antimicrobials. The importance of achieving an adequate peak:MIC was first described in patients by Moore and colleagues, who found that the likelihood of having a positive clinical response was greater than 90% when peak concentrations were 8 to 10 times the MIC.[53] Individualized dosing strategies were used to achieve peak concentrations of ~8 mg/L for critically ill patients with expanded Vd, such as those with abdominal infections. Longer intervals were gradually used to ensure that trough concentrations were less than 1 to 2 mg/L. A later study found that time to defervescence and normalization of leukocytosis was greater than 90% when peak:MIC was 10 or greater.[54] Achieving high peak aminoglycoside concentrations (10 × MIC) is fundamental to successful treatment and is now the standard of practice. These doses dictate the need for an extended dosing interval to allow sufficient time to eliminate the drug, ideally achieving a drug-free period to reduce tissue accumulation (especially renal and cochlear/vestibular) and potential toxicity. Critically ill patients with a high Vd often need more than 24 hours between doses to achieve a drug-free interval, even with good renal function, as a result of expanded Vd and reduced ke.

A wide variety of doses have been used in extended interval dosing (EID) strategies. Typical doses are 5 to 7 mg/kg for gentamicin and tobramycin.[55] These doses were chosen to achieve peak concentrations 10 times the MIC for typical gram-negative bacteria in patients with a normal Vd, approximately 0.3 L/kg. Dosing nomograms (such as the Hartford nomogram) using a single concentration to define the frequency of repeated doses have been designed for patients with normal Vd, but they should not be used in critical care patients with expanded Vd or for doses that differ from the original dosing model.[56] Critical care patients exhibit substantial interpatient and intrapatient variability in PK owing to changes in Vd, clearance, and ke. The use of standard doses of amikacin (15–20 mg/kg) was shown inadequate to achieve a peak more than 8 times the MIC breakpoints owing to larger Vd values of 0.41 (0.29–0.51) L/kg. A dose of at least 28 mg/kg (dosing weight) or 25 mg/kg of actual weight is suggested for patients with sepsis.[57–59]

Individualized dosing is needed for patients who are not expected to have a normal Vd or who have unpredictable CrCl, especially if treatment is continued for more than one dose. Two post-dose concentrations should be drawn after the first dose (e.g., 2 and 12 hours after) to calculate Vd and ke. When designing an ongoing regimen, a patient-specific dose based on the MIC of the organism should be considered. A dose to achieve 10 times the MIC using the calculated Vd may be different from the standard 5 to 7 mg/kg for tobramycin or 25 mg/kg for amikacin, A dosing interval should be chosen that is sufficient to achieve near-complete elimination. Computer programs are available to facilitate the calculation of patient-specific PK parameters. Volume resuscitation or renal function changes during this monitoring interval may alter the accuracy of these parameters to predict ongoing dosing needs, and a concentration should be rechecked 4 hours before a subsequent dose to confirm near-complete elimination.

As mentioned, the use of aminoglycosides is limited by their potential to induce nephrotoxicity. Nephrotoxicity is the result of accumulation in the epithelial cells of the proximal renal tubule. Of great importance is the fact that the rate of accumulation is saturable at relatively low concentrations in the tubule lumen of the rat.[60] This means that toxicity is not concentration dependent but rather time dependent. Once saturated, the rate-limiting step of tissue accumulation becomes the duration of exposure. Because EID regimens should be designed to produce a drug-free period near the end of the dosing interval, it reduces drug accumulation, potentially reducing toxicity. In vivo studies have confirmed that EID reduces renal accumulation and enzymatic markers of nephrotoxicty.[61,62] There is no standard to define the optimal drug-free interval, but extensive patient experience suggested safety when targeting a 4-hour drug-free interval (e.g., tobramycin concentration <0.5 mg/L).[56] It has been shown that a threshold of accumulation is needed before nephrotoxicity is produced and that this threshold is typically reached after 5 to 7 days of therapy.[63] The risk of ototoxicity also appears related to duration of therapy but other undefined factors may also contribute. Although often not recognized acutely, dizziness, vertigo, tinnitus, and hearing loss may be permanent.[64]

Vancomycin

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most important pathogens causing infection in critically ill patients.[65] Vancomycin has been a drug of choice for nearly 50 years. It inhibits cell wall formation in gram-positive bacteria in a fashion similar to the action of β-lactams. However, vancomycin binds a different receptor and produces a slower bactericidal effect. This slow rate of killing may explain the slower symptom resolution and higher failure rates with vancomycin compared with β-lactams in the treatment of methicillin-susceptible *S. aureus* infections.[66] The current breakpoint for vancomycin susceptibility against *Staphylococcus* species is an MIC of 2 mg/L, but recognition of heteroresistant strains with intermediate susceptibility (MIC 1-2 mg/L) has heightened concern over inadequate dosing.[67,68] In recent years, studies have identified AUC:MIC > 400 as the preferred PK parameter associated with clinical success.[69] In clinical practice, however, monitoring a predose level during intermittent infusion therapy has been used as a practical surrogate for AUC:MIC, with a target trough of 15 to 20 mg/L in complicated infections such as endocarditis, osteomyelitis, bacteremia, meningitis, and pneumonia (MIC ≤1 mg/L).[70] Use of the trough level as a surrogate is based on PK models that assume a predictable peak concentration for any given dose, although this may not be an accurate assumption in critically ill patients. Physiologic and PK differences in individual patients may alter the relationship between trough level and AUC:MIC target attainment.

A standard Vd of approximately 0.7 to 0.8 L/kg is used in many vancomycin dosing protocols. In reality, a broad range of Vd values is reported for adults, 0.5 to 1.7 L/kg of total body weight (TBW), depending on the population.[71] Estimates in obese patients range from 0.26 to 1.7 L/kg in obese and morbidly obese individuals.[72] Some reported small Vd values could be the result of incomplete distribution at the time of the postdose measurement—sampling earlier than 1 to 2 hours after the end of the infusion—leading to a factitiously high peak. Some large Vd values, as reported in critically ill patients, may be the result of vigorous volume resuscitation and low plasma protein concentrations. In reality, if the peak value for a given dose is significantly different from the

TABLE 21.3 Equations to Determine Body Size Indicators

Descriptor	Equation
Body mass index (kg/m^2)	TBW/(height in m)^2
Body surface area (m^2) (Mosteller formula)	$\sqrt{\left[\frac{(\text{Height (cm)} \times \text{TBW})}{3600}\right]}$
Ideal body weight (kg)	Men: 50 kg + 2.3 kg per inch in height >5 ft Women: 45 kg + 2.3 kg per inch in height >5 ft
Adjusted body weight (kg)	0.4 × [TBW − IBW] + IBW
Lean body weight (kg)	Men: [1.1 × TBW] × 120[TBW/height (cm)]^2 Women: [1.07 × TBW] − 148[TBW/height (cm)]^2
Percentage of IBW (%)	(TBW/IBW) × 100
Fat-free mass (kg)	Men: = (9270 × TBW)/[6680 + (216 × BMI)] Women: = (9270 × TBW)/[8780 + (244 × BMI)]

IBM, Ideal body weight in kilograms; *LBW*, lean body weight in kilograms; *TBW*, total body weight in kilograms.

model used to extrapolate a single trough level, clinicians may not achieve the target AUC:MIC.

Further complicating the use of population parameters for estimation of initial doses or Vd is the conflicting data on optimal weight to use. The American Society of Health-System Pharmacists guideline recommends TBW based on a single trial; however, data in obese patients (>120% above ideal body weight) have suggested that adjusted body weight (ABW) is more accurate for the prediction of vancomycin clearance (Table 21.3).[70,73,74] Additional testing is needed to determine the most appropriate weight parameters in various populations. See the obesity section for more discussion.

Patient-specific dosing of vancomycin with more than a single trough level is advocated to ensure target attainment.[75,76] Serum concentration monitoring with extensive sampling indicates that vancomycin is best characterized with at least a two-compartment model (see Fig. 21.4). A prolonged distribution phase, up to 3 hours after the infusion has been demonstrated, indicates that a postdose level should be delayed several hours if attempting to characterize the elimination rate in an individual patient.[77] Individualized dosing of vancomycin has been studied using the techniques that are widely accepted for individualized aminoglycoside dosing. One group has published a series of articles on the use of intensive serum concentration monitoring after steady state to individualize later doses. Both a Bayesian and an equation-based methodology have been developed, but only the equation-based method was reported in obese patients.[77–79] At steady-state, predose and postdose (1–2 hours after dose) concentrations were measured and the first-order elimination rate constant (ke) calculated. This ke is used to back extrapolate from the postdose level to a mathematical value at the time of infusion initiation (*Csoi'*) and to forward calculate from the predose level to the actual level at the start of the next infusion (C*t*). The AUC for the dosing interval (int) is then estimated as follows:

$$\text{AUC}_{\text{int}} = \frac{Csoi' - Ct}{\text{ke}}$$

To determine a 24-hour AUC, multiply AUC_{int} by the number of intervals in 24 hours. If the AUC target is not achieved, an individualized dose can be calculated. Delayed dose optimization is a disadvantage of this method, occurring 2 to 3 days into therapy, but this technique can be directed toward patients with documented *Staphylococcus* spp. infections. Levels drawn after a loading dose helped to establish dosing needs more rapidly in a small number of patients with CrCl less than 60 mL/min and SIRS/sepsis.[80] Patients received a fixed vancomycin dose of 25 mg/kg and were then randomly assigned to individualized monitoring with levels after the loading dose. Use of a one-compartment model for a two-compartment drug like vancomycin risks drug accumulation, so steady-state trough monitoring is still needed. Validation of the benefit of these methods is needed in larger populations to be widely recommended. Although it is not incorrect to monitor vancomycin with a single trough level at steady state, clinicians can use more detailed methods to improve vancomycin dosing and target attainment in serious staphylococcal infections or for patients with abnormal drug clearance, Vd, or at extremes of weight.

The targeted AUC:MIC greater than the 400 endpoint is not achievable with conventional dosing methods when MIC is elevated. A meta-analysis found a 64% relative increase in mortality risk comparing high-MIC (>1.5 mg/L) isolates to low-MIC (<1.5 mg/L) isolates.[69] Balancing effectiveness and safety is a consideration if vancomycin is used instead of potentially more effective agents. Higher doses of vancomycin could be used to treat staphylococcal isolates with a high MIC to achieve higher trough levels of 25 to 30 mg/L and thus the target AUC:MIC, but nephrotoxicity risk may increase with doses above 4000 mg/day.[70] A meta-analysis of studies where vancomycin trough levels were maintained between 15 and 20 mg/L showed an odds ratio of 2.67 (95% confidence interval 1.50–3.65) for the risk of nephrotoxicity compared with levels below 15 mg/L, so the incremental risk of higher troughs may be substantial.[81] An alternate strategy may be to combine other antimicrobials such as a β-lactam agent with vancomycin for increased bactericidal effect. A retrospective study of vancomycin versus vancomycin plus various β-lactams was associated with higher microbial eradication compared with vancomycin alone.[82] However, the combination of vancomycin with piperacillin/tazobactam has been associated with a greater risk of nephrotoxicity compared with vancomycin alone or in combination with cefepime or meropenem in some reports.[83,84] An adequately powered prospective randomized trial is needed to address safety and efficacy of this combination.

Continuous infusion of vancomycin has been evaluated to maintain an optimal AUC:MIC; however, significant differences in effectiveness have not been demonstrated. A meta-analysis found a high degree of heterogeneity between studies and concluded that continuous infusion was associated with a significantly lower risk of nephrotoxity but that prospective, randomized trials were needed to evaluate mortality rate or other outcomes.[85] Thus a continuous infusion may be considered for patients at high risk of nephrotoxicity.

The vancomycin infusion dose should be patient-specific, with a loading dose of 35 mg/kg TBW and a daily dose adjusted for renal function and supported by serum concentration monitoring.[86] A dosing model to achieve a concentration of 20 to 30 mg/L in ICU patients was developed and tested in a small number of

patients with measured CrCl (8-hour clearance × 1.73/body surface area [BSA]).[87] After a loading dose of ~20 mg/kg, the daily vancomycin dose (in grams/day) was calculated as = [(0.021 × 8-hour CrCl) + 2.3] × 0.6 and achieved the goal in 84% of patients. The potential benefit of an infusion must be weighed against the challenge of limited compatibility data with other agents and the use of one infusion site for a single therapy.

Dosing Considerations in Select Critical Care Patients

Renal Disease

Acute kidney injury (AKI) is a common occurrence in the ICU. Using a consensus definition, rates of AKI range from 10% to 30% in the general ICU population and 40% to 60% in patients with severe sepsis and septic shock.[88] In addition, approximately 5% will require some form of hemodialysis. Therefore it is important for ICU practitioners to understand the basic approach to drug dosing in renal failure and insufficiency.

Assessing Renal Function

Accurate assessment of renal function is imperative to make appropriate dosing decisions. This assessment may include a measurement or estimate of the GFR. Inulin is the gold standard for the assessment of renal function.[89] However, with limited availability and high cost, it is rarely used outside a research setting. Laboratories routinely report estimated GFR using the Modification of Diet in Renal Disease (MDRD) equation as a screening tool for GFR below 60 mL/min per 1.73 m^2, although this formula lacks validation in critical care patients, at extremes of weight, or abnormal creatinine production.[90] In 2009 the National Kidney Disease Education Program suggested that either the Cockcroft-Gault (CG) formula with serum creatinine or MDRD equation could be used for drug dosing purposes[91] (Table 21.4). For very large or very small people, adjustment of the MDRD equation to account for BSA is recommended. However, in critical care patients with early AKI, both have unacceptably high errors and poor precision compared with infusion clearance of chromium 51 complexed with ethylene diamine tetraacetic acid (^{51}Cr-EDTA), a gold standard method.[92] Significant between-patient variability exists with overpredicted and underpredicted CrCl.

The clinical reference standard method is via a carefully collected, timed urine creatinine collection. The traditional 24-hour collection period has multiple opportunities for error and is often impractical because a practitioner must wait longer than 24 hours for data that influences drug dosing. The ideal duration of collection is unclear, but shorter collections have been studied. A 2-hour collection was similar to a 24-hour collection in a mixed medical-surgical ICU population and an 8-hour collection in a critical care population.[93,94] Direct measurement of urine creatinine should be considered when making dosing decisions in patients who are receiving narrow therapeutic index drugs, may have ARC, or are at the extremes of age or weight or in early AKI.

Predictive equations using creatinine concentrations are used more routinely to estimate GFR.[95] Formulas to predict GFR based on serum creatinine concentrations in critically ill patients exhibit low accuracy and precision with a tendency to overestimate GFR.

TABLE 21.4 Equations Commonly Used to Estimate Renal Clearance[96,97,101,105,109]

Equation	Measure	Equation	Considerations
Cockcroft-Gault	CrCl (mL/min)	(140 − age) BW/(SCr × 72) (0.85 if female)	• Inaccurate in patients with acutely changing renal function • Optimal weight parameter is controversial in obese patients
Reexpressed MDRD (4 variable)	GFR (ml/min/1.73 m^2)	$175 \times SCr^{-1.154} \times age^{-0.203} \times$ (0.742 if female) × (1.21 if AA)	• Inaccurate in patients with acutely changing renal function • Must be individualized for BSA by multiplying estimated GFR × (estimated BSA/1.73 m^2) • Little information available in obese, elderly, or hepatic disease patients
Obesity 1 (Winter et al.[97])	CrCl (mL/min)	(140 − age) BW/(S_{Cr} × 72) × (0.85 if female) Use various weights	• Underweight use actual weight • Normal weight use ideal weight • If BMI 26–50, use adjusted weight using 40% factor = [(actual − ideal weight) × 0.40] + ideal weight
Obesity 2 (Demirovic et al.[109])	CrCl (mL/min)	(140 − age) LBW/(S_{Cr} × 72) × (0.85 if female)	• For BMI >40 kg/m^2 • LBW_{male} = (9270 × TBW)/(6680 + 216 × BMI) • LBW_{female} = (9270 × TBW)/(8780 + 244 × BMI)
Cystatin C	eGFR (mL/min)	$135 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-0.601} \times \min(S_{cys}/0.8, 1)^{-0.375} \times \max(S_{cys}/0.8, 1)^{-0.711} \times 0.995^{Age}$ × 0.969 [if female] × 1.08 [if AA] κ = –0.7 (if female), 0.9 (if male) α = –0.248 (if female)], 0.207 (if male) $\min(S_{Cr}/\kappa$ or 1) = minimum of S_{Cr}/κ or 1 $\max(S_{Cr}/\kappa$ or 1) = maximum of S_{Cr}/κ or 1 $\min(S_{cys}/0.8, 1)$ = minimum of $S_{cys}/0.8$ or 1 $\max(S_{cys}/0.8, 1)$ = maximum of $S_{cys}/0.8$ or 1	

AA, African American; *BMI,* body mass index; *BSA,* body surface area; *BW,* body weight in kg; *CrCl,* creatinine clearance; *eGFR,* estimated glomerular filtration rate; *LBW,* lean body weight; *GFR,* glomerular filtration rate; *MDRD,* Modification of Diet in Renal Disease equation; S_{Cr}, serum creatinine; S_{cys}, serum cystatin C.
Ideal weight = (height in inches – 60) × 2.3 + 50 kg for males or 45.5 kg for females.

Creatinine secretion is dependent on muscle mass and not body mass. Creatinine production does not increase in proportion to TBW, which also represents fat weight. Use of TBW to estimate CrCl in obese patients creates potential for significant error. The CG formula is widely used for drug dosing, although it was developed for outpatients with stable renal function, using actual body weight.[96] Use of the CG formula with early AKI, unstable creatinine, oliguria, extremes of weight, or patients with reduced muscle mass (amputation, prolonged bedrest, plegia, malnourishment, and so on) adds the potential for inaccuracy. Manipulation of the parameters (weight, creatinine) to arbitrary values for abnormal patients has been widely used by clinicians, but routinely rounding creatinine to an arbitrary minimum value reduces the accuracy of CrCl prediction and should not be a standard of practice.[97,98] In the search for better tools in clinical care, cystatin C has been evaluated as a marker of GFR.[95] It is a serum protein that is filtered by the kidney and concentrations are less dependent on age, sex, race, and muscle mass compared with creatinine.[99–102] Laboratories may not routinely assay cystatin C (cystC) and other factors such as malignancy may alter its accuracy. Although a formula that considered both creatinine and cystatin C (CKD-EPI$_{creat\text{-}cystC}$) performed better than either marker alone in a non-ICU study, a clear role for this approach has not been delineated.[101] Although cystatin C formulas may prove to be more accurate than creatinine-based approaches for selected patients, the data do not support routine use at this time.[102,103] Nevertheless, preliminary work with cystatin C has been studied as part of a vancomycin dosing quality improvement project and suggested to improve achievement of goal concentrations.[104] Table 21.5 lists the commonly used equations and considerations for their use.[96,105,106] Several other less frequently used equations to estimate CrCl or GFR can be found in more detailed reviews on estimating renal clearance.[89]

Other patient populations that require specific considerations are patients at the extremes of weight and elderly patients. Both CG and MDRD equations have varied results in patients older than 65 years of age. The MDRD equation has been shown to overestimate kidney function in elderly patients, and the CG equation may either overestimate or underestimate renal clearance.[90,107] Obese patients also present problems when determining renal clearance for the purposes of drug dosing. The MDRD equation has been shown to underestimate renal clearance in obese patients, and the CG equation overestimates renal clearance in obese patients when the TBW is used.[108] Formulas to predict CrCl have used TBW, ABW, and lean body weight (LBW) in various ways; no consensus has emerged for all weight ranges, and none are specific to critical care. With the CG formula, it is reasonable to use TBW for underweight and normal weight patients (body mass index [BMI] <25 kg/m^2) and for overweight patients (BMI 25–30 kg/m^2) use either TBW or ABW, for obese patients (BMI 30–40 kg/m^2) use ABW, and for morbidly obese patients (BMI >40 kg/m^2) use LBW.[96,97,109,110] Regardless of which approach to renal function assessment is used, it is important to remember that all have limitations relative to the population studied and accuracy of height and weight of an individual patient. Because changes in serum creatinine are delayed compared with changes in actual renal function, calculations based on this marker are unreliable in rapidly changing renal function.

With the inherent limitations of renal function assessment in critically ill patients, many renal dose adjustment decisions are done with a fair deal of uncertainty. Accordingly, it is essential for the clinician to have a clear understanding of the risks of toxicity associated with excessive dosing as well as the consequences of therapeutic failure associated with underdosing. As discussed, patients with septic shock may benefit from loading doses and early aggressive dosing of antimicrobials owing to their relative safety. However, drugs with a narrow therapeutic index (i.e., digoxin, lidocaine) may not allow as much latitude because of potential dose-related adverse effects and the need for close monitoring.

TABLE 21.5 Child-Pugh Classification of Liver Disease

Indicator	1 Points	2 Points	3 Points
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds > control)	<4	4–6	>6
Total bilirubin (mg/dL)	<2	2–3	>3
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	None	Slight	Moderate

Total score: 5–6 points (mild/group A); 7–9 points (moderate/group B); 10–15 points (severe/group C).
From Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60:646–649.

Dosing in Renal Replacement Therapy

Several factors contribute to drug clearance in patients receiving renal replacement therapy (RRT). They can generally be broken down into dialysis mode/device, drug, and patient factors. The two methods by which dialysis can remove drugs are diffusion and convection. Diffusion is a passive process during which substances move over a concentration gradient across a hemodialysis (HD) filter and into the dialysate. Convection/hemofiltration is an active process during which drugs are cleared across a pressure gradient if their size and protein binding permit passage. Hemofiltration removes a smaller percentage of drug and is more dependent on effluent rates and the sieving coefficient of the drug. However, sieving coefficients are not readily available for most drugs, and therefore the fraction of unbound drug is often used to assess the likelihood of drug clearance. Additional loss may occur by adsorption to the dialysis filter, although this is less well quantified.

The three main drug factors that affect clearance are molecular weight, protein binding, and Vd. The clearance of drugs relative to their molecular weight is determined by the efficiency of the filter. Synthetic membrane filters (e.g., polysulfone, polycarbonate, polyamide, or polymethylmethacrylate) are used for acute HD because of their efficiency and are referred to as high-flux membranes. These have greater permeability for large molecules, including drugs up to 20,000 Da.[111] Most research done on drug removal with HD is done with a single filter and may not be applicable to other membranes. Similar to endogenous clearance mechanisms, clearance by RRT is inversely related to the degree of protein binding and Vd. Because large Vd (>1.5 L/kg) drugs distribute well into tissue, the low serum levels make less drug available for elimination. Small Vd drugs (<0.7 L/kg) reside primarily in the serum, increasing the efficiency of extracorporeal removal.

Either continuous or intermittent modes of RRT may be used in critically ill patients. Although intermittent hemodialysis (IHD) is the most common form of chronic dialysis, and drug clearance data are readily available, it may not apply to critically ill patients with AKI. Most intermittent hemodialysis drug dosing data are

derived from patients with end-stage renal disease with adaptive changes in nonrenal clearance mechanisms—such as reduced hepatic metabolic activity. Patients with AKI may not require the same degree of dose alteration in the acute phase of injury. End-stage renal disease dosing recommendations should be used only as an initial guide to therapy in patients with AKI and individualized with close monitoring when possible.[111]

Continuous renal replacement therapy (CRRT) can be done with hemofiltration (continuous venovenous hemofiltration [CVVH]), continuous venovenous hemodiafiltration, or just as dialysis (continuous venovenous hemodialysis). A target effluent rate of 20 to 25 mL/kg per hour is recommended, but a higher prescribed dose of 25 to 30 mL/kg per hour may be required to achieve that target considering potential interruptions in treatment.[112,113] Drug dosing data with CRRT often differ from study to study and depends on mode (diffusion, convection, or both), site of replacement fluid (prefiltesr vs. postfilter), filter composition, and most importantly, the dialysis dose (effluent rate and dialysate rate).[111,114] Patients may also have preserved endogenous renal elimination. Therefore it is important that practitioners evaluate how published doses were derived before applying them broadly. Concern with potential underdosing of drugs during CVVH is becoming widespread.[115] An in-depth review of the types of RRT and degree of drug removal is beyond the scope of this chapter, but several references are available that provide this information.[113,116,117] A simplified assessment of the impact of RRT has been proposed using piperacillin as an example. It has an 81% free fraction, thus continuous venovenous hemodialysis clearance using 25 mL/kg per hour in a 100-kg patient could be estimated as 0.81 ×100 kg × 25 mL/(kilograms/hours) × 1 hour/60 min or about 35 mL/min. Dosing would be compatible with that level of GFR using typical dosing references, piperacillin/tazobactam 3.375 g every 8 hours.[118] Use of high-flow RRT (rates 4–6 L/h) for selected patients makes dosing more difficult, as many early studies were done for patients receiving replacement rates ~2 L/h. A meropenem dose of 1 g every 8 hours (via 30-minute infusion) was suggested for high-flow continuous hemofiltration for target attainment with susceptible organisms (MIC = 4 mg/L); this is a more frequent dose than suggested in common drug references.[119] Extended infusions (3–4 hours) or continuous infusion may reduce the amount of drug eliminated with high-volume RRT, as demonstrated with piperacillin/tazobactam.[120]

Thus although the general degree of drug removal is generally as follows: continuous venovenous hemodiafiltration > continuous venovenous hemodialysis > continuous venovenous hemofiltration > slow extended daily dialysis > intermittent hemodialysis, the use of high-volume effluent rates may alter this sconvention.

Once a dosing recommendation has been made in patients receiving CRRT it is important to continue monitoring patients for changes in their dialysis prescription and residual renal function. Dialysis flow rates and ultrafiltration rates often change. Although CRRT implies that a patient is receiving treatment for 24 hours per day, this is frequently not the case. In fact, the reported mean daily stop times for CRRT range from 3 to 8 hr/day owing to filter clotting, procedures done while off the filter, catheter exchange, patient mobilization, and surgery.[121]

Hepatic Disease

Assessing Hepatic Function

Hepatic dysfunction is caused by infection associated with cholestasis or hepatocellular injury, ischemic hepatitis (shock liver through hypoperfusion), hemolysis, or direct damage from hepatotoxic pharmaceuticals or prior alcohol use. Hepatic dysfunction is reflected by elevated liver enzymes, bilirubin, and ammonia or reduced synthesis of coagulant factors. A reduction of at least 90% of the metabolic capacity of the liver is needed to substantially affect drug clearance. Most data regarding changes in drug clearance are in patients with cirrhosis and therefore do not necessarily apply to acute changes in liver perfusion. Few data are available in patients with acute hepatic dysfunction, making assessments and recommendations in this patient population difficult.

Unfortunately, owing to the complexity of hepatic elimination there are few data to guide drug dosing recommendations, and a simple method to quantify liver function does not exist. Elevated liver transaminases (i.e., aspartate aminotransferase, alanine aminotransferase) indicate hepatocellular injury and do not reflect synthetic function. Although international normalized ratio and albumin reflect synthetic capacity, they do not adequately capture the complex process of drug metabolism, and are altered by volume status and critical illness such as sepsis. Scoring systems have been developed to assess severity of liver disease, but no score has been developed for the sole purpose of drug dosing. The Pugh modification of the Child-Turcotte scoring system (see Table 21.5) has been shown to predict changes in drug clearance that occur in hepatic disease.[122] The utility of this score has led to the U.S. Food and Drug Administration (FDA) recommendation that it be used to categorize degree of liver impairment in patients enrolled in hepatic PK studies completed during drug development.[123] There are several limitations to use in the ICU setting, including dynamic changes in perfusion and inability to quantify the degree of change in metabolism. The Child-Pugh score may be used to guide dosage adjustment of caspofungin, clindamycin, esomeprazole, metronidazole, tigecycline, verapamil, and voriconazole (to name a few) in clinical practice, despite not being validated in critically ill patients (with depressed albumin synthesis) or those with acute hepatic dysfunction.[124–126] Despite these limitations, it is still the most useful tool to assess hepatic function at the bedside. Another scoring system, primarily used for prognostication and prioritizing liver transplantation recipients, is the Model for End-Stage Liver Disease (MELD) score. It has not been adequately studied for drug dosing, and therefore recommendations should not be made based on the score.

Dosing in Hepatic Disease

The Child-Pugh score uses five clinical features to assess prognosis of cirrhosis and chronic liver disease.[126] It was originally developed to predict surgical outcomes in patients presenting with bleeding esophageal varices. Because drug dosing recommendations based on the Child-Pugh score are lacking, a decision must be made based on clinical judgment. Some general considerations include avoiding drugs metabolized by the CYP 450 system in favor of drugs that undergo phase 2 metabolism (i.e., glucuronidation) or renal elimination. If all available choices undergo phase 1 metabolism, then consider the agent with the shortest duration of action. The doses of many drugs with hepatic elimination may need reduction, particularly those with a high extraction ratio (large first-pass effect) as bioavailability may be increased. Patients with a prior transjugular intrahepatic portosystemic shunt may also have improved bioavailability owing to bypass of a first-pass effect and risk an exaggerated response to drugs with high extraction.[127] Reduced plasma protein levels in chronic hepatic disease may lead to alteration in unbound fraction of drugs, and accumulation of endogenous compounds such as bilirubin may alter protein binding.

Expanded Vd in ascites may reduce peak serum concentrations and prolong the half-life of hydrophilic drugs. Further adding to the complexity is that changes in drug metabolism and activity of specific CYP 450 enzymes may not be uniform. A model suggests that CYP 2C19 activity decreases quickly in hepatic dysfunction but reductions in CYP 1A2, CYP 2D6, and CYP 2E1 may occur later or only in more severe disease.[128]

As mentioned earlier, use of drugs with phase 2 clearance mechanisms such as glucuronidation may be preferred, as cirrhotic patients may have compensatory upregulation of uridine diphosphate (UDP)–glucuronosyltransferase enzymes or increased extrahepatic glucuronidation. Nevertheless, use caution with agents such as morphine, oxazepam, lamotrigine, zidovudine, or mycophenolate in advanced cirrhosis.[128] Biliary clearance of drugs such as ceftriaxone, clindamycin, and ciprofloxacin may be reduced with biliary obstruction. Although there are few data to support a specific dose reduction with most medications, a reduction of at least 50% is probably warranted in patients with severe disease. Selected references provide more detailed dosing recommendations on a number of medications, and they should be consulted before making dosing decisions in these patients.[124,125,129–131]

The PD of drugs may be altered in liver disease, in particular β blockers owing to a reduction in receptor density, or increased as in the case of opioid analgesics and sedatives, whether owing to an altered blood-brain barrier, increased gamma-aminobutyric acid tone or receptors, but patients are typically more sensitive to their sedating effects.

Obese Patients

More than 36.5% of adults in the United States are considered obese (BMI >30 kg/m^2).[132] Available data suggest more than 25% of all patients admitted to ICUs can be categorized as obese, with 6% to 7% of patients morbidly obese.[133,134] These alterations in body weight present potential pharmacokinetic challenges with many drugs that have not been adequately studied in this population.

Pharmacokinetic Alterations in Obesity

The two primary pharmacokinetic parameters, Vd and clearance, may be altered in obese patients, but prediction is difficult as body composition is quite variable within the same BMI values. Further, gender and ethnic differences in body composition warrant careful assessment when making dosing decisions. The increase in adipose tissue seen in obesity may lead to a higher Vd for highly lipophilic drugs. This can result in two important changes: a decrease in peak concentration and a longer half-life compared with nonobese patients. In addition, adipose tissue has less water per unit of weight, but obese patients have higher extracellular water than normal weight persons.

The effects of obesity on clearance are less clear. Some studies have shown higher renal and hepatic blood flow in obese individuals, which could lead to increased clearance. In addition, there is evidence of glomerular hyperfiltration in obese patients, but less information on tubular secretion or reabsorption. Less clear is how clearance changes relative to increasing degrees of obesity, although it is proposed that LBW is correlated with drug clearance.[135]

Dosing Considerations in Obesity

The first step in determining a drug dosage for an obese patient is deciding what weight to use. This presents a significant challenge as the ideal weight parameter to use for drug dosing varies among agents. Drugs may be dosed based on ideal body weight (IBW), ABW, TBW, LBW, or BSA (see Table 21.3).[135–139] TBW may be appropriate for very lipophilic drugs, as Vd increases in a nearly linear fashion with body weight. Hydrophilic drugs do not distribute completely into adipose tissue and TBW-based recommendations may lead to overdosing.

LBW can be a useful predictor of pharmacokinetic behavior of drugs that are highly water soluble as it accounts for nonfat cell mass and intercellular connective tissue. The term IBW was based on historical data that compared the relative mortality rate of people of different height-weight combinations. It has frequently been used as a surrogate for LBW in many pharmacokinetic studies owing to ease of calculation.[137,138] Hydrophilic drugs may also be dosed based on ABW. Different correction factors have been used to calculate ABW, but the most common factor is 0.4. The equations to calculate these values are listed in Table 21.3.[136–138]

As with renal and hepatic disease, it is imperative to assess the risk/benefit ratio with each drug before making any dosing decisions in obese patients. Some drugs have been studied using different weight parameters and it is always beneficial to know this information before deciding on a drug dose. Lists of drugs and dosing strategies in obese patients are frequently updated in the literature.[140–142] Awareness of the literature for individual agents is essential. Use of standardized dosing was economically favorable in one hospital after they developed detailed dosing guidelines for obese patients.[141]

Antimicrobial Dosing in Obesity

Using the appropriate weight to dose antimicrobial drugs is extremely important as underdosing may lead to therapeutic failures and overdosing (use of standard milligram/kilogram doses and TBW) may lead to toxicity (i.e., nephrotoxicity with aminoglycosides or acyclovir).[141–144] Infection-related mortality is higher in obese patients, possibly because of underdosing or poor drug penetration into adipose tissue.[145] Antimicrobial dosing is discussed extensively in the Pharmacodynamics section. Several antibiotic classes are not normally dosed based on weight, including penicillins, cephalosporins, carbapenems, linezolid, and fluoroquinolones. There is relatively limited pharmacodynamic data in obese patients for these classes.[145,146] However, these drugs are generally well tolerated and therefore it is probably reasonable to use aggressive dosing strategies such as maximal studied doses. This approach may not be prudent in patients at increased risk of adverse effects such as seizures with imipenem or cefepime or rate-corrected QT interval prolongation with fluoroquinolones. A prospective linezolid study and case reports show high interpatient PK variability and lower concentrations in patients with higher BMI (up to 32 kg/m^2).[146] Despite this, a clear relationship between concentration and treatment failure has not been demonstrated, and increasing the dose to 600 mg every 8 hours may produce greater hematologic toxicity.

Sedative Dosing in Obesity

Benzodiazepines, dexmedetomidine, and propofol are the most commonly used sedatives in the ICU. The benzodiazepines are highly lipophilic compounds that have significantly higher Vd and clearance in obese patients.[147] The use of TBW has been suggested for bolus doses of benzodiazepines. However, the risk of respiratory depression in patients without an advanced airway is an important consideration. Because parenteral benzodiazepines have relatively rapid onset, the use of smaller doses based on IBW repeated every 5 to 15 minutes is a reasonable approach in patients without an

advanced airway. In one study midazolam half-life was increased nearly threefold in obese patients.[147] This effect increases the risk of accumulation, oversedation, and delirium in obese patients, especially with continuous infusions.

Although propofol is a highly lipophilic compound, available data do not demonstrate changes in Vd or clearance in obese patients. This information would suggest that TBW should be used for maintenance doses in this patient population.[148,149] However, propofol is associated with several significant adverse effects, including hypotension with bolus dosing and the life-threatening propofol-related infusion syndrome (PRIS) with high doses or extended durations of infusion.[150] Owing to the hemodynamic complications associated with propofol an initial bolus based on IBW followed by additional small doses might be reasonable. Because propofol is a short half-life drug it can be rapidly titrated to effect. High doses and the risk of PRIS represent a more complicated therapeutic dilemma. One of the recognized risk factors is a dose of propofol exceeding 83 mcg/kg per minute, but total dose has also been suggested as a risk.[150,151] It is not known how dosing based on TBW versus IBW would affect the development of PRIS. Therefore these patients should be closely monitored for symptoms of PRIS, including significant creatine kinase elevation, metabolic acidosis, lactate elevation, hyperkalemia, rhabdomyolysis, or cardiac failure. Pharmacokinetic data for dexmedetomidine in critically ill patients is not readily available. However, dexmedetomidine has been studied in patients up to 285 kg using TBW and the manufacturer provides dosing recommendations based on TBW for patients weighing up to 185 kg.[152] If TBW is used, then it is important that the dose be titrated to effect with monitoring for hypotension and bradycardia.

Anticoagulant Dosing in Obesity

Anticoagulant dosing in obesity presents challenges because overdosing may result in bleeding complications but underdosing can result in worsening of thrombosis. Weight has been reported to be the single best predictor of unfractionated heparin (UFH) requirements and a weight-based nomogram should be used for dosing.[153,154] TBW is frequently used for UFH dosing in nonobese patients because the Vd of UFH approximates total blood volume. However, the exact weight parameter that should be used in obesity (BMI 30–40 kg/m^2) and morbid obesity (BMI >40 kg/m^2) is unclear. When TBW is used in morbid obesity, there is a higher rate of high activated partial thromboplastin time (aPTT) and anti–factor Xa measurements.[155,156] Despite the potential for higher than anticipated aPTTs or factor Xa levels, there was no difference in major bleeding events or rates of primary event recurrence when UFH was dosed on TBW, although obese patients required lower weight-based infusion rates to achieve the target compared with nonobese patients.[155,156] Individualized heparin dosing based on either TBW or ABW has been suggested without a standard upper limit but data are inadequate.[157,158] The decision regarding which weight to use may be influenced by the indication and risk for bleeding, with practitioners using a more aggressive approach in the treatment of venous thromboembolism (VTE) and a less aggressive dosing approach for atrial fibrillation or acute coronary syndrome.[159,160] Regardless of what weight is used for the bolus dose, the subsequent infusion should be titrated based on aPTT or anti-Xa heparin level.

Unlike UFH there has been more research on the ideal weight parameter for low–molecular-weight heparins (LMWHs) with TBW being identified as the best predictor of LMWH requirements.[161] Pharmacodynamic data for enoxaparin and dalteparin are available in patients weighing up to 159 and 190 kg and demonstrate little to no accumulation.[161–164] Retrospective data suggest similar rates of values at goal and elevated anti-Xa results in patients weighing more than 150 kg versus those weighing less than 150 kg.[161,163] Because of the limited data in patients weighing more than 190 kg, some practitioners use a maximum dose limit at this weight. There are no data to suggest this will limit bleeding risk and it may in fact increase the risk of VTE. The use of anti–factor Xa monitoring in patients weighing more than 190 kg has been advocated to avoid excessive exposure.[165] An anti–factor Xa level should be checked 4 hours after the third dose of a LMWH, although data are insufficient to establish if this improves safety or efficacy. The use of trough monitoring to assess for accumulation has been suggested as a method to assess for increased risk of bleeding, and may be especially important with renal insufficiency.[164]

When used for VTE prophylaxis both UFH and LMWH are commonly given as fixed-dose regimens irrespective of weight. However, when used in obese patients, standard fixed doses of enoxaparin (30 mg twice daily or 40 mg daily) result in low rates of goal anti–factor Xa achievement.[165] Current guidelines for the prevention of VTE suggest that bariatric surgery and other obese patients may require higher doses without providing dose recommendations.[166] Although various high-dose prophylactic regimens of both enoxaparin and UFH have been evaluated, there is not a consensus on the optimal drug, dose, or even patient population that would benefit.[167,168] The largest retrospective study suggests that patients with a BMI of 40 kg/m^2 or higher are less likely to develop VTE with a high-dose prophylactic regimen (enoxaparin 40 mg twice daily or UFH 7500 units three times daily) rather than a standard dose regimen.[168] However, it should be noted that there are currently no prospective trials to support a reduced risk of VTE in obese patients with higher doses of chemical VTE prophylaxis. If higher doses of enoxaparin or UFH are used, practitioners must monitor patients closely for bleeding.

Pregnancy

Pregnancy is a dynamic state with physiologic changes occurring throughout gestation. These changes include alterations in cardiovascular, pulmonary, GI, renal, and hepatic function that may result in clinically significant changes in drug PK.[169] Pregnant patients are frequently excluded from PK trials, limiting data that describe PK/PD and fetal adverse effect profiles for many drugs commonly used in critically ill pregnant patients. An in-depth discussion of all drug classes in pregnancy is beyond the scope of this chapter.[170,171]

Pharmacokinetic Changes in Pregnancy

Pregnancy results in multiple physiologic changes that affect absorption, distribution, metabolism, and elimination of various drugs.[169,170] Absorption may be decreased owing to a reduction in GI motility and an increased gastric pH. However, these changes are minimal and therefore are unlikely to significantly alter outcomes. Distribution is potentially increased owing to changes in volume (up to 50% increase in blood volume) and decreases in protein binding (up to 30% decrease in albumin). These changes may lead to either lower or higher concentrations of free drug in the serum depending on the properties of the agent administered. Pregnancy increases hepatic blood flow and has variable effects on CYP enzymes.[169] Available data suggest an increased activity of CYP 2D6 (metoprolol, selective serotonin reuptake inhibitors, citalopram), CYP 2C9 (nonsteroidal antiinflammatory drug,

phenytoin), CYP 2A6, UDP-glucuronosyltransferase, and CYP 3A4 (midazolam) and a decrease in the activity of CYP 1A2 (theophylline, olanzapine, ondansetron) and CYP 2C19 (diazepam, omeprazole, pantoprazole, propranolol) in the second and third trimesters.[169–171] Transporters also increase activity in the third trimester, including P-glycoprotein. The interplay between enzyme and transporter changes in different tissues makes interpretation of animal models more difficult. After delivery, some of these revert to normal as soon as 3 to 14 days, requiring dose adjustment to prepregnancy doses. Renal elimination increases throughout gestation with an 80% increase in renal plasma flow during the second trimester, leading to a 50% increase in GFR. Consequently, pregnant women often require higher doses of drugs with renal elimination; however, this requirement changes throughout pregnancy.[172]

Medical emergencies occur in pregnant women, including trauma, hemorrhage, sepsis, and thrombosis.[173–175] Awareness of the changes in maternal body composition and consideration of the effects on fetal development are important. The FDA label requirements for pregnancy and lactation have changed from a lettering system to a system that includes more detail regarding risk summary, clinical considerations—whether disease-associated maternal/fetal risk, dose adjustments in pregnancy, maternal adverse reactions, and labor/delivery concerns.[176] Drug labels should include available human and animal data. The new lactation section provides information to inform prescribers on minimizing exposure and monitoring for adverse effects, with applicable data. However, data remain inadequate for many critical care medications and the risk to the fetus, as pregnant patients are not included in clinical drug trials. Clinicians must balance the need to care for the mother, their primary patient, but also with care of the baby.

Burn Injury

The two distinct physiologic phases of burn injury have significant effects on PK and PD. The first 48 hours after injury are characterized by hypovolemia, edema, hypoalbuminemia, and decreases in GFR. During this initial resuscitative phase prolonged drug distribution, reduced maximum serum concentrations, and lower drug clearance are likely. The second phase occurs beyond 48 hours and is a hyperdynamic state characterized by increased renal and hepatic blood flow, altered serum protein production, and insensible drug losses through exudate leakage.[177] During this phase, faster drug distribution, increased maximum serum concentrations, increased renal drug clearance, decreased oxidative (CYP 450) metabolism, and altered volumes of distribution may occur.[177] These changes vary from patient to patient and may be affected by a number of factors, including burn-related factors (i.e., total body surface area burn, fluid resuscitation) and nonburn-related factors (preexisting comorbidity, age, and presence of sepsis). Further complicating matters, some patients may experience alterations in drug pharmacokinetics and dynamics that last up to 1 to 3 years after burn injury.[178]

The potential PK/PD changes along with interpatient variability complicate drug dosing. Data assessing drug dosing in burn injury are limited to small PK/PD analysis and Monte Carlo simulation (a broad class of computational algorithms that rely on repeated random sampling to arrive at numerical results). In addition to small sample sizes, these studies are limited by significant interpatient and intrapatient variation along with model design.[179] Despite these variations, available data indicate that, for most antimicrobials, the doses recommended in package labeling result in suboptimal target attainment in patients with burn injuries greater than 20% total BSA.[180]

Burn patients are at risk for ARC and initial doses should be maximized. Specific dosing recommendations for agents commonly used in burn injury have been published.[177,180] Given the significant interpatient and intrapatient variability, these recommended doses should function as a starting point, with therapeutic drug monitoring (TDM) used to optimize therapy. Because significant changes in serum proteins are common, the use of levels that detect free drug concentrations is preferred. If free levels are not available, clinicians must be aware that a total level in the therapeutic range does not necessarily reflect an appropriate drug dose. In these situations, physical and laboratory assessment to evaluate therapeutic efficacy and adverse effects is warranted. If TDM is not available and the agent is a drug with a wide therapeutic index, then using maximal drug dosing is acceptable to ensure therapeutic effect.

Hypothermia

The process of cooling patients to mild hypothermia (32°C–35°C) has been studied to minimize neurologic injury in several conditions, including TBI, spinal cord injury, stroke, cardiac surgery, and cardiac arrest.[181] Hypothermia is a recommended treatment in comatose adult patients after ventricular fibrillation cardiac arrest. In addition, the guidelines from the American Heart Association suggest it may be beneficial for other cardiac arrest patients including in-patients and those with nonshockable rhythms.[182] With the increasing prevalence of hypothermia for cardiac arrest and the potential for use in other indications it is important to understand the impact hypothermia has on drug PK.

Therapeutic hypothermia has been studied for the impact on the PK and PD of various drugs.[183] Although the PK of drugs has been reported in small trials and series, the PD effects are more difficult to study owing to the confounding effect of the hypothermia itself. Significant interindividual variation in PK parameters has been reported and is not surprising considering concurrent changes in hemodynamics and organ function that may accompany cardiac arrest or TBI and resuscitation. Most PK studies have been done with target cooling to 32°C to 34°C.

Hypothermia has been shown to reduce the activity of metabolic processes, including metabolic enzymatic reactions and active transport mechanisms, including drug absorption and excretion.[184] Selected drugs illustrate the changes that have been reported, but likely reflect a more global issue in medication management. Enteral absorption appears to be delayed after gastric drug administration and as a result, clopidogrel has been shown ineffective in the inhibition of platelet aggregation during hypothermia. There may also be diminished conversion of this prodrug to its active moiety.[185,186] Crushing clopidogrel tablets for nasogastric tube administration may also affect bioavailability owing to incomplete dose administration and loss of the acid-resistant coating. Prasugrel and ticagrelor absorption is also delayed, but the impact of hypothermia on platelet aggregation appears to be less significant.[187–190] The impact on patient outcome and stent thrombosis has not been adequately studied.

During hypothermia, hepatic drug metabolism of drugs is altered. Midazolam is a substrate of CYP 3A4 and is also an important marker of activity of this enzyme. Animal studies suggest that cardiac arrest reduces midazolam clearance and in human volunteers, cooling produces an 11% decrease in midazolam clearance per each 1°C reduction.[191,192] It is difficult to interpret the data for midazolam metabolism during hypothermia as steady state is not achieved, even with multiple days of cooling. The midazolam half-life approached 7000 hours in patients with TBI with body

temperature below 35°C, although the observation period was too short to validate this value, so accumulation may continue almost indefinitely while cooled.[192] Post–cardiac arrest studies with 12 to 24 hours of cooling have not demonstrated significant midazolam accumulation because of the short observation periods.[193,194] Initiation of rewarming appears to accelerate clearance of midazolam once core temp is above 35°C.[192,193] Altering midazolam doses to prevent accumulation during therapeutic hypothermia does not appear to be necessary unless the duration of cooling is prolonged.

Propofol, morphine, and remifentanil exhibit a similar biphasic pattern of metabolism, dependent on temperature (slow when cool and faster when rewarmed despite their different clearance mechanisms) remifentanil by blood and tissue esterases, whereas propofol and fentanyl are high extraction drugs dependent on hepatic blood flow and morphine is metabolized by glucuronidation.[195,196] Doses of these agents may not require adjustment during short periods of hypothermia. Fentanyl clearance is also reduced during hypothermia, but unlike other sedatives, does not increase rapidly with rewarming.[193,195]

Reduced hepatic metabolism via CYP 3A4 also affects the neuromuscular blocking agents, vecuronium and rocuronium, during hypothermia.[197,198] Atracurium is cleared by ester hydrolysis and Hoffman degradation, and has reduced clearance during cooling of surgical patients, leading to potential delay in recovery of neuromuscular function.[196]

Morphine is an example of hypothermia affecting phase 2 metabolism with glucuronidation catalyzed by UDP-glucuronosyltransferase. It also appears to display biphasic changes in clearance with cooling and rewarming, similar to midazolam.[193] This enzyme also metabolizes phenobarbital, propranolol, aspirin, and acetaminophen.

The effect of hypothermia on plasma protein binding is poorly studied, although cooling to 34°C did not change phenytoin binding to albumin.[199] Hepatic metabolism of phenytoin is via CYP 2C9 and CYP 2C19, and the metabolic rate slows during cooling.[200] Close monitoring of serum concentrations is warranted during hypothermia and after rewarming to minimize the risk of seizures. Changes in phenytoin binding to albumin should also be monitored. Drugs that are basic bind to AGP, an acute-phase reactant that would be expected to increase after cardiac arrest or TBI, but data on specific changes during hypothermia are not available.

Heparin is a drug that is partially cleared by renal mechanisms, especially at high doses. At low concentrations, a saturable clearance mechanism that includes reticuloendothelial macrophage and endothelial cell-bound heparinase and desulfatase enzymes plays a more significant role. The use of standard weight-based heparin doses may produce an exaggerated aPTT response in hypothermic patients, but the exact PK mechanism (enzyme activity, protein binding, or filtration) has not been defined.[201,202]

Pharmacogenetics

Pharmacogenetics (PG) is the study of genetic polymorphisms between patients, and pharmacogenomics takes a genome-wide approach in the study of drug response polymorphisms. The first reports of genetic polymorphisms affecting drug response were published in the 1950s. One of these early reports involved prolonged apnea after succinylcholine administration in patients with a variant of the enzyme responsible for succinylcholine metabolism.[203] It has become an area of increasing interest with variants identified that cause alterations in metabolism, transport, and drug interactions. Most of the data on the impact of polymorphisms on drug therapy relate to the risk of adverse drug effects. A review of pharmacogenomics and adverse drug reactions includes discussions of some critical care drugs, but the majority are not ICU specific.[204] However, patients with drug-induced liver injury, adverse cardiac effects, or severe skin reactions are often in the ICU. Ideally, information on genomic risk factors could minimize the risk of some of those reactions. Data on important polymorphisms are growing rapidly in the areas of antiplatelet and anticoagulant drugs and pain management. A 2010 review discusses some of the genetic polymorphisms that are most likely to affect drug therapy in the ICU.[205] Serious adverse events with the use of vasopressin and norepinephrine in septic shock have been associated with poor patient outcome. A genetic polymorphism located near the vasopressin receptor 1b gene is associated with serious adverse events in patients with sepsis receiving vasopressin and norepinephrine, and also in a validation cohort.[206] If further research confirms this risk and if the PG data could be obtained early in treatment, this type of information could benefit patients. However, the challenge in complex patients is great as many different drugs are administered to ICU patients, each is metabolized by various enzymes, transported by numerous proteins, and may interact with multiple receptor targets. Each step in the sequence may be affected by genetic variation, and that compounds the difficulty of identifying specific risks based on genetic testing.[207] Genomics also affects the response to critical illness, potentially affecting the regulation of inflammatory response and sepsis-related complications or mortality, although patient heterogeneity and inadequate study populations have led to inconsistent research findings.[207]

Genetic variations in drug metabolism are some of the best understood genetic polymorphisms. Variations have been described for both phase 1 and phase 2 reactions. These variations may result in patients becoming extensive or poor metabolizers and may result in increased toxicity or decreased efficacy. Research has focused on the CYP 450 family because it is responsible for approximately 75% of all drug metabolism. Within the CYP family most research has focused on 2D6, 2C19, and 2C9. The most studied of these enzymes is 2D6, with variants associated with increased serum concentrations of carvedilol, metoprolol, and flecainide, although decreased response is observed with codeine and tramadol. Other drugs metabolized by CYP 2D6 and potentially affected by polymorphisms include neuroleptics, diltiazem, hydrocortisone, oxycodone, and propafenone. Variants in CYP 2C9 metabolism may affect amiodarone, metronidazole, pantoprazole, valproic acid, and variants in CYP 2C19 are associated with decreased efficacy of clopidogrel, diazepam, phenobarbital, phenytoin, propranolol, voriconazole, and the proton pump inhibitors.[205] Slow acetylators of hydralazine, procainamide, and sulfamethoxazole are at an increased risk of immune-related toxic conditions such as systemic lupus erythematosus. On the other hand, slow acetylators of isoniazid are at increased risk of neurotoxicity and rapid acetylators have an increased risk of hepatitis.

Even though a number of commonly used ICU drugs are metabolized by these enzymes, prescribing based on pharmacogenetics and phenotyping is still uncommon, although several drugs have the potential to model this scenario. For example, 20% of patients using clopidogrel may be nonresponders, as demonstrated by failure to adequately inhibit platelet aggregation.[208] Prospective recognition of patients who are poor or intermediate metabolizers of this prodrug, owing to CYP 2C19 genetic polymorphism, could reduce the risk of thrombosis in this subset of patients.[209] The Clinical Pharmacogenetics Implementation Consortium provides guidelines for the avoidance of clopidogrel in at-risk patients with

acute coronary syndrome and similar guidance for a growing number of drug products.[210] Guidelines from the American College of Cardiology now suggest consideration of genetic testing for clopidogrel response.[211] Although not as well developed, it is known that voriconazole serum concentration monitoring improves efficacy and reduces adverse effects. Thus there is potential for prior knowledge of CYP 2C19 polymorphisms in voriconazole metabolism to improve initial dosing. The most well-developed example is with warfarin in which CYP 2C9, VKORC1, and CYP 4F2 are known to affect metabolism and influence at least half of dosing requirements, although most dosing is done through iterative monitoring and adjustment over weeks. Use of genotype-guided warfarin therapy may shorten the time to achieve the goal level of anticoagulation, but data on clinical benefits such as improved efficacy or reduced bleeding have been lacking until recently.[212] Despite these examples, based on current studies there is not much of a role for routine pharmacogenetic testing in critically ill patients.

Principles of Therapeutic Drug Monitoring

Several factors must be assessed before TDM can be performed in any medication. A reliable assay with a reasonably rapid turnaround is needed, the relationship between concentration and effect or toxicity has been defined, and understanding of the proper dosing model is available for interpretation of the result. Intermittent doses should be given on a predictable schedule and sampling should be done at a uniform time, relative to the dose, and both documented accurately. Predose levels are often more consistent than peak levels because of unpredictable absorption or delayed distribution after an IV dose. There must be a relationship between the sampling site—typically serum—and the site of drug effect. Although total drug concentrations are typically measured, the free (unbound) level may be more relevant to drug action. Unfortunately, availability of free levels and insight into interpretation are often limited. Finally, the clinical effect of the drug may be more important than concentration, so concentration interpretation must be relative to the desired effect and clinical assessment.

Dosing decisions based on limited sampling requires an understanding of the disease state tangent (improvement or worsening), the pharmacokinetics of the drug (measure levels at steady state), and often requires some prediction of patient needs or status on subsequent days. Clinicians need to reevaluate dosing relative to changes in clinical status, but to weigh that with the need to avoid excessive or burdensome sampling.

Conclusion

To maximize the efficacy and minimize toxicities associated with medications it is important for practitioners to understand the basic principles of PK and PD and the emerging role of PG. This knowledge becomes even more important in critically ill patients who undergo significant physiologic changes and have disease states that result in altered drug responses. All medication regimens in critically ill patients should be individualized based on knowledge of a drug's kinetics and dynamics along with an understanding of the impact the patient's comorbid conditions will have on these parameters. In addition, TDM and dose individualization should be used if available, particularly with drugs with narrow therapeutic indices. Through the vigilant use of this knowledge practitioners can maximize therapeutic outcomes in their patients while minimizing toxicity.

Key Points

- Most drug dosing recommendations are based on studies in healthy volunteers and often do not account for the pharmacokinetic and pharmacodynamic alterations seen in critically ill patients.
- Alterations in drug absorption, distribution, metabolism, and clearance are common in critically ill patients, and failure to modify drug dosages based on these changes may result in increased drug toxicity or treatment failure.
- The pharmacodynamic parameter that determines efficacy varies among drug classes as demonstrated by the different targets to maximize bacterial kill among aminoglycosides (concentration dependent, peak:MIC ratio), β-lactams (time-dependent, T > MIC), and vancomycin (time- and concentration-dependent, AUC/MIC).
- Physiologic changes seen with critical illness may alter the rate and extent of medication absorption from the GI tract or subcutaneous sites, making IV administration the preferred route in patients with hemodynamic instability or therapeutic hypothermia.
- Commonly encountered factors in critically ill patients that affect drug PK and PD include augmented renal clearance, renal dysfunction, hepatic disease, obesity, advanced age, pregnancy, thermal injury, and hypothermia.
- Current data do not support routine pharmacogenetic testing for critically ill patients; however, as more data become available it may become a standard of care for some medications.
- When available, patient-specific PK based on appropriately timed serum concentrations (i.e., therapeutic drug monitoring) and measured creatinine clearance should be used to minimize toxicity and maximize the efficacy of drug therapy.

Acknowledgment

The authors thank Todd Miano, PharmD, MSCE, for his contributions to this chapter.

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Review Questions

1. What statement best describes augmented renal clearance (ARC)?
- **a.** Readily identified with the Cockcroft-Gault formula.
- **b.** Not a significant concern in 24-year-old trauma patient.
- **c.** Can quantify with a 4-hour urine creatinine clearance.
- **d.** The high creatinine clearance persists for several weeks.

Answer: c. ARC, with values exceeding the traditional value of 125 mL/min, has been described in young, hyperdynamic patients admitted with trauma, subarachnoid hemorrhage, or other acute illnesses/injuries. The time course is not well defined but appears to subside in about a week. Recognition of patients who are at risk and measured urine for creatinine clearance is recommended to quantify the degree of change.

2. What is the best strategy to increase the likelihood of target attainment with an antimicrobial against a more resistant organism?
- **a.** Continuous infusion of cefepime
- **b.** Continuous infusion of tobramycin
- **c.** Extended infusion of ceftriaxone over 2 hours
- **d.** Increase ciprofloxacin to 800 mg every 12 hours

Answer: a. Rationale: Each antimicrobial and therapeutic class has a defined treatment goal in terms of concentration. Agents that are concentration dependent should achieve a peak:minimum inhibitory concentration (MIC) ratio for optimal effectiveness. Time-dependent agents rely on achieving an adequate time above the MIC but may be limited by the risk of adverse reactions with high peak serum concentrations. Ciprofloxacin doses above 600 mg may not be well tolerated, and tobramycin should be dosed intermittently with adequate time for near-complete elimination to minimize renal injury. Methods to achieve an optimal time above the MIC include continuous infusion of β-lactam agents such as cefepime or prolonged infusions (3–4 hours) for β-lactam agents with a short half-life.

3. What is the best therapeutic option to maintain anticonvulsant effect in a patient with a polymicrobial infection who is receiving chronic valproic acid therapy?
- **a.** Initiate meropenem and double the dose of valproic acid.
- **b.** Initiate piperacillin/tazobactam and maintain the current valproic acid dose.
- **c.** Initiate cefepime and metronidazole and double the dose of valproic acid.
- **d.** Initiate meropenem and maintain the dose of valproic acid.

Answer: b. Monobactam antimicrobial agents contribute to profoundly low valproic acid concentrations that occur very rapidly after initiation of the antimicrobial. Increasing the dose of valproate products is not effective to counteract this interaction; thus it is best to avoid the combination. If unavoidable, however, the clinician would add an additional antiepileptic agent.

4. After vigorous volume resuscitation for septic shock, what change in hydrophilic cephalosporin dosing is needed?
- **a.** Start continuous-infusion antibiotic.
- **b.** Give intermittent intravenous push antibiotic doses.
- **c.** Give a loading dose and then use prolonged infusion doses.
- **d.** Give intermittent doses with each infused over 1 hour.

Answer: c. Expansion of the body water through volume resuscitation will dilute the concentration of water-soluble drugs and, over time, will prolong the half-life. A loading dose of hydrophilic drugs will achieve the desired concentration and a prolonged infusion will facilitate target attainment. A continuous infusion would be acceptable but would ideally be initiated after a loading dose. Rapid administration of β-lactam agents makes target attainment (time > MIC) more difficult to achieve.

5. What approach to sedation should be considered for a patient cooled to 32°C–34°C for 24 hours?
- **a.** Use propofol infusion because it does not accumulate during cooling.
- **b.** Use a reduced dose of midazolam infusion to avoid accumulation.
- **c.** A continuous sedative is not needed while cooled owing to central nervous system depression.
- **d.** Use standard midazolam dose via infusion because accumulation is not an issue.

Answer: d. The pharmacokinetics of hepatically metabolized drugs such as midazolam is affected during moderate hypothermia below 35°C. Hepatic metabolism is dramatically reduced, and although an agent such as midazolam will accumulate over the usual short cooling periods, the serum concentrations fall rapidly with rewarming, minimizing a clinical impact. Propofol is an option for sedation but may cause undesirable cardiac effects, such as bradycardia. Although the need for sedation has not been clearly defined during cooling, the use has been endorsed for patient comfort.

22

Shock: Classification, Pathophysiology, and Approach to Management

ANAND KUMAR, VICTOR TREMBLAY, GLORIA VAZQUEZ-GRANDE, AND JOSEPH E. PARRILLO

CHAPTER OUTLINE

History

Definitions and Categorization of Shock

Classification
- Hypovolemic Shock
- Cardiogenic Shock
- Obstructive Shock
- Distributive Shock

Pathogenesis and Pathophysiology of Shock
- Hemodynamic Basis of Shock
- Microvascular Function in Shock
- Mechanisms of Cellular Injury in Shock
- Compensatory Responses to Shock

Organ System Dysfunction Owing to Shock

Diagnostic Approach and Evaluation
- Clinical Evaluation
- Laboratory Studies
- Imaging
- Invasive Hemodynamic Monitoring
- Ancillary Monitoring Techniques

Management and Therapy
- Aims
- Resuscitation

Conclusion

The syndrome of shock in humans is often the final pathway through which a variety of pathologic processes lead to cardiovascular failure and death. As such, it is perhaps the most common and important problem with which critical care physicians contend. The importance of shock as a medical problem can be appreciated by the prominence of its three dominant forms. Cardiogenic shock, related to pump failure, is a major component of the mortality associated with cardiovascular disease, the leading cause of death in the United States with almost 800,000 deaths annually.[1] Similarly, hypovolemic shock remains a major contributor to early mortality from trauma, the most common cause of death in those between the ages of 1 and 45 years (approximately 200,000 cases annually).[1,2] Finally, despite improving medical and surgical therapy, the ranking of septicemia as a cause of death has increased over the past two decades from the 13th to the 11th most frequent cause of death in the United States.[1,3,4] Most current estimates suggest more than 100,000 cases of septic shock annually in the United States alone.[5,6] In addition, all forms of shock increase the probability of other major comorbidities, such as serious infection, adult respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS).

This chapter provides an overview of circulatory shock with an emphasis on the common elements and important differences in the pathophysiology and pathogenesis of the various forms of the syndrome. This focus on common elements of different forms of shock continues through sections on systemic shock hemodynamics, microvascular dysfunction, mechanisms of cellular injury, oxygen supply dependency, compensatory responses, diagnostic approach/evaluation, and management/therapy.

History

Despite recognition of a posttraumatic syndrome by Greek physicians such as Hippocrates and Galen, the origin of the term *shock* is generally credited to the French surgeon Henri François Le Dran, who in his 1737 *A Treatise of Reflections Drawn from Experience with Gunshot Wounds,* coined the term *choc* to indicate a severe impact or jolt.[7] An inappropriate translation by the English physician Clarke, in 1743, led to the introduction of the word *shock* to the English language to indicate the sudden deterioration of a patient's condition with major trauma.[7] It was Edwin A. Moses,[8] however, who began to popularize the term, using it in his 1867 *A Practical Treatise on Shock After Operations and Injuries.* He defined it as "a peculiar effect on the animal system, produced by violent injuries from any cause, or from violent mental emotions." Before this definition, the rarely used term *shock* referred in a nonspecific sense to the immediate and devastating effects of trauma, not a specific posttrauma syndrome. Although not entirely accurate by today's standards, his definition was one of the first to separate the syndrome involving the body's response to massive trauma from the immediate, direct manifestations of trauma itself.

By the late 1800s, two theories of traumatic shock physiology dominated. The first, based on observations by Bernard, Charcot, Goltz, and others, was proposed by Fischer in 1870.[9–11] He suggested that traumatic shock was caused by generalized "vasomotor paralysis"

resulting in splanchnic blood pooling. The corollary was that total circulating blood volume is preserved in shock. The second dominant theory, articulated by Mapother in 1879, suggested that decreased cardiac output (CO) in traumatic shock is caused by intravascular volume loss owing to extrusion of plasma through the vessel wall from the intravascular space to the interstitium.[12] He proposed that this was a consequence of the failure of "vasodilator nerves" in traumatic shock and subsequent generalized arteriolar vasoconstriction. With the 1899 publication of *An Experimental Research into Surgical Shock* (perhaps the first experimental studies of shock), George W. Crile provided scientific data supporting a variation of the vasomotor paralysis theory.[13] After documenting the importance of decreased central venous pressure (CVP) and venous return in experimental shock as the result of hemorrhage and demonstrating the potential for intravascular volume replacement as therapy, he proposed that traumatic shock was caused by exhaustion of the overstimulated "vasomotor center" and subsequent generalized relaxation of large vessels (veins), leading to decreased ventricular filling and CO.

Further advances in shock research were substantially driven by military concerns. During World War I, Walter B. Cannon and other physiologists/physicians studied the early clinical response to battlefield trauma. Their work eventually led to the publication of the classic monograph *Traumatic Shock* in 1923.[14] Cannon and his colleagues were the first to relate trauma-associated hypotension in a large group of patients to a fall in blood volume, loss of bicarbonate, and accumulation of organic acids. Others, using dye dilution techniques, demonstrated that severity of shock was directly related to the decrease in intravascular volume.[15] Clinical data from war casualties also suggested the importance of reduced blood flow (independent of blood pressure) in shock.[16] The observation that blood in the capillaries of victims of massive trauma was hemoconcentrated compared to venous blood was to lead to the practice of resuscitating trauma patients with dried pooled plasma rather than whole blood in the early part of World War II.[17]

Although work originating from the battlefields of World War I clearly linked traumatic shock associated with substantial, obvious bleeding to a loss of circulating blood volume, the origin of traumatic shock in the absence of defined hemorrhage was unclear. The accepted explanation for this phenomenon remained a variation of the vasomotor paralysis theory of shock. It was postulated that nonhemorrhagic, posttraumatic shock ("wound shock") was caused by the liberation of "wound toxins" (histamine and/or other substances), which resulted in "neurogenic" vasodilation and peripheral blood pooling. However, after the war, Blalock and others demonstrated in animal models that nonhemorrhagic traumatic shock was due to the loss of blood and fluids into injured tissue rather than circulating toxins resulting in stasis of blood within the circulation.[18]

Additional advances occurred during World War II. Using injured subjects from the European front, Henry Beecher confirmed that hemorrhage and fluid loss leading to metabolic acidosis was a major cause of shock.[19] In the first use of indicator dye techniques in humans for studying blood flow, Cournand and Riely, in 1943, demonstrated that CO was typically reduced in shock.[20] They also reinforced Blalock's findings regarding non-hemorrhagic "wound shock" in trauma patients by demonstrating that circulating blood volume was reduced in such patients through loss of fluid into damaged tissues. The importance of maintaining intravascular volume in traumatic and hemorrhagic shock was supported by the well-known cardiovascular physiologist, Carl J. Wiggers, who published a landmark series of studies[21] in the 1940s using a standardized animal model which showed that prolonged hypovolemic shock resulted in a resuscitation-resistant state that he termed *irreversible shock.* He defined it as condition resulting from "a depression of many functions but in which reduction of the effective circulating blood volume is of basic importance and in which impairment of the circulation steadily progresses until it eventuates in a state of irreversible circulatory failure." Aggressive fluid support became the standard of resuscitation for trauma and shock.

Subsequently, the Korean War fueled the research demonstrating the relationship of acute tubular necrosis (ATN) and acute renal failure (ARF) to circulatory shock.[22] In addition, studies of battlefield casualties clearly demonstrated the relationship between early resuscitation and survival.[22] During the Vietnamese conflict, with the widespread use of ventilator technology, the dominant research concern became postshock infection and "shock lung" (ARDS), a concern that has evolved to the present interest in shock-related MODS.

Definitions and Categorization of Shock

The definition of shock has evolved in parallel with our understanding of the phenomenon. As noted, until the late 1800s, the term *shock* was used to indicate the immediate response to massive trauma, without regard to a specific posttrauma syndrome. The definition consisted of descriptions of its obvious clinical signs. In 1895, John Collins Warren[23] referred to shock as "a momentary pause in the act of death" that was characterized by an "imperceptible" or "weak, thread-like" peripheral pulse and a "cold, clammy sweat."

Subsequently, with the introduction of noninvasive blood pressure monitoring devices, most clinical definitions of shock added the requirement for arterial hypotension. In 1930 Blalock[9] included arterial hypotension as one of the required manifestations of shock when he defined it as "peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid." Simeone,[24] as recently as 1964, suggested that shock exists when "the cardiac output is insufficient to fill the arterial tree with blood under sufficient pressure to provide organs and tissues with adequate blood flow."

Current technology, which allows assessment of perfusion independent of arterial pressure, has shown that hypotension does not define shock. The emphasis in defining shock is now on tissue perfusion in relation to cellular function. According to Fink,[25] shock is "a syndrome precipitated by a systemic derangement of perfusion leading to widespread cellular dysoxia and vital organ dysfunction." Cerra[26] has emphasized supply/demand mismatch in his definition: "a disordered response of organisms to an inappropriate balance of substrate supply and demand at a cellular level."

The appropriate definition of shock varies with the context of its use. For paramedical personnel, a definition that incorporates the typical clinical signs of shock (arterial hypotension, tachypnea, tachycardia, altered mental status, and decreased urine output) may suffice. For the physiologist, shock may be defined by specific hemodynamic criteria involving alterations of ventricular filling pressures, venous pressures, arterial pressures, CO, and systemic vascular resistance (SVR). Similarly, in the appropriate context, shock could also be defined by alterations of biochemical/bioenergetic pathways or intracellular gene expression. For the physician, however, we find the most appropriate definition to be "the state in which profound and widespread reduction of effective

• BOX 22.1 Determinants of Effective Tissue Perfusion in Shock

1. Cardiovascular performance (total systemic perfusion/cardiac output)
   - Cardiac function
     - Preload
     - Afterload
     - Contractility
     - Heart rate
   - Venous return
     - Right atrial pressure (dependent on cardiac function)
     - Mean circulatory pressure
     - Stressed vascular volume
     - Mean vascular compliance
     - Venous vascular resistance
     - Distribution of blood flow
2. Distribution of cardiac output
   - Intrinsic regulatory systems (local tissue factors)
   - Extrinsic regulatory systems (sympathetic/adrenal activity)
   - Anatomic vascular disease
   - Exogenous vasoactive agents (inotropes, vasopressors, vasodilators)
3. Microvascular function
   - Precapillary and postcapillary sphincter function
   - Capillary endothelial integrity
   - Microvascular obstruction (fibrin, platelets, WBC, RBC)
4. Local oxygen unloading and diffusion
   - Oxyhemoglobin affinity
   - RBC 2,3-DPG
   - Blood pH
   - Temperature
5. Cellular energy generation/utilization capability
   - Citric acid (Kreb) cycle
   - Oxidative phosphorylation pathway
   - Other energy metabolism pathways (e.g., ATP utilization)

2,3-DPG, *2,3-diphosphoglycerate;* ATP, *adenosine triphosphate;* RBC, *red blood cell;* WBC, *white blood cell.*

tissue perfusion leads first to reversible, and then, if prolonged, to irreversible cellular injury."

"Effective" tissue perfusion, as opposed to tissue perfusion per se, is an important issue. Effective tissue perfusion may be reduced by either a global reduction of systemic perfusion (CO) or by increased ineffective tissue perfusion owing to a maldistribution of blood flow or a defect of substrate utilization at the subcellular level (see Box 22.1).

Classification

Although hypovolemic shock associated with trauma was the first form of shock to be recognized and studied, by the early 1900s it became broadly recognized that other clinical conditions could result in a similar constellation of signs and symptoms. Sepsis as a distinct cause of shock was initially proposed by Laennec in 1831 and subsequently supported by Boise in 1897.[27,28] In 1934, Fishberg and colleagues introduced the concept of primary cardiogenic shock caused by myocardial infarction (MI).[29] Later the same year, Blalock developed the precursor of the most commonly used classification systems of the present.[30] He subdivided shock into four etiologic categories: hematogenic or oligemic (hypovolemic), cardiogenic, neurogenic (e.g., shock after spinal injury), and vasogenic (primarily septic shock). Shubin and Weil, in 1967, proposed the additional etiologic categories of hypersensitivity (i.e., anaphylactic), bacteremic (i.e., septic), obstructive, and endocrinologic shock.[31] However, as the hemodynamic profiles of the different forms of shock were uncovered, a classification based on cardiovascular characteristics (initially proposed in 1972 by Hinshaw and Cox[32]) came to be accepted by most clinicians. The categories include the following:

1. Hypovolemic shock, caused by a decreased circulating blood volume in relation to the total vascular capacity and characterized by a reduction of diastolic filling pressures and volumes;
2. Cardiogenic shock related to cardiac pump failure as the result of loss of myocardial contractility/functional myocardium or structural/mechanical failure of the cardiac anatomy and characterized by elevations of diastolic filling pressures and volumes;
3. Extracardiac obstructive shock involving obstruction to flow in the cardiovascular circuit and characterized by either impairment of diastolic filling or excessive afterload;
4. Distributive shock caused by loss of vasomotor control resulting in arteriolar and venular dilation and (after resuscitation with fluids) characterized by increased CO with decreased SVR.

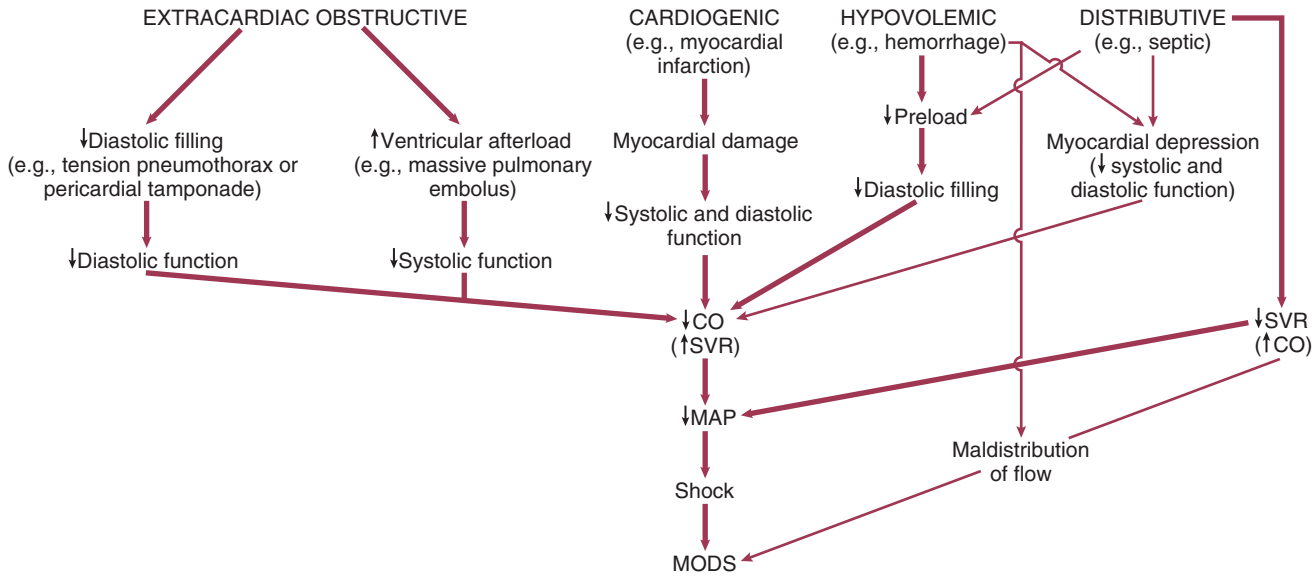
We have adapted these categories into an etiologic/physiologic classification of shock that is summarized in Fig. 22.1 and Box 22.2. This figure and table represent our current understanding of the causes and typical hemodynamic features of different forms of shock.

Despite this hemodynamic-based categorization system, it is important to note the mixed nature of most forms of clinical shock. Septic shock is nominally considered a form of distributive shock. However, before resuscitation with fluids, a substantial hypovolemic component may exist as the result of venodilatation and third spacing. In addition, depression of the myocardium in human septic shock is well documented (see Fig. 22.1).[33–35] Similarly, hemorrhagic shock in experimental models has been linked to both myocardial depression[36,37] and vascular dysfunction (Fig. 22.1).[38,39] Cardiogenic shock typically presents with increased ventricular filling pressures. However, many patients have undergone aggressive diuresis before the onset of shock and may have a relative hypovolemic component. In addition, SVR is only inconsistently increased in cardiogenic shock, suggesting that an inflammatory element may exist under some circumstances. Finally, shock from any cause may cause a deterioration of the coronary perfusion pressure, the difference between mean arterial pressure (MAP) and the higher of left ventricular diastolic pressure or the right atrial pressure, resulting in some degree of myocardial ischemia and myocardial dysfunction.[40] Although four categories of shock exist based on hemodynamic profile, clinical shock states tend to combine components of each (Fig. 22.1).[33–40]

Hypovolemic Shock

Hypovolemic may be related to dehydration, internal or external hemorrhage, gastrointestinal fluid losses (diarrhea or vomiting), urinary losses resulting from either diuretics or kidney dysfunction, or loss of intravascular volume to the interstitium owing to increased vascular permeability (in response to sepsis or trauma). Alternately, venodilation secondary to sepsis, spinal injury, various drugs, and toxins can result in a relative hypovolemic condition that contributes to shock (Box 22.2, see Fig. 22.1).

Hemodynamically, hypovolemic shock is characterized by a fall in ventricular preload resulting in decreased ventricular diastolic pressures and volumes (Table 22.1). Cardiac index (CI) and stroke volume index (SVI) are typically reduced. In addition to hypotension, a decreased pulse pressure may be noted. Because of a decreased output and unchanged or increased metabolic demand, mixed



• **Fig. 22.1** The interrelationships between different forms of shock. For cardiogenic, hypovolemic, and obstructive shock, hypotension is primarily due to decreased cardiac output with systemic vascular resistance rising secondarily. With distributive (and particularly, septic) shock, hypotension is primarily due to a decrease in systemic vascular resistance with a secondary increase of cardiac output. In many forms of shock, the hemodynamic characteristics are influenced by elements of hypovolemia, myocardial depression (ischemic or otherwise), and vascular dysfunction (which may affect afterload). Dominant pathophysiologic pathways are denoted by *heavier lines*. *CO,* Cardiac output; *MAP,* mean arterial blood pressure; *MODS,* multiple organ dysfunction syndrome; *SVR,* systemic vascular resistance.

venous oxygen saturation (Mv_{O_2}) may be decreased and the arteriovenous oxygen content difference widened. Clinical characteristics include pale, cool, clammy skin (often mottled); tachycardia (or if severe shock, bradycardia[8,41]); tachypnea; flat, nondistended peripheral veins; decreased jugular venous pulse; decreased urine output; and altered mental status.

Several factors can influence the development and hemodynamic characteristics of hypovolemic shock in humans. Studies in animals and humans have demonstrated a clear relationship between the degree of circulating blood volume loss and clinical response.[42–45] Acute loss of 10% of the circulating blood volume is well tolerated and compensated by tachycardia. CI may be minimally decreased despite a compensatory increase in myocardial contractility. SVR typically increases slightly, particularly if sympathetic stimulation augments MAP. Compensatory mechanisms begin to fail with a 20% to 25% volume loss. Mild to moderate hypotension and decreased CI may be present. Orthostasis (with a blood pressure decrease of 10 mm Hg and increased heart rate [HR] of 20 to 30 beats/min) may become apparent. There is a marked increase in SVR and serum lactate may begin to rise. With decreases of the circulating volume of 40% or more, marked hypotension with clinical signs of shock is noted. CI and tissue perfusion may fall to less than half normal. Lactic acidosis is usually present at this stage and predicts a poor outcome.[46,47] The case fatality rate can exceed 50% in hemorrhagic shock associated with trauma.[48]

The rate of loss of intravascular volume and the preexisting cardiac reserve is of substantial importance in the development of hypovolemic shock. As an example, although an acute blood loss of 1 L in a healthy adult may result in mild to moderate hypotension with a reduced pulmonary artery occlusion pressure (PAOP) and CVP,[43] the same loss over a longer period may be well tolerated owing to compensatory responses, such as tachycardia, increased myocardial contractility, increased red blood cell 2,3-diphosphoglycerate (2,3-DPG), and increased fluid retention. On the other hand, a similar slow loss may lead to substantial hemodynamic compromise in a person with a limited cardiac reserve even while their PAOP and CVP remain elevated.

Hypovolemic shock represents more than a simple mechanical response to loss of circulating volume. It is a dynamic process involving competing adaptive (compensatory) and maladaptive responses at each stage of development. Thus although intravascular volume replacement is always a necessary component of resuscitation from hypovolemia or hypovolemic shock, the biologic responses to the insult may progress to the point where such resuscitation is insufficient to reverse the progression of the shock syndrome. Patients who have sustained a greater than 40% loss of blood volume for 2 hours or more may be unable to be effectively resuscitated.[38,42,45] A series of inflammatory mediator, cardiovascular, and organ responses to shock are initiated that supersede the importance of the initial insult in driving further injury.

Cardiogenic Shock

Cardiogenic shock results from the failure of the heart as a pump (see Box 22.2 and Fig. 22.1). It is the most common cause of in-hospital mortality in patients with Q-wave MI.[49,50] Hemodynamically, cardiogenic shock is characterized by increased ventricular preload (increased ventricular volumes, pulmonary wedge pressure and CVP) (see Table 22.1). Otherwise hemodynamic characteristics are similar to those for hypovolemic shock (see Table 22.1). In particular, both involve reduced CI, SVI, and ventricular stroke work indices with increased SVR. As the result of inadequate tissue perfusion, the Mv_{O_2} is substantially reduced and the arteriovenous oxygen content difference increased. The degree of lactic acidosis may predict mortality.[51] Clinically, the specific signs of shock are similar. However, signs of congestive heart failure (CHF, volume

• BOX 22.2 Classification of Shock

1. Hypovolemic (Oligemic)
   - Hemorrhagic
     - Trauma
     - Gastrointestinal
     - Retroperitoneal
   - Intravascular fluid depletion (nonhemorrhagic)
     - External fluid loss
       - Dehydration
       - Vomiting
       - Diarrhea
       - Polyurea
     - Interstitial fluid redistribution
       - Thermal injury
       - Trauma
       - Anaphylaxis
   - Increased vascular capacitance (venodilatation)
     - Sepsis
     - Anaphylaxis
     - Toxins/Drugs
2. Cardiogenic
   - Myopathic
     - Myocardial infarction
       - Left ventricle
       - Right ventricle
     - Myocardial contusion (trauma)
     - Myocarditis
     - Cardiomyopathy
     - Post-ischemic myocardial stunning
     - Septic myocardial depression
     - Drug toxicity
       - Anthracycline cardiotoxicity
       - Calcium channel blockers
   - Mechanical
     - Valvular failure (stenotic or regurgitant)
     - Hypertropic cardiomyopathy
     - Ventricular septal defect
   - Arrhythmic
     - Bradycardia
     - Sinus (e.g., vagal syncope)
     - Atrioventricular blocks
     - Tachycardia
     - Supraventricular
     - Ventricular
3. Extracardiac Obstructive
   - Impaired diastolic filling (decreased ventricular preload)
     - Direct venous obstruction (vena cava)
       - Intrathoracic obstructive tumors
     - Increased intrathoracic pressure (decreased transmural pressure gradient)
       - Tension pneumothorax
       - Mechanical ventilation (with positive end-expiratory pressure [PEEP] or volume depletion)
     - Decreased cardiac compliance
       - Constrictive pericarditis
       - Cardiac tamponade
         - Acute
           - Post MI free wall rupture
           - Traumatic
           - Hemorrhagic (anticoagulation)
         - Chronic
           - Malignant
           - Uremic
           - Idiopathic
   - Impaired systolic contraction (increased ventricular afterload)
     - Right ventricle
       - Pulmonary embolus (massive)
       - Acute pulmonary hypertension
     - Left ventricle
       - Saddle embolus
       - Aortic dissection
4. Distributive
   - Septic (bacterial, fungal, viral, rickettsial)
   - Toxic shock syndrome
   - Anaphylactic, anaphylactoid
   - Neurogenic (spinal shock)
   - Endocrinologic
     - Adrenal crisis
     - Thyroid storm
   - Toxic (e.g., nitroprusside, bretyllium)

overload) are typically present in cardiogenic shock. The jugular and peripheral veins may be distended. An S_3 and evidence of pulmonary edema are usually found.

Cardiogenic shock is most commonly due to ischemic myocardial injury with a total of 40% of the myocardium nonfunctional.[50,52–54] Such damage may involve a single large myocardial infarction (MI) or may involve accumulation of damage from multiple infarctions. In addition, viable but dysfunctional "stunned" myocardium may temporarily contribute to cardiogenic shock after infarction. Cardiogenic shock usually involves an anterior MI with left main or proximal left anterior descending artery occlusion. Historically, the incidence of cardiogenic shock caused by Q-wave infarction has ranged from 8% to 20%.[49,55–57] Although several large studies demonstrate lower incidence rates (4%–7%) when patients receive thrombolytic interventions,[56,58–61] retrospective community studies suggest no overall decrease in incidence of postinfarction cardiogenic shock or cardiogenic shock mortality (70%–90%) in the first decades after the introduction of this therapy.[49] Further, no trials have demonstrated that thrombolytic therapy reduces mortality rates in patients with established cardiogenic shock.[58,62] In contrast, several major studies suggest that mortality of infarction-related cardiogenic shock may be improved by emergent angioplasty.[63–65] Accordingly, recent data suggest a reduction in incidence of acute infarction-related cardiogenic shock to less than 2% in 2003 in association with widespread use of emergent percutaneous coronary intervention.[63] This intervention has also been associated with a reduction of cardiogenic shock mortality risk from 60% to 84% to 43% to 47% in two large analyses.[63,66,67]

Mortality is better for cardiogenic shock resulting from surgically remediable cardiac lesions. Mitral valve failure may be associated with rupture or dysfunction of chordae or papillary muscles owing to myocardial ischemia or infarction, endocarditis, blunt chest trauma, or prosthetic valve deterioration and is characterized by "v" waves of greater than 10 mm Hg on a PAOP tracing. Ischemic papillary muscle rupture frequently occurs 3 to 7 days after an infarct in left anterior descending coronary artery territory and may be preceded by the onset of a mitral regurgitant murmur.[68] Mortality is high in the absence of surgical therapy.[68] Acute aortic valve failure is most commonly the result of endocarditis but may involve mechanical failure of prosthetic valves, or aortic dissection.

TABLE 22.1 Hemodynamic Profiles of Shock[a]

Diagnosis	CO	SVR	PWP	CVP	$S\bar{V}O_2$	Comments
Cardiogenic Shock						
Caused by myocardial dysfunction	↓↓	↑	↑↑	↑↑	↓	Usually occurs with evidence of extensive myocardial infarction (>40% of left ventricular myocardium nonfunctional), severe cardiomyopathy, or myocarditis
Caused by a mechanical defect						
Acute ventricular septal defect	LVCO ↓↓ RVCO > LVCO	↑	nl or ↑	↑↑	↑ or ↑↑	If shunt is left to right, pulmonary blood flow is greater than systemic blood flow; oxygen saturation "step-up" (≥5%) occurs at right ventricular level; ↑ $S\bar{V}O_2$ is caused by left to right shunt
Acute mitral regurgitation	Forward CO ↓↓	↑	↑↑	↑ or ↑↑	↓	Large V waves (≥10 mm Hg) in pulmonary wedge pressure tracing
Right ventricular infarction	↓↓	↑	nl or ↑	↑↑	↓	Elevated right atrial and right ventricular filling pressures with low or normal pulmonary wedge pressures
Extracardiac Obstructive Shock						
Pericardial tamponade	↓ or ↓↓	↑	↑↑	↑↑	↓	Dip and plateau in right and left ventricular pressure tracings. The right atrial mean, right ventricular end-diastolic, pulmonary artery end-diastolic, and pulmonary wedge pressures are within 5 mm Hg of each other.
Massive pulmonary emboli	↓↓	↑	nl or ↓	↑↑	↓	Usual finding is elevated right-sided heart pressures with low or normal pulmonary wedge pressure
Hypovolemic Shock						
	↓↓	↑	↓↓	↓↓	↓	Filling pressures may appear normal if hypovolemia occurs in the setting of baseline myocardial compromise
Distributive Shock						
Septic shock	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑	The hyperdynamic circulatory state (↑CO, ↓SVR) associated with distributive forms of shock usually depends on resuscitation with fluids; before such resuscitation, a hypodynamic circulation is typical
Anaphylaxis	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑	

[a]The hemodynamic profiles summarized in this table refer to patients with the diagnosis listed in the left column who are also in shock (mean arterial blood pressure <60–65 mm Hg).
CO, Cardiac output; *CVP,* central venous pressure; *LV,* left ventricular; *nl,* normal; *PWP,* pulmonary wedge pressure; *SVR,* systemic vascular resistance; $S\bar{V}O_2$, mixed venous oxygen saturation; ↑↑ or ↓, mild to moderate increase or decrease; ↑↑ or ↓, moderate to severe increase or decrease.
Modified from Parrillo JE. Septic shock: clinical manifestations, pathogenesis, hemodynamics, and management in a critical care unit. In: Parrillo JE, Ayers SM, eds. *Major Issues in Critical Care Medicine.* Baltimore: Williams & Wilkins; 1984.

Ventricular septal defects caused by MI may also result in the abrupt onset of cardiogenic shock and can be diagnosed by a 5% step-up in hemoglobin oxygen saturation between the right atrium and the pulmonary artery (owing to left to right shunting of blood through the septum).[69] As with ischemic papillary muscle rupture, rupture of the intraventricular septum is most frequently seen with occlusions of the left anterior descending artery a few days after infarction.[69]

The pathophysiology of cardiogenic shock caused by a right ventricular infarction and failure is different than other forms of cardiogenic shock. Although some degree of right ventricular involvement is seen in half of inferior MIs, only the largest 10% to 20% result in right ventricular failure and cardiogenic shock.[70] These infarctions usually involve part of the left ventricular wall as well. Isolated infractions of the right ventricle are rare.[70,71] Because therapy for this form of shock requires fluid resuscitation and inotropes (rather than vasopressors), differentiation from other causes of cardiogenic shock is crucial. Conditions compromising right ventricular function, such as cardiac tamponade, restrictive cardiomyopathy, constrictive pericarditis, and pulmonary embolus, are also included in the differential diagnosis. Each of these conditions may present with some of the typical clinical and hemodynamic findings of right ventricular infarction, including Kussmaul sign, pulsus paradoxus with elevation and equalization of CVP, right ventricular systolic pressure, pulmonary artery diastolic pressure, and PAOP. Prognosis in this form of cardiogenic shock is distinctly better than that of cardiogenic shock owing to left ventricular infarction[72,73]; however, an inferior infarction with right ventricular injury has a substantially worse prognosis than such an infarction without significant right-sided involvement.[74]

As with hypovolemic shock, a number of interactions may complicate the development of cardiogenic shock. Optimal cardiac

performance in patients with impaired myocardial contractility may occur at substantially higher than normal PAOP (i.e., 20–24 mm Hg). Yet patients in whom cardiogenic shock develops are frequently initially treated with diuretics and may have a degree of hypovolemia (relative to their optimal requirements). Thus patients should not be diagnosed with cardiogenic shock unless hypotension (MAP < 65 mm Hg) and reduced CO (CI < 2.2 L/min per m^2) coexist with an elevated ventricular filling pressure.[75] Cautious fluid challenge may be required (in the absence of overt pulmonary edema) to increase the filling pressures to an optimal range. Other interactions include increased right ventricular ischemia owing to decreased right coronary perfusion pressure (MAP decreased while right ventricular end-diastolic pressure is increased) and increased right ventricular afterload owing to pulmonary hypertension. Right ventricular ischemia may also lead to right ventricular dilatation, septal shift, and impairment of left ventricular function.

Other causes of cardiogenic shock include acute myocarditis, end-stage cardiomyopathy, bradyarrhythmias or tachyarrhythmias, hypertrophic cardiomyopathy with obstruction, and traumatic myocardial contusion (see Box 22.2).

Obstructive Shock

Extracardiac obstructive shock results from an obstruction to flow in the cardiovascular circuit (see Box 22.2 and Fig. 22.1). Pericardial tamponade and constrictive pericarditis directly impair diastolic filling of the right ventricle. Tension pneumothorax and intrathoracic tumors indirectly impair right ventricular filling by obstructing venous return. Massive pulmonary emboli (two or more lobar arteries with >50% of the vascular bed occluded), nonembolic acute pulmonary hypertension, large systemic emboli (e.g., saddle embolus), and aortic dissection may result in shock owing to increased ventricular afterload.

The characteristic hemodynamic/metabolic patterns are, in most ways, similar to other low-output shock states (see Table 22.1). CI, SVI, and stroke work indices are usually decreased. Because tissue perfusion is decreased, the MvO_2 is low, the arteriovenous oxygen content difference increased, and serum lactate frequently elevated. Other hemodynamic parameters are dependent on the site of the obstruction. Tension pneumothorax and mediastinal tumors may obstruct the great thoracic veins, resulting in a hemodynamic pattern (decreased CI and elevated SVR) similar to hypovolemia (although distended jugular and peripheral veins may be seen). Cardiac tamponade typically causes increased and equalized right and left heart ventricular diastolic pressures, pulmonary artery diastolic pressure, CVP, and PAOP. In constrictive pericarditis, right and left ventricular diastolic pressures are elevated and within 5 mm Hg of each other. Mean right and left atrial pressures may or may not be equal as well. Massive pulmonary embolus results in right ventricular failure with elevated pulmonary artery and right heart pressures, whereas PAOP remains normal. A systemic saddle embolus or aortic occlusion owing to dissection cause peripheral hypotension and signs of left ventricular failure including an elevated PAOP. Clinical signs are similarly dependent on the site of the obstruction.

As with other forms of shock, the time course of development of the insult has a substantial impact on the clinical response. Ischemic rupture of the left ventricular free wall (usually 3 to 7 days after MI) leads to immediate cardiac tamponade and shock with as little as 150 mL blood in the pericardium.[76–78] Survival requires emergency surgery.[77,78] Similar situations may develop with bleeding into the pericardium after blunt chest trauma or thrombolytic therapy. Pericardial tamponade owing to malignant or inflammatory pericardial effusions usually develops much more slowly. Although shock may still develop, it usually requires substantially more pericardial fluid (1–2 L) to cause critical failure of right ventricular diastolic filling.[76] No large reliable studies examining mortality rates with and without therapy in these conditions are available because of the small numbers of cases.

A similar time course–dependent risk is seen with major pulmonary emboli. In those without preexisting cardiopulmonary disease, a massive embolus involving two or more lobar arteries and 50% to 60% of the vascular bed[79,80] may result in obstructive shock. However, if recurrent smaller pulmonary emboli result in right ventricular hypertrophy, a substantially larger total occlusion of the pulmonary vascular bed may be required to cause right ventricular decompensation. Recent analyses have suggested that the presence of shock owing to pulmonary embolus (regardless of underlying chronic cardiopulmonary dysfunction) indicates a three- to sevenfold increase in mortality risk with the majority of deaths occurring within an hour of presentation.[81,82] An analysis of more than 70,000 unstable (hemodynamic instability or ventilator-requiring) patients with pulmonary embolus in the National Inpatient Sample shows that mortality in untreated patients is approximately 47%.[83] Systemic thrombolysis is associated with a substantial reduction in mortality to 15%. Where available, catheter-directed therapy may be even more efficacious with lower risk of serious hemorrhage.[84] Shock resulting from pulmonary embolism is an indication for urgent thrombolytic or catheter-directed intervention.

Distributive Shock

The defining feature of distributive shock is loss of peripheral resistance. Septic shock is the most common form and has the greatest impact on intensive care unit (ICU) morbidity and mortality.

Hemodynamically, distributive shock is characterized by an overall decrease in SVR (see Table 22.1). However, resistance in any specific organ bed or tissue may be decreased, increased, or unchanged. Initially, CI may be depressed and ventricular filling pressures decreased. After fluid resuscitation, when filling pressures are normalized or increased, CI is usually elevated. Owing to hypotension, left and right ventricular stroke work indices are normally decreased. MvO_2 is increased above normal. Concomitantly, the arteriovenous oxygen content difference is narrowed despite the fact that oxygen demand is usually increased (particularly in sepsis). The basis of this phenomenon may be that while total body perfusion (CI) is increased, perfusion is not effective in that either it does not reach the necessary tissues or the tissues cannot use the substrates presented. As a reflection of this inadequate "effective" tissue perfusion, lactic acidosis may ensue. Clinical characteristics of resuscitated distributive shock include, in contrast to the other forms of shock, warm, well-perfused extremities, a decreased diastolic blood pressure, and an increased pulse pressure. Nonspecific signs of shock include tachycardia, tachypnea, decreased urine output, and altered mentation. In addition, evidence of the primary insult may exist (urticaria for anaphylaxis, spinal injury for neurogenic shock, and evidence of infection in septic shock).

Septic shock (shock caused by infection) and sepsis-associated multiple organ failure are the most common cause of death in ICUs of the industrialized world. As many as 800,000 patients with sepsis are admitted every year to American hospitals

(comparable to the incidence of first MIs), half of whom develop septic shock and about half (200,000) who die.[85] The past four decades have seen a progressive increase in the incidence of and total deaths from sepsis and septic shock.[86] The total toll of septic deaths is comparable to deaths from MI and far exceeds the impact of illnesses such as AIDS or breast cancer together.[85,87]

Septic shock is caused by the systemic activation of the inflammatory cascade. Numerous mediators, including cytokines, kinins, complement, coagulation factors, and eicosanoids, are activated or systemically released, resulting in profound disturbances of cardiovascular and organ system function[88] (see Table 22.2). These mediators, particularly tumor necrosis factor α (TNF-α), interleukin

TABLE 22.2 Inflammatory Mediators in Sepsis and Septic Shock

Mediator	Major Reported Effects
Proinflammatory Cytokines	
TNF-α	Stimulates release of IL-1, IL-6, IL-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may be able to stimulate macrophages directly to promote its own release
	Stimulates production of polymorphonuclear cells by bone marrow; enhances phagocytic activity of polymorphonuclear cells
	Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and, occasionally, lymphocytes by inducing increased expression of adhesion molecules
	Activates common pathway of coagulation and complement system
	Directly toxic to vascular endothelial cells; increases microvascular permeability
	Acts directly on hypothalamus to produce fever
	Reduces transmembrane potential of muscle cells and depresses myocardial contractility
	Decreases arterial pressure, systemic vascular resistance, and ventricular ejection fraction; increases cardiac output
IL-1β	Stimulates release of TNF, IL-6, IL-8, platelet-activating factor, leukotrienes, thromboxane A_2, prostaglandins; may also be capable of stimulating its own production
	Activates resting T cells to produce lymphocytes and other products; supports B-cell proliferation and antibody production; is cytotoxic for insulin-producing B cells
	Promotes adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, monocytes, and occasionally, lymphocytes by inducing increased expression of adhesion molecules
	Promotes polymorphonuclear cell activation and accumulation
	Increases endothelial procoagulant activity
	Acts synergistically with TNF; enhances tissue cell sensitivity to TNF
	Depresses myocardial contractility
	Acts directly on hypothalamus to produce fever
IL-2	May promote release of TNF and INF-γ
	Decreases arterial pressure, systemic vascular resistance, and ejection fraction; increases cardiac output
IL-4	Enhances lymphocyte adhesion to endothelial cells
	Induces antigen expression on macrophages
	Synergistically increases TNF- or IL-1–induced antigen expression on endothelial cells, but inhibits the increased expression of adhesion molecules by TNF, IL-1, or INF-γ
IL-6	Induction of hepatic acute-phase protein response
	Induces myelomonocytic and terminal B lymphocyte differentiation; activates T cells/thymocytes
	May contribute to septic myocardial depression
	Inhibits TNF production
IL-8	Chemotactic for both neutrophils and lymphocytes; induces tissue infiltration of both
	Inhibits endothelial-leukocyte adhesion; decreases the hyperadhesion induced by those molecules
IL-17	Induces synthesis of TNF-α, IL-1β, IL-6, G-CSF, GM-CSF, TGF-β, and other chemokines
IL-18	Initiates cell-mediated immune response
	Increases secretion of interferon-γ
INF-γ	Promotes release of TNF, IL-1, IL-6 (possibly because of its ability to augment effects of endotoxin on macrophages); augments production of adhesion molecules
	May act synergistically with TNF to produce cytotoxic and cytostatic activity; interacts with other cytokines in variable ways
	Encourages polymorphonuclear cell activation and accumulation; enhances the phagocytic activity of polymorphonuclear cells
	Promotes macrophage activation, macrophage microbicidal function, and expression of cellular receptors for TNF-α
Macrophage migration inhibitory factor	Increases TNF-α and Toll-like receptor 4 expression
	Activates T lymphocytes
	Increases mortality in experimental peritonitis
High-mobility group box protein 1	Possesses both cytokine and intracellular signaling activity
	May generate late organ failure of sepsis
	Impairs vascular endothelial integrity

Continued

TABLE 22.2 Inflammatory Mediators in Sepsis and Septic Shock—cont'd

Mediator	Major Reported Effects
Antiinflammatory Cytokines	
IL-4	Induction of differentiation of naïve helper T cells to T helper type 2 cells
IL-10	Downregulation of macrophage function, leading to decreased TNF-α release
IL-1 receptor antagonist	Antagonistic blockade of IL-1β
Transforming growth factor β1	Broad immunomodulatory activity (protective in endotoxic shock)
	Inhibition of effect of proinflammatory cytokines on a variety of tissues
	Suppression of macrophage proinflammatory responses
	Interference with phagocytic activation
Endothelial Factors	
Endothelin 1	Strongly promotes vasoconstriction
Nitric oxide	Mediates vascular smooth muscle relaxation and arteriovenular dilatation in septic shock
	May be responsible for septic myocardial depression
	Involved in leukocyte/macrophage antimicrobial activity
Arachidonic Acid Pathway Factors and Metabolites	
Phospholipase A_2	Releases arachidonic acid (the precursor of eicosanoids such as leukotrienes, prostaglandins, and thromboxanes)
	Decreases arterial pressure, systemic vascular resistance, and ventricular ejection fraction; increases cardiac output
Leukotrienes	Promote neutrophil chemotaxis and adhesion of neutrophils to endothelium (neutrophils have specific receptors for leukotriene B_4)
	Increase vascular permeability, either directly or through interaction of neutrophils and endothelial cells
	Decrease coronary blood flow and myocardial contractility
Thromboxane A_2	Produces vasoconstriction of vascular beds; secondarily promotes release of endothelium-derived relaxing factor and may stimulate prostacyclin production
	Causes platelet aggregation and neutrophil accumulation
	Increases vascular permeability; enhances permeability of both single- and double-unit membranes
	Produces pulmonary bronchoconstriction
Prostaglandin E_2	Inhibits IL-1 production
	Low concentrations stimulate TNF release; higher concentrations suppress TNF production at a dose-dependent level
	Causes vasodilation and increased blood flow
	Has a beneficial effect on tissue perfusion and may thereby decrease the severity of tissue damage
	Acts synergistically with prostacyclin to increase the effects of serotonin and bradykinin on vascular permeability
Prostacyclin (prostaglandin I_2)	Inhibits platelet aggregation and adhesion
	Causes vasodilation and increased blood flow; in early sepsis, exerts a beneficial effect on tissue perfusion
	Produces smooth muscle relaxation
Others	
Platelet-activating factor	Stimulates release of TNF, leukotrienes, thromboxane A_2
	Promotes leukocyte activation and subsequent free radical formation
	Encourages platelet aggregation, leading to thrombosis
	Markedly alters microvascular permeability, thereby promoting microvascular fluid loss
	Exerts a negative inotropic effect on the heart; lowers arterial blood pressure
Complement fragment C3a	Causes mast cell degranulation and vasodilatory mediator release
Fragment C5a	Causes smooth muscle contraction and mucous secretion
	Causes mast cells to degranulate and release vasodilatory mediators
	Promotes TNF release
	Enhances polymorphonuclear cell activation, migration, adherence, and aggregation
	Induces capillary leakage
	May decrease systemic vascular resistance and produce hypotension

IL, Interleukin; *INF-γ,* interferon γ; *TNF,* tumor necrosis factor.
Adapted from Bone RC. The pathogenesis of sepsis. *Ann Intern Med.* 1991;115:457–459.

(IL) 1β (IL-1β), platelet-activating factor (PAF), and prostaglandins are thought to mediate reduced peripheral vascular resistance seen in septic shock.

The triggers for systemic activation of the inflammatory cascade include a large number of constitutive and/or inducible elements of invasive microorganisms. Beyond endotoxin (lipopolysaccharide), which represents a major trigger in gram-negative bacilli (that cause as much as 50% of septic shock cases with an identified pathogen), other major initiators of the systemic inflammatory response characteristic of sepsis include various exotoxins (all bacteria), peptidoglycans (streptococci), and techioic acid (*Staphylococcus aureus*); lipoarabinomannan of mycobacteria; bacterial DNA and ribonucleic (RNA); and mannoproteins and β-glucan of fungi.[89–95] Recent investigations suggest a surprising commonality

of signaling mechanisms in septic shock via Toll-like receptors from a broad range of etiologic agents.[90,96–99]

More than any other form of shock, distributive and, particularly, septic shock involves substantial elements of the hemodynamic characteristics of other shock categories (see Fig. 22.1 and Table 22.1). As noted, all forms of distributive shock involve decreased mean peripheral vascular resistance. Before fluid resuscitation, distributive shock also involves a relative hypovolemic component. The first element of this relative hypovolemia is an increase of the vascular capacitance as the result of venodilatation. This phenomenon has been directly supported in animal models of sepsis[100–104] and is reinforced by the fact that clinical hypodynamic septic shock (low CO) can usually be converted to hyperdynamic shock (high CO) with adequate fluid resuscitation.[105–107] Relaxation of vascular smooth muscle is attributed to a number of the mediators known to circulate during sepsis. These same mediators also contribute to the second cause of hypovolemia in sepsis: third-spacing of fluid to the interstitium owing to loss of endothelial integrity. In addition, a number of studies have demonstrated that human septic shock is characterized by myocardial depression (biventricular dilatation and decreased ejection fraction).[33–35] Circulating substances such as TNF-α, IL-1β, PAF, leukotrienes, and most recently, IL-6 have been implicated in this process.[108–115]

Anaphylactic shock is a form of distributive shock caused by release of mediators from tissue mast cells and circulating basophils. Anaphylaxis, an immediate hypersensitivity reaction, is mediated by the interaction of immunoglobulin (Ig) E (IgE) antibodies on the surface of mast cells and basophils with the appropriate antigen. Antigen binding results in release of the primary mediators of anaphylaxis contained in the basophilic granules of mast cells and basophils. These include histamine, serotonin, eosinophil chemotactic factor, and various proteolytic enzymes.[116] Subsequently, a number of secondary lipid mediators are synthesized and released, including PAF, bradykinin prostaglandins, and leukotrienes (slow-reacting substance of anaphylaxis).[116] An anaphylactoid reaction (clinically indistinguishable from anaphylaxis) results from direct, nonimmunologic release of mediators from mast cells and basophils and can also result in shock.

Anaphylaxis is triggered by insect envenomations (*Hymenoptera* bees, hornets, and wasps), foods (including eggs and nuts, especially peanuts) and certain drugs, particularly antibiotics (β-lactams, cephalosporins, sulfonamides, and vancomycin).[116] In addition, less frequently, heterologous serum (e.g., tetanus antitoxin, snake antitoxin, antilymphocyte antisera), blood transfusion, immunoglobulin (particularly in IgA-deficient patients) and egg-based vaccine products have been implicated.[116] Anaphylactoid reactions can be caused by a wide range of medical agents, including ionic contrast media, protamine, opiates, polysaccharide volume expanders, such as dextran and hydroxyethyl starch, muscle relaxants, and anesthetics.[116]

The hemodynamic features of anaphylactic shock are very similar to septic shock and include elements of hypovolemia (owing to interstitial edema and venodilatation) and myocardial depression.[117–121] CO and ventricular filling pressures may be reduced until patients are fluid resuscitated.[117,122] In addition to typical findings of shock, patients may demonstrate urticaria, angioedema, laryngeal edema, and severe bronchospasm.

Neurogenic shock involves loss of peripheral vasomotor control as the result of dysfunction or injury of the nervous system. The classic example is shock associated with spinal injury. A similar phenomenon is active in vasovagal syncope and spinal anesthesia, but such conditions are self-limited and transient. The major cause of shock in spinal injury appears to be loss of venous tone resulting in increased venous capacitance. Arteriolar tone may also be affected, resulting in increased CO after fluid resuscitation.

Adrenal crisis is an uncommon cause of shock which can be difficult to diagnose since it occurs in patients with other active disease processes and the clinical features may mimic infection. It is a life-threatening emergency which requires prompt diagnosis and management.

Adrenal crisis is caused by a deficiency of adrenal production of mineralocorticoids and glucocorticoids. It may occur de novo in patients with critical illness or against a background of occult adrenal insufficiency. In the critical care setting, the most common cause of de novo acute adrenal insufficiency is bilateral adrenal hemorrhage in association with overwhelming infections (classically meningococcal, but frequently gram-negative bacteria), human immunodeficiency virus infection, or anticoagulation.[123,124] In addition, fungal infections such as histoplasmosis, blastomycosis, and coccidioidomycosis and malignant infiltration of the adrenal glands may cause acute adrenal insufficiency in ICU patients.[123] In some patients, steroid production remains adequate for the baseline state despite adrenal disease. Once stressed, however, adrenal response is inadequate, leading to decompensation and adrenal crisis. Stressors may be relatively innocuous or may be severe. A febrile illness, infection, trauma, surgery, dehydration, or any other intercurrent illness may trigger the crisis. Abrupt cessation of glucocorticoid therapy or replacement may also result in adrenal crisis.

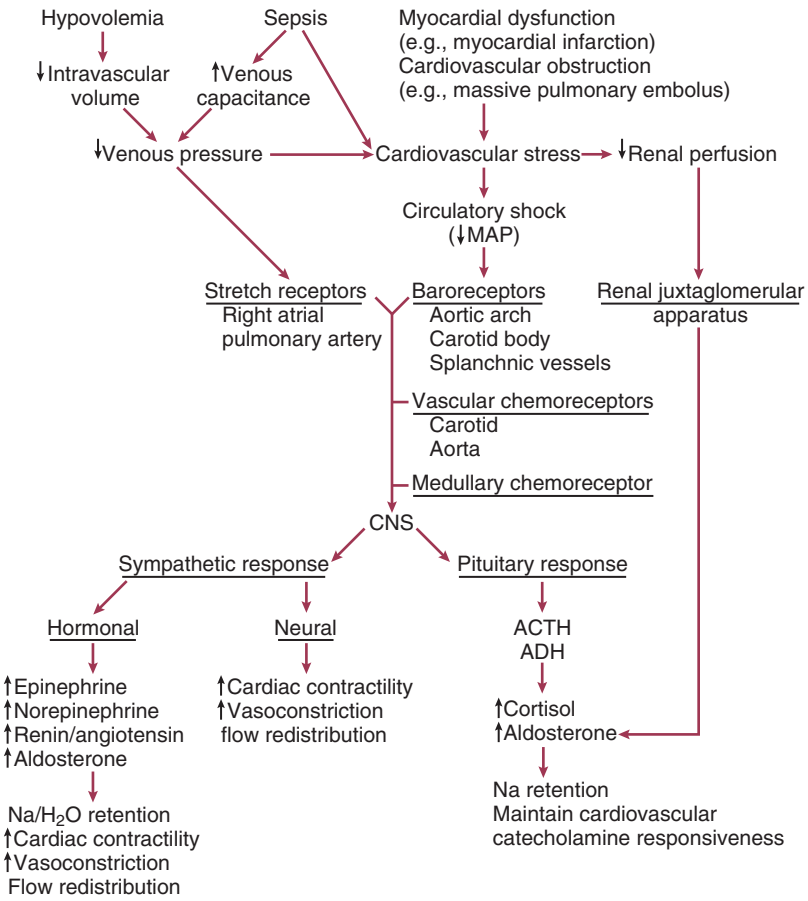
Symptoms are generally nonspecific and may include anorexia, nausea, vomiting, diarrhea, abdominal pain, myalgia, joint pains, headache, weakness, confusion, and agitation or delirium.[123,125] Fever (often out of proportion to any minor infection) is almost always present, and hypotension, initially caused by hypovolemia, is frequent.[123] The initial hemodynamic pattern may resemble hypovolemic shock (if shock is due only to adrenal crisis). With volume resuscitation, a high-output, vasopressor-refractory shock may become apparent.[126,127]

Shock owing to adrenal crisis may be masked by or contribute to shock owing to other concomitant critical illness, particularly septic shock. Thus if vasopressor-refractory shock occurs in patients potentially predisposed to adrenal insufficiency, a cortisol level and rapid adrenocorticotropic hormone stimulation test must be performed and the patient given glucocorticoids and other therapy.

An unrecognized "relative" adrenal insufficiency has been implicated in the pathogenesis of human septic shock.[128–135] In this circumstance, sepsis is associated with a suboptimal adrenal response with an improvement in cardiovascular parameters and/or outcome with "stress" dose corticosteroid administration.[128,129,132–137] One randomized controlled trial suggested that prospective "stress dose" therapy with a combination of hydrocortisone (50 mg intravenous [IV] every 6 hours) and fludrocortisone (50 μg oral/nasogastric daily) for 7 days improved outcome in nonresponders to corticotropin challenge.[138] Confirmatory randomized trials have failed to reproduce this finding.[139,140] However, given solid data suggesting a vasopressor-sparing effect,[136,137] the current recommendation is to consider administration of hydrocortisone only in refractory septic shock (when there is a suboptimal response to appropriate fluid resuscitation and vasopressors).[141–143]

Pathogenesis and Pathophysiology of Shock

The inability of cells to obtain and/or use oxygen in sufficient quantity to optimally meet their metabolic requirements has



• **Fig. 22.2** Neurohormonal response to shock. During early cardiovascular stress, the neurohormonal response may be limited to increased activity of the juxtaglomerular apparatus and stimulation of right atrial and pulmonary artery low-pressure mechanoreceptors. With further hypotension, high-pressure vascular baroreceptors, vascular chemoreceptors, and the medullary chemoreceptor are sequentially stimulated resulting in augmented neurohormonal activity with increased pituitary hormone (adrenocorticotropic hormone *[ACTH]* and antidiuretic hormone *[ADH]*) release and increased sympathetic outflow from the central nervous system *(CNS)*. Volume retention, increased venous tone, increased cardiac contractility, and blood flow redistribution to vital organs results. *MAP,* Mean arterial pressure; *Na,* sodium; H_2O, water.

classically been considered to be the pathophysiologic basis of all forms of shock. In the first half of the 20th century, the study of shock focused on the relatively distinct hemodynamic physiology that characterizes the different forms of shock. Since then evidence has accumulated that the various types of clinical shock have significant overlap in their hemodynamic characteristics. In parallel, shock of most causes has been shown to involve similar biochemical and metabolic pathways. In the following section, the pathophysiology and pathogenesis of shock are reviewed from the hemodynamic to the molecular level. (See the online supplement for discussion on the "Hemodynamic Basis of Shock," "Microvascular Function in Shock," and "Mechanisms of Cellular Injury in Shock.")

Compensatory Responses to Shock

Shock is usually not a discrete condition occurring abruptly after injury or infection. With the onset of hemodynamic stress, homeostatic compensatory mechanisms engage to maintain effective tissue perfusion. At this time, subtle clinical evidence of hemodynamic stress may be apparent (tachycardia, decreased urine output) but overt evidence of shock (hypotension, altered sensorium, metabolic acidosis) may not. Therapeutic interventions have a high probability of preventing ischemic tissue injury and initiation of progressive systemic inflammatory cascades during this early compensated stage. Adaptive compensatory mechanisms fail and organ damage/failure ensues if the injury that initiates shock is too extensive or progresses despite therapy.[284] As the duration of established shock increases, therapy is less likely to be effective in preventing organ failure and death.

Various sensing mechanisms involved in physiologic compensatory responses exist to recognize hemodynamic and metabolic dyshomeostasis (Fig. 22.2). Low-pressure right atrial and pulmonary artery stretch receptors sense volume changes. A decrease in circulating volume (or increase of venous capacitance) results in an increase in sympathetic discharge from the medullary vasomotor center.[144,285,286] Aortic arch, carotid, and splanchnic high-pressure baroreceptors sense early blood pressure changes close to the physiologic range.[144,285,286] An increase of sympathetic discharge from the medullary vasomotor center results from a small to moderate decrease in blood pressure associated with early shock.

Hemodynamic Basis of Shock

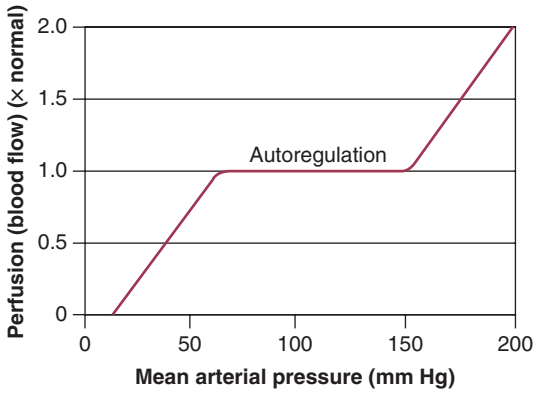
From a hemodynamic perspective, shock is the failure of cardiovascular adaptation to systemic dyshomeostasis induced by trauma, infection, or other insult such that CO and/or blood pressure are compromised. This failure is manifested by inadequate organ and tissue perfusion. Although effective perfusion is also dependent on microcirculatory and intracellular factors (see Box 22.1), the hemodynamic aspects of shock can be described, in part, by the contributions of cardiac and arterial vascular function to blood pressure and CO.

Arterial Pressure

Although CO may be expressed as a function of MAP and vascular resistance [CO = (MAP – CVP)/SVR], CO is not directly dependent on MAP in most physiologic states. Instead, blood pressure is typically dependent on CO and vascular resistance. Blood pressure, however, does provide a mechanism to indirectly sense CO and global perfusion perturbations for autoregulatory purposes.

The ability of all organ vascular beds to support normal blood flow is dependent on maintenance of blood pressure within the defined range for that organ (eFig. 22.1).[144] Vital organs, such as the brain and heart, in particular, are able to autoregulate blood flow over a wide range of blood pressure. Failure to maintain the minimal MAP and perfusion pressure required for autoregulation during hypodynamic circulatory shock indicates a severe reduction in CO. Pharmacologic support of blood pressure in such situations (with α-adrenergic agonists) usually results in decreased total systemic perfusion as sensitive vascular beds constrict and overall vascular resistance increases. However, because of their strong autoregulatory capacity, vital organs will maintain increased perfusion under these conditions.

In addition to sufficient CO, effective perfusion requires appropriate distribution of blood flow. Failure to maintain blood pressure within the autoregulatory range results in distribution of blood flow which is strictly dependent on the passive mechanical properties of the vasculature.[145] This may result in inappropriate distribution of perfusion between and within tissues and organs. Late hemorrhagic shock has been shown to be characterized by abnormal microvascular flow with dilatation of precapillary sphincters.[38]



• **eFig. 22.1** Idealized representation of blood flow autoregulation. Within the autoregulatory range of blood pressure for a tissue or organ, perfusion can be held relatively constant. Outside this range, autoregulation fails and perfusion becomes a function of mean arterial pressure.

Cardiac Output

The fact that total systemic perfusion is defined by CO underlies its importance in shock. The product of HR and stroke volume (SV) determines CO (CO = HR × SV). SV (a measure of myocardial performance) is dependent on preload, afterload, and contractility.

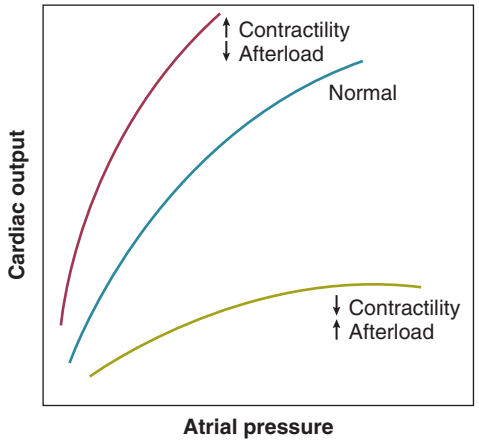
Preload represents the extent of precontraction myocardial fiber (or sarcomere) stretch. In vivo, preload is the end-diastolic ventricular volume. Because measurement of such volumes in the clinical context is difficult, intracardiac pressures, which can be determined more easily, are frequently substituted. There are difficulties with this approach. The relationship of ventricular end-diastolic volume (preload) to end-diastolic pressure is nonlinear. Further, alterations of myocardial compliance render CVP and PAOP unreliable as estimates of preload in critically ill patients.[146]

Preload is dependent on circulating volume, venous tone, atrial contraction, and intrathoracic pressure among other factors.[144,147] Atrial contraction is particularly important in those with impaired ventricular function. Although accounting for only 5% to 10% of CO in healthy humans, synchronized atrial contraction contributes as much as 40% to 50% of the CO in patients with severe left ventricular dysfunction.[147] Increased intrathoracic pressure or increased venous capacitance affect preload by reducing venous return.[144,148] Nitrovasodilators such as nitroglycerin may decrease CO despite arteriolar vasodilation owing to their venodilatory (decreased preload) effects. Conversely, the earliest increases in CO seen with sympathetic stimulation and exogenous catecholamine infusion are related to venoconstriction-induced increases of venous return and preload.[149] Cardiogenic and some forms of obstructive shock are typically characterized by increased preload. Preresuscitation distributive shock and hypovolemic shock are uniformly associated with decreased preload.[144]

Afterload refers to the total resistance to ejection of blood from the ventricle during contraction. Increasing afterload results in decreased extent and velocity of myocardial contraction.[144] Excessive afterload (aortic dissection, pulmonary embolus) causes some forms of obstructive shock. Ex vivo, afterload can be easily defined as a resistive force applied to an isolated papillary muscle. Because the heart does not displace a fixed mass but rather rhythmically moves a viscous, non-Newtonian fluid through branching viscoelastic conduits, the definition of afterload in vivo is difficult.

Afterload has been suggested to be equivalent to systolic myocardial wall stress. This definition suggests that afterload is substantially dependent on intrinsic cardiac mechanical and functional properties.[150] An alternative approach equates left ventricular afterload with the mechanical properties of the arterial side of the circulatory system. Aortic input impedance, which represents the total resistance to flow from outside the left ventricle, is determined by the inertial and viscous properties of blood, and the resistive and viscoelastic properties of the arterial system. The term is inclusive of SVR, HR effects, and pulse wave reflections in the arterial tree.[150] Although an accurate measure of afterload in pulsatile systems, assessment of impedance is technically difficult, requiring continuous harmonic analysis of rhythmic variations of aortic pressure and flow. SVR is a limited approximation of aortic input impedance based on a model that assumes nonpulsatile flow. At an HR of 0, SVR and aortic input impedance are equivalent. From a clinical point of view, SVR is the most practical way of assessing afterload.

Afterload is increased in pathologic conditions such as aortic stenosis, systemic embolism, and hypertension. Vasopressors including α-agonists (e.g., phenylephrine, norepinephrine) and



• **eFig. 22.2** Cardiac function curve demonstrating the effect of variations of preload (atrial pressure), contractility, and afterload on cardiac performance.

vasopressin also increase afterload, whereas nitrates and other vasodilator agents decrease it. Increased intrathoracic pressure owing to mechanical ventilation and positive end-expiratory pressure decrease left ventricular afterload while increasing right ventricular afterload. Hypodynamic and hyperdynamic shock are usually characterized by increased and decreased afterload, respectively.

Contractility refers to the intrinsic ability of myocardial fibers to shorten under given loading conditions. Under normal conditions determinants of contractility include myocardial mass and sympathoadrenal activation state. In pathologic states (e.g., shock), hypoperfusion/ischemia, myocardial cell injury (e.g., reperfusion injury, myocarditis), acidosis, and circulating myocardial depressant substances (such as seen in sepsis) depress cardiac contractility (eFig. 22.2).

As with preload and afterload, the ex vivo/in vitro assessment of contractility is straightforward. Assessment of in vivo contractility (even in experimental animals) is substantially more difficult owing to intrinsic lability of preload and afterload. Relatively load-independent variables, such as the peak systolic pressure/end-systolic volume ratio, may be the most clinically useful measures of contractility.[151] Many of these variables can be obtained echocardiographically.[152,153]

Venous Function in Shock

Given that the cardiovascular circuit is a closed system and CO cannot exceed the rate of return of blood to the right ventricle, venous return can be considered a fundamental determinant of cardiac performance. Although preload is a related variable, it primarily reflects ventricular properties related to compliance and HR, whereas venous return is substantially dependent on the extracardiac properties of the systemic venous circulation. Maximum venous return is described by the following equation:

$$(Pmc - Pa)/Rv, \quad (1)$$

where Pmc is the mean circulatory pressure (the upstream driving pressure of the systemic venous circulation—i.e., the intravascular pressure measured when the heart is stopped), Pa is the right atrial pressure (the downstream pressure that opposes flow to the right ventricle), and Rv is the venous resistance (resistance of the conduit to flow). Pmc equals the stressed volume or Vs (the portion of the vascular volume that contributes to venous pressure) divided by the mean vascular compliance (C):

$$Pmc = Vs/C \quad (2)$$

Vs is dependent on total vascular volume (Vt) and the state of venous tone (i.e., venoconstriction). It is defined as the difference between Vt and the unstressed vascular volume (V_0), the intravascular volume that remains when the vascular circuit is equalized to atmospheric pressure (i.e., the volume remaining after passive exsanguination). Vs volume is approximately 30% of total blood volume in both humans and in experimental animals.[154–156] Compliance refers to the total elastic properties of the entire cardiovascular circuit inclusive of the heart and vasculature.

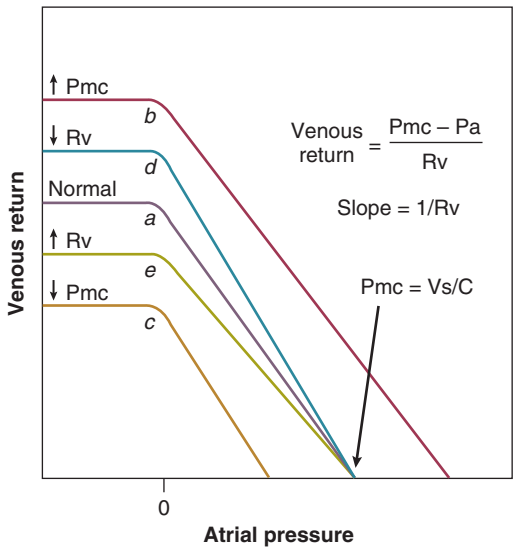
As Eq. (1) shows, the only direct role the heart plays on venous return is by altering right atrial pressure (Pa). MAP has no direct effect at all despite the fact that it is closely related to CO in the systemic circulation (MAP − CVP = CO × SVR).

Rapid alterations of venous return are typically mediated by changes of Pmc or Rv. Pmc is acutely influenced by changes of Vs, either directly through alterations of venous capacitance, which primarily involves changes of small vein and venular tone (exogenous vasopressors or vasodilators, sympathetic stimulation); or indirectly by changes of Vt (volume depletion or infusion). Compliance is substantially a passive mechanical property of the vasculature and does not cause acute alterations of Pmc or venous return. Rv to flow is acutely altered by changes of the caliber of large-diameter veins, particularly the vena cava and great veins of the thorax. However, although resistance resides primarily in large veins and the vena cava, and venous capacitance resides primarily in small veins and venules, all veins contribute to resistance and capacitance to some extent. Alterations of venous tone (either pharmacologic or physiologic) therefore tend to induce opposing changes in Pmc and Rv with respect to venous return. Vasodilatation decreases Pmc by decreasing Vs but it also decreases Rv. Vasoconstriction results in increases of both Pmc and Rv. Only alterations in Vt alter Pmc without affecting Rv.

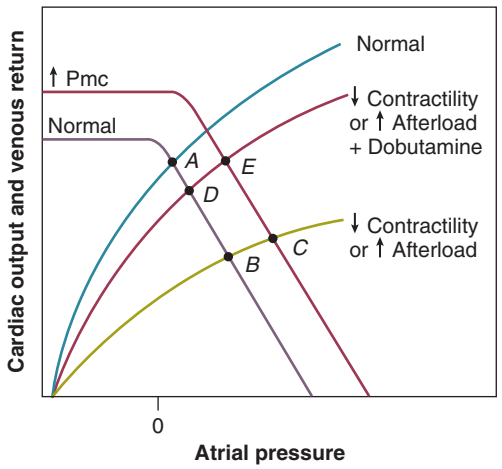
The venous return relationship is shown in eFig. 22.3.[144,157–159] Because the systemic venous bed constitutes the bulk of venous capacitance, the systemic venous vasculature dominates the physiology of venous return. Venous return is linearly related to Pa down to 0 cm H_2O (= atmospheric pressure), at which point intermittent collapse of the great veins results in limitation of return producing the plateau.[144,159,160] The slope of the line representing venous return is the inverse of the resistance (1/Rv). The ordinate intercept denotes the Pa at which venous return is zero. But according to Eq. (1), venous return is zero only when Pa equals the Pmc. Thus the intercept of the atrial pressure axis represents Pmc. Changes of Pmc shift the curve to the left or right without changing the slope of the line (Fig. 22.3, line a to lines b and c). Changes of Rv change the slope of the line without changing the Pmc (eFig. 22.3, line a to lines d and e).

Graphic Analysis of Venous-Cardiac Interactions During Shock

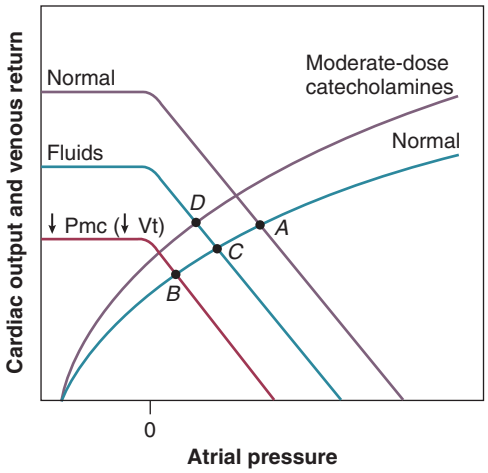
In a closed system, CO as determined by HR, preload, afterload, and contractility must equal venous return as determined by mean circulatory pressure, right atrial pressure, and Rv. CO therefore is not strictly a product of cardiac or vascular function but is dependent on their interaction. Because venous return and CO are equal and are dependent on atrial pressure, the right heart Starling function curves can be superimposed on the systemic venous return curves using the same graphic parameters. The intersection of the two



• **eFig. 22.3** Graphic representation of venous return with varying atrial pressures, mean circulatory pressures and venous resistance. Altering mean circulatory pressure displaces the line representing venous return (line *a* to line *b* or *c*) without changing the slope (which represents venous resistance to flow). Altering venous resistance changes the slope of the venous return curve (line *a* to line *d* or *e*) without changing the intercept point of the venous return line with the ordinate (which defines mean circulatory pressure). *C,* Mean vascular compliance; *Pa,* right atrial pressure; *Pmc,* mean circulatory pressure; *Rv,* venous resistance; *Vs,* stressed volume. See text for details.



• **eFig. 22.4** Graphic representation of systemic venous return–right heart performance interactions during cardiogenic shock (point *A* to *B*) and therapy (see text for details). *Pmc,* Mean circulatory pressure.

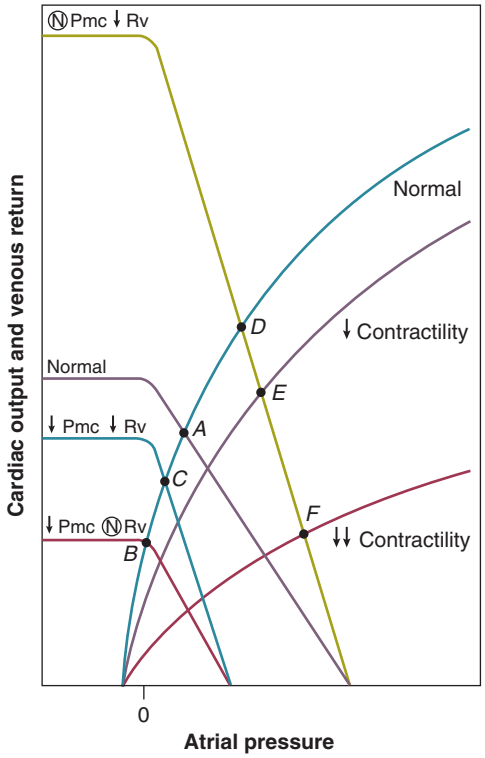


• **eFig. 22.5** Graphic representation of systemic venous return–right heart performance interactions during hypovolemic shock (point *A* to *B*) and therapy (see text for details). *Pmc,* Mean circulatory pressure; *Vt,* total vascular volume.

curves defines CO and venous return for any given set of conditions involving the right heart and the systemic venous circulation. The circulatory physiology of shock can be described by the interaction of cardiac function and venous return curves.

Cardiogenic shock and obstructive shock owing to increased afterload of the right or left ventricle (e.g., massive pulmonary embolus) result in a common change of the right ventricular Starling function curves. In the case of primary left ventricular loading or damage, this occurs because increased left ventricular filling pressures are passively transmitted to the right ventricle. The Starling curves are shifted downward and to the right (flatter) (eFig. 22.4, point A to B), resulting in decreased CO at increased atrial pressures. Therapy can consist of fluid resuscitation (increased Vt and Pmc), which may result in only modest augmentation of CO despite significant increases of atrial pressures and ventricular filling pressures (point C); dobutamine, a β_1- and β_2-agonist that increases CO by increasing contractility (point D); and both fluids and dobutamine (point E). Other catecholamines such as dopamine and norepinephrine, which both increase myocardial contractility and reduce venous capacitance, also increase afterload and have variable effects on CO and venous return depending on which effect is dominant. Resistance to therapy may be noted if myocardial damage is sufficiently severe to flatten the Starling function curve to the point that increasing Pmc has little effect on increasing venous return/CO and insufficient functional myocardium remains to respond to inotropes with increased contractility (a steeper Starling relationship).

Hypovolemic shock results from decreased Vt, Vs, and Pmc (eFig. 22.5, point A to B). The venous return curve is shifted downward and to the left, resulting in a reduced venous return and CO at lower Pas. Although late depression of myocardial contractility with shift of the Starling function curve downward and to the right (analogous to myocardial depression during cardiogenic shock) has been noted in experimental hemorrhagic shock,[36,37] this phenomenon is not considered here. Volume therapy, whether with crystalloid or colloid, tends to correct Pmc and venous return toward the original value (point C). Although optimal therapy of hypovolemic shock involves volume resuscitation, low-dose catecholamines exert similar hemodynamic effects; Pmc (and venous return) are augmented by an increase of the Vs while the total (reduced from baseline) circulating volume (Vt) is unchanged (also point C).[158,161,162] These changes outweigh any deleterious effect on increasing Rv. Cardiac contractility and vascular resistance are minimally affected at these doses. At moderate infusion rates (and with sympathetic stimulation), cardiac contractility is also augmented (point D). With higher catecholamine infusion rates, Vr and afterload may increase resulting to the point of decreasing CO and venous return (not shown). For that reason, vasopressors may be used only with great caution in hypovolemic shock.[163]



• **eFig. 22.6** Graphic representation of systemic venous return–right heart performance interactions during septic shock (point *A* to *B*) and therapy (see text for details). *Pmc,* Mean circulatory pressure; *Rv,* venous resistance.

Septic shock is especially complicated. Sepsis may involve elements of hypovolemia, myocardial depression, and altered distribution of CO. Vt and Vs are decreased owing to loss of fluids to the interstitium (third-spacing) and insensible losses. Vs is further decreased as the result of active dilation of small venules/veins, resulting in increased venous capacitance. This increase in Vt and decrease in Vs has been confirmed in experimental animal models of canine and porcine endotoxemia.[101,164] Thus in unresuscitated septic shock, Pmc is almost universally decreased, resulting in reduced venous return and CO (eFig. 22.6, point A to B). Sepsis is also associated with dilatation of large veins and shunting of arterial blood flow to low-resistance (fast time constant) vascular beds, both of which decrease Vr and tend to augment venous return. Decreased Vr, however, does not fully compensate for decreased Pmc in unresuscitated septic shock. CO remains depressed (point B to C). With fluid resuscitation Pmc may be corrected back toward normal, allowing the decreased Rv to be manifested by supernormal CO and venous return (point D).[101] Patients with septic shock also develop myocardial depression, which is typically masked by the overall increase in CO (point E). In about a fifth of patients, however, myocardial depression is sufficiently severe that venous return and, therefore, CO remains depressed even after resuscitation (point F).

Human data suggest that sepsis is associated with a decrease of total vascular compliance.[165,166] However, it is unclear whether this represents a primary septic phenomenon or a neurohumorally mediated compensatory response.[149,165,167] After fluid resuscitation, therapy of septic shock primarily involves catecholamines such as norepinephrine and dopamine. These affect the venous and cardiac function curves as specified earlier, although some data suggest that both vascular and myocardial responsiveness to sympathomimetics may be reduced. In addition, they may also affect vascular compliance, similar to the potential compensatory neurohumoral effects described earlier.

Obstructive forms of shock such as those caused by pericardial tamponade and tension pneumothorax can also be analyzed in the context of venous/cardiac interactions. For a detailed review of this subject matter, the reader is referred to several excellent reviews of this subject.[149,168,169]

Ventricular function of each distinct form of shock can also be examined by using end-systolic and end-diastolic pressure-volume analysis. Such analysis can be demonstrated graphically using ventricular pressure-volume loops. Changes in SV and ventricular contractility can be examined with respect to ventricular volume and pressure alterations in circulatory shock states. Although this represents a useful approach to the study of circulatory shock physiology, a review of the subject is beyond the scope of this chapter. The interested reader is referred to a number of cogent reviews.[170–172]

Microvascular Function in Shock

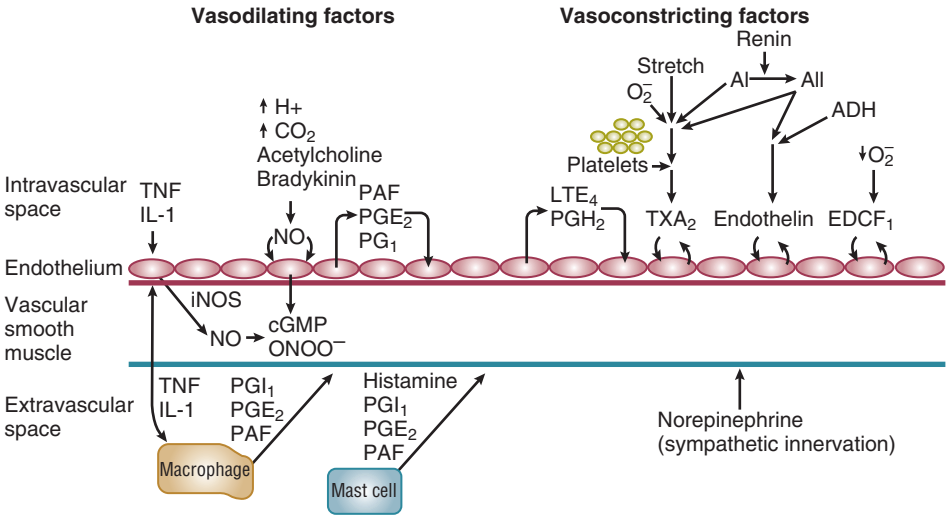
Preserved microvascular (vessels <100–150 μM in diameter) function is a critical determinant of appropriate tissue perfusion during shock. Although adequate CO at sufficient blood pressure is required for appropriate global perfusion and systemic hemodynamics, effective tissue perfusion also requires intact local and systemic microvascular function.

Distribution of CO is a complicated process involving local intrinsic autoregulation and extrinsic regulation mediated by autonomic tone and humoral factors. Blood flow to individual organs may be affected by system-wide changes in microarteriolar tone or by local alterations in metabolic activity. Blood flow within organs also requires microvascular regulation to match blood flow to areas of highest metabolic activity.

Intrinsic control (autoregulation) of blood flow is thought to occur through two mechanisms. Rapid alterations of microvascular tone are mediated through endothelial stretch receptors so that sudden changes in perfusion pressure can be compensated by opposing changes in vascular resistance to maintain perfusion.[173] In addition, increases in metabolic activity within tissues and organs are thought to cause local elevation of various metabolites (carbon dioxide [CO_2], hydrogen ion [H^+], and so on), resulting in vasodilation and increased perfusion to match substrate demand.[173]

Extrinsic control of vascular tone is primarily exerted through the autonomic nervous system. Parasympathetic release of acetylcholine to blood vessels results in nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) generation in endothelial cells and vascular smooth muscle, leading to vascular relaxation. Increases of sympathetic tone cause local norepinephrine release, activation of vascular α-adrenoreceptors, and increased vascular tone (eFig. 22.7). Under stress, epinephrine and norepinephrine can be systemically released by sympathetic stimulation of the adrenal medulla. Basal control of blood pressure and flow resides in the activity of the renin-angiotensin system.

Alterations in microvascular function are effected through precapillary and postcapillary sphincters that are sensitive to both intrinsic and extrinsic control mechanisms. Because exchange of CO_2, oxygen, and other substrates/metabolites and compartmental regulation of fluids occur at the capillary level, alteration of tone of either sphincter may have varying effects. Opening of either



• **eFig. 22.7** Physiologic and pathophysiologic vasoactive factors. *AI,* Angiotensin I; *AII,* angiotensin II; *ADH,* antidiuretic hormone (vasopressin); *cGMP,* cyclic guanosine monophosphate; CO_2, carbon monoxide; *EDCF,* endothelium-derived contracting factor; H^+, hydrogen ion; *IL-1,* interleukin 1β; *iNOS,* inducible nitric oxide synthetase; LTE_4, leukotriene E_4; *NO,* nitric oxide; O_2^-, superoxide anion; $ONOO^-$, peroxynitritel; *PAF,* platelet-activating factor; PGE_2, prostaglandin E_2; PGH_2, prostaglandin H2; PGI_2, prostacyclin; *TNF,* tumor necrosis factor-α; TXA_2, thromboxane A_2.

nonnutrient capillary sphincters (microanatomic shunts)[174] or increased flow to hypometabolic tissues (functional shunts)[175] results in suboptimal distribution of substrate supply with increased MvO_2. Failure to dilate sphincters supplying metabolically active tissues may result in ischemia and anaerobic metabolism with lactate production. Increased precapillary tone as seen with sympathetic stimulation results in increased blood pressure systemically and decreased hydrostatic pressure locally. This decreased hydrostatic pressure favors redistribution of volume from the interstitium to the circulation. Increased postcapillary tone (relative to precapillary) results in vascular pooling of blood and loss of fluid to interstitium (owing to increased hydrostatic pressure).

Organ blood flow changes are well characterized in shock states. Autoregulation of blood flow is dependent on maintenance of blood pressure within a defined range that varies among organs. The autoregulatory capacity of various organs can be determined by mechanically altering blood pressure in the organ vascular bed. With isolated local hypotension, the brain exhibits dominant autoregulatory capability with the ability to maintain blood flow over a wide range of pressures (30–200 mm Hg in dogs).[145] Coronary perfusion is also substantially autoregulated between 40 and 100 mm Hg. In contrast, mesenteric and renal blood flow becomes pressure dependent below about 60 mm Hg, whereas the vascular bed of skeletal muscle behaves in a passive manner at pressures outside 50 and 100 mm Hg. Human data suggest that, overall, good autoregulation of blood flow exists in humans between pressures of 60 and 100 mm Hg.[145] In the context of normal physiology, blood flow is not effectively autoregulated outside this range. Without local adaptation, this would result in mismatching of blood flow and metabolic demands, producing organ failure and the metabolic correlates of shock. However, extrinsic adaptive mechanisms to protect the most vital organs come into play.

During hypovolemia and other hypodynamic forms of shock, extrinsic blood flow regulatory mechanisms overwhelm the autoregulatory response of most vascular beds. Blood flow to the heart and brain are well preserved owing to dominant local autoregulation of flow. Blood flow to other organs is reduced relative to the decrease in total CO as organ vascular resistance increases to maintain blood pressure.[176] This effect is mediated in part by both sympathetic neural activity and adrenal release of catecholamines.[145,176] This adaptive mechanism maintains perfusion to vital organs at mild to moderate levels of reduced CO. If the insult is sufficiently severe or prolonged, organ ischemia and subsequent organ failure may develop. Even if resuscitation restores systemic circulatory hemodynamics, microvascular perfusion abnormalities persist for days.[177] Experimental data suggest that perfusion of brain, kidneys, liver, and other splanchnic organs remains impaired after resuscitation from hemorrhagic shock.[177] Persistence of inadequate matching of tissue substrate demand and delivery after resuscitation of shock can lead to continued ischemia/hypoxia of some tissues. This may explain why hemorrhagic shock-related tissue injury can be irreversible if the duration and severity of is excessive. Animal models suggest this irreversible phase of severe hemorrhagic shock is characterized by vasodilatation of precapillary sphincters.[178]

During sepsis and septic shock, organ blood flow is disturbed at higher MAP, suggesting a primary defect of microvascular function. Cerebral blood flow to the brain in humans has been shown to be depressed even before the onset of septic shock in patients with systemic inflammatory response syndrome.[179] This pathologic vasoconstriction (apparently a unique response of the cerebral circulation to sepsis) does not appear to be the cause of septic encephalopathy. Cerebral autoregulation remains intact during sepsis.[180] The greater decrease in coronary than SVR during human septic shock may suggest that myocardial autoregulation also remains intact despite the fact that, in contrast to the brain, myocardial perfusion is often increased during septic shock.[181,182]

Animal models demonstrate that all other vascular beds (splanchnic, renal, skeletal, cutaneous) exhibit decreased vascular resistance, with flow in these beds becoming increasingly dependent on CO. This suggests both an active vasodilatory process and failure of extrinsic control of blood flow.[145] Inappropriate levels

of splanchnic and skeletal muscle perfusion are also observed in humans during sepsis.[183] Other experimental data suggest that sepsis and septic shock are also associated with aberrant distribution of flow within organs.[175] In sepsis, vasodilatation and autoregulatory failure of the microvasculature may be responsible for mismatches of oxygen delivery and results in anaerobic glycolysis with lactate production despite increased mixed venous oxygen saturation.

During both irreversible hemorrhagic shock and septic shock, peripheral vascular failure results in worsened matching of tissue demand and substrate supply leading to failure of all organs and death. The following are among the potential responsible mechanisms:

1. Tissue acidosis[184]
2. Catecholamine depletion and mediator-related vascular resistance to catecholamines[185]
3. Release of vasodilating and vasoconstricting arachidonic acid metabolites[186]
4. Decreased sympathetic tone as the result of altered central nervous system (CNS) perfusion[187]
5. Pathologic generation of NO by vascular smooth muscle cells[39,188]

In addition to vasomotor dysfunction, shock is associated with other microvascular pathology recently referred to as shock-induced endotheliopathy.[189,190] Prime among these is disruption of endothelial cell barrier integrity. The endothelial layer is responsible for maintaining oncotic proteins (mostly albumin) within the circulatory space. During shock capillary permeability is increased, resulting in loss of plasma proteins into the interstitium. Endothelial injury, through the action of neutrophil-generated free radicals[191] and NO/peroxynitrite generation,[192,193] may account for this phenomenon. Release of vasoactive intermediaries such as histamine, bradykinin, PAF, leukotrienes, and TNF-α appear to drive this pathologic process. Injury is initiated by leukocyte-endothelial cell interactions via adhesion molecules (integrins, selectins) that allow emigration of neutrophils to the tissues. Blockade of such activity or depletion of neutrophils attenuates tissue injury in animal models of shock.[194] With the loss of plasma proteins, the plasma oncotic pressure drops, interstitial edema develops, and circulating volume falls.

There is also evidence of intravascular hemagglutination of red blood cells, white blood cells, and platelets in almost all shock syndromes.[175,189,195] This may be due to primary microvascular clotting leading to microthrombi. Alternately, clotting may occur as a consequence of primary endothelial damage owing to circulating cytokines, free radicals produced by reperfusion and neutrophils, or complement activation.[189] In any case, the result may be further endothelial cell injury, microvascular abnormalities, and inadequate distribution of perfusion within tissues. Decreased deformability of erythrocytes caused by membrane free radical injury may also play a role in microcirculatory alterations in hemorrhagic and septic shock.[196]

Mechanisms of Cellular Injury in Shock

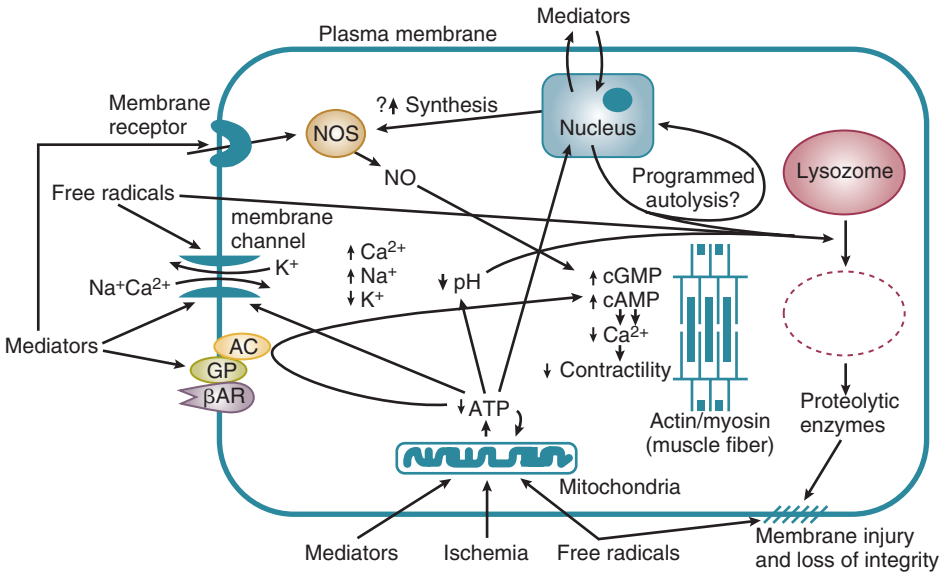
Although different forms of shock have their different precipitants, they do share common mechanisms of cellular dysfunction and injury. Eventually, events at the cellular level result in organ dysfunction and death. The pathogenesis of the cellular dysfunction is a combination of the interrelated precipitants and consequences of shock, including (1) ischemia, (2) inflammation, and (3) free radical injury (eFig. 22.8). Genetic factors are also felt to play a role in an individual's susceptibility and response to shock.

The metabolic pathways involved in shock, like all cellular pathways, involve multiple levels of feedback. Some pathways have positive feedback mechanisms, where an initial small signal results in accelerating downstream effects, and negative feedback mechanisms, where downstream effects results in downregulation of upstream processes. Because cellular mechanisms from different signal transduction pathways often share common elements, different pathways have positive and negative feedback effects on each other; this is termed *crosstalk*.

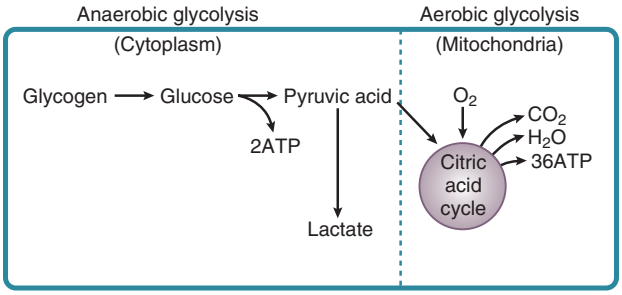
In all forms of shock, the hemodynamic changes involved eventually result in decreased oxygen delivery to target organs, with resultant cellular ischemia. The degree to which this is important in the development of organ damage and death in the different shock forms may vary, but it clearly is the major factor in hypodynamic forms of shock, and it also plays a large role in the ultimate mortality of hyperdynamic, hypermetabolic shock.

In the stressed preshock phase, physiologic adaptive mechanisms attempt to compensate and perfusion to vital organs is maintained. With the onset of shock, these mechanisms fail, and thus oxygen delivery to tissues is not maintained. At the cellular level, a lack of oxygen prevents the mitochondrial citric acid cycle from functioning and pyruvate accumulates (eFig. 22.9). The failure of aerobic respiration requires shunting of pyruvate into the lactic acid pathway to recycle nicotinamide adenine dinucleotide (NAD) and allow glycolysis to continue. However, the loss of the aerobic citric acid cycle results in a large decrease in adenosine triphosphate (ATP) production (net 2 molecules of ATP per molecule of glucose versus a theoretical net of 38 molecules of ATP per glucose molecule in the entire aerobic pathway). In addition, shunting to the lactic acid pathway results in the accumulation of hydrogen ions. Thus loss of perfusion results in a rapid decrease in cellular energy stores, with inadequate ATP regeneration rates. As ATP is the primary source of energy in the cell, energy-dependent cellular systems cease functioning. This includes energy-dependent enzymes, maintenance of transmembrane gradients including electrical potential,[197] mitochondrial function,[198] carbohydrate metabolism,[199] and even the glycolysis pathway itself, which requires two ATP molecules to prime each glucose molecule at the entry point into the pathway. Some cell types are more sensitive than others to depletion of energy stores, such as in the liver and kidney, but eventually all organs are affected.[197,200–203] With the loss of energy-dependent cell maintenance functions, ultrastructural breakdown, including mitochondria, occurs.[204] Systemically, the combination of worsening acidosis and loss of energy stores results in a positive feedback loop of worsening shock, organ failure, and eventual death.

Ischemia is felt to play a minor role in early sepsis, with high COs maintaining perfusion to more sensitive, higher energy-consuming tissues, and that ATP levels remain normal in these tissues, with mitochondrial function preserved. Instead, early septic organ dysfunction results from other causes.[205–207] However, localized areas of ischemia are not ruled out. Potentially, microthrombi may result in small areas of decreased microcirculatory flow, resulting in localized ischemia. Evidence to support a role for ischemia in cellular dysfunction in sepsis includes oxygen supply–dependent oxygen consumption, washout of organic acids from ischemic areas in patients in septic shock receiving vasodilators, and elevated ATP degradation products. In any case, the role of ischemia in septic shock remains a question. For example, alterations of liver and skeletal muscle transmembrane potential occur early in shock before the decrease in levels of high-energy phosphates and onset of hypotension. Further, this membrane defect is not prevented by



• **eFig. 22.8** Mechanisms of cellular dysfunction and injury in shock. Cell injury is mediated by multiple mechanisms during shock. Tissue ischemia may result in limitation of aerobic adenosine triphosphate (*ATP*) generation. This results in further mitochondrial impairment owing to deficits of mitochondrial membrane function, altered signal transduction including decreased muscle contractility (ATP is the precursor of cyclic adenosine monophosphate [AMP]), impaired energy-dependent maintenance of transmembrane potential and ion gradients, increased intracellular pH owing to anaerobic metabolism, and possible initiation of autolytic mechanisms. Free radicals may result in broad injury to cellular membranes, resulting in impaired maintenance of transmembrane potential and ion gradients, mitochondrial generation of ATP, and activation of autolytic pathways involving DNA degradation and lysosomal rupture (apoptosis). Various circulating mediators (including cytokines, kinins, eicosanoids, and complement components) may result in mitochondrial dysfunction, signal transduction abnormalities, membrane protein channel alterations, and possibly alterations of gene expression. Any of these may lead to cell death through metabolic failure and lysosomal enzyme release. *AC,* adenylate cyclase; *Ca^{2+},* calcium ion; *cAMP,* cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *GP,* G proteins; *K^+,* potassium; *Na^+,* sodium ion; *NO,* nitric oxide; *NOS*, nitric oxide synthetase; *βAR,* β-adrenergic receptor.



• **eFig. 22.9** Aerobic and anaerobic glucose metabolism. Under anaerobic conditions, pyruvic acid cannot enter the citric acid cycle in the mitochondria (to optimally produce adenosine triphosphate [*ATP*]) and is shunted to lactate in the cytoplasm. This produces less high-energy phosphates per mole of glucose metabolized. Hydrolysis of ATP molecules in an anaerobic environment results in production of hydrogen ions that cannot be metabolized or cleared resulting in intracellular acidosis. *ATP,* Adenosine triphosphate; *CO_2,* carbon dioxide; *H_2O,* water; *O_2*, oxygen. Adapted with permission.[401]

administration of membrane-permeable forms of high-energy phosphates such as ATP-magnesium chloride ($MgCl_2$).[208]

Inflammation, on the other hand, is a major contributor to the development of septic shock and its effects on cellular and organ dysfunction.[209,210] Other forms of shock also result in activation of the inflammatory cascade—for example, in hemorrhagic shock with tissue trauma.[211] Indeed, shock is associated with systemic activation of the inflammatory cascade. The resulting cellular and tissue dysfunction and hypermetabolic state contribute to organ dysfunction and failure. The inflammatory cascade in sepsis can be roughly broken down into initiation, transduction, and release of inflammatory mediators.

Initiation of the inflammatory cascade in sepsis is thought to rely largely on the innate immune response.[212–214] This ancient immune pathway evolved to recognize nonself molecular signatures, produced by pathogens including bacteria, yeast, and viruses, which have remained invariant over time. These signatures are called pathogen-associated molecular patterns (PAMPs), and they are recognized by a series of receptors known as pattern recognition receptors (PRRs). In addition, signature host proteins can also be released extracellularly in response to cellular damage, and these proteins, also called alarmins, are known as damage-associated molecular patterns (DAMPs), and these too may be recognized by PRRs. Thus both nonself PAMPs and self-expressed DAMPs may lead to initiation of the inflammatory cascade via the PRRs. Known PRRs include the following:

1. Toll-like receptors (TLRs)
2. C-type lectin receptors (CLRs)
3. Nucleotide oligomerization domain (NOD)-like receptors (NLRs)
4. Retinoic acid–inducible gene I–like receptors (RLRs)

The TLRs and CLRs, as transmembrane receptors, are presented on the cell surface or within the lumens of endosomes or lysosomes.[209,214,215] Currently 10 families of TLRs have been identified in humans. Different TLR families on the cell surface recognize various bacterial lipoproteins, lipopolysaccharides, or flagellins, with sources that may be bacterial, viral, or protozoan. In contrast, those TLR families located in endosomal lumens recognize single-stranded RNA, double-stranded RNA, and modified oligodeoxynucleotide-DNA, which may be of viral or bacterial origin. Interestingly, different individual families of TLRs can form both homodimers and heterodimers on the cell surface, increasing their range of ligand recognition. Meanwhile, the CLRs are presented on the cell surface, and as lectins, recognize polysaccharides present in yeast and fungi, mycobacteria, and viruses.

In contrast, the NLRs and RLRs are intracellular, and require that their ligands be present in the cytoplasm of the cell.[215] NLRs recognize bacterial peptidoglycans; the RLR ligands consist primarily of double-stranded RNA, cytoplasmically produced either by dsRNA viruses or as an intermediate step in the replication of single-stranded RNA viruses.

Once initiated by recognition of PAMPs or DAMPs, the inflammatory cascade involves a large number of protein, kinase, and second-messenger cascades. These cascades can lead to activation of transcription factors or to posttranscriptional or posttranslational activation of inflammatory mediators.

The TLRs have been shown to use two primary pathways.[215] All the TLRs, with the exception of TLR3, use a pathway dependent on the myeloid differentiation adaptor protein (MyD88), which binds to the intracellular sections of the TLRs; for some of the TLRs, another adaptor protein is required to bind MyD88. Upon activation of the TLR, MyD88 recruits a serine/threonine kinase, IRAK-4 (IL-1 receptor–associated kinase 4), in turn recruiting further kinases such as IRAK-1 and IRAK-2. Ultimately, the cytoplasmic cascade results in phosphorylation and degradation of IκB, an inhibitor of the transcription factor nuclear factor κ light-chain enhancer of activated B cells (NF-κB). This allows NF-κB to enter the nucleus, resulting in the activation of transcription of a suite of inflammatory mediators and modulators. In contrast, TLR3 uses a pathway dependent on the TRIF adaptor protein, which also ultimately results in NF-κB activation. In both pathways, other adaptor proteins may be required for individual TLRs to activate these cascades; for example, TLR4 can also use the TRIF-dependent pathway but is dependent on the TRAM adaptor protein to do this. Different cell types may express different adaptor proteins, resulting in intertissue variation in the cascades. In addition, protein inhibitors of the cascades can be expressed variably in different cell types.

In contrast, the NLRs act via formation of a multiprotein complex, termed the *inflammasome*.[209,215,216] The caspases,[217] a family of cysteine proteases, are central to this cascade. Upon activation, the NLR recruits a pro-caspase, along with an adaptor protein ASC, which recruits a second pro-caspase. This complex allows the pro-caspase pair to autoactivate, resulting in active caspase. The best studied of these is caspase-1, although other caspases may be involved. Once activated, caspase-1 in turn activates the inflammatory cytokine IL-1β, allowing its release from the cell. Similarly, caspase-1 is also responsible for the activation and release of other cytokines, including IL-18. In this way, the NLR's prime function is to regulate inflammatory mediator release through a posttranslation system. Crosstalk from the TLR cascades may also activate some NLRs and result in inflammasome formation.

At the center of these cascades is transcriptional regulation of inflammatory cytokines and mediators. The transcription factor NF-κB sits at the end of many of these cascades and plays a crucial role in the regulation of expression of many of these factors.[209,215,218] NF-κB is present in an inactive form in the cytoplasm, in complex with repressor proteins.[219] When the repressors, known as IκB proteins, are phosphorylated and subsequently degraded, NF-κB is released and transported into the nucleus, where it can act on its target sequences. By being stored in inactive form in the cytoplasm, no new NF-κB need be expressed, allowing for rapid response to the signals received by the PRRs. Inflammatory mediators under the control of NF-κB include cytokines such as TNF-α, IL-1β, and IL-6, enzymes involved in inflammation, such as inducible NO synthase and others.[209]

Inflammatory mediator effects on cellular metabolism are of prime importance in organ dysfunction owing to sepsis and septic shock. Circulating inflammatory mediators may also play a substantial role in other forms of shock, including hemorrhagic shock associated with extensive tissue trauma.[220,221] Both sepsis and trauma are associated with generalized, systemic activation of the inflammatory response. Resulting cell injury and hypermetabolism may culminate in organ failure. A number of triggers can result in activation of the inflammatory cascade. The best studied is endotoxin from gram-negative bacteria, but other bacterial antigens and cell injury itself can also initiate the cascade. Macrophage production of cytokines such as TNF-α, IL-1β, and IL-6 appears to be central.

TNF-α is a 51-kD trimeric peptide produced by macrophages in response to a variety of inflammatory stimuli, including bacterial antigens and other cytokines. Circulating levels of TNF-α are transiently elevated soon after the onset of shock (particularly septic shock).[222] Administration of TNF-α to animals or humans results in a hyperdynamic circulatory state (± dose-dependent hypotension) similar to untreated sepsis and septic shock.[111] Although clinical trials to date have yielded disappointing results, anti–TNF-α strategies protect animals from experimental endotoxic and septic shock.[223] Among the many effects of TNF-α are release of IL-1β, IL-6, IL-8, PAF, leukotrienes, thromboxanes, and prostaglandins; stimulation of production and activity of polymorphonuclear leukocytes; promotion of immune cell adhesion to endothelium; activation of coagulation and complement systems; direct endothelial cell cytotoxicity; depression of myocardial contractility; and fever production by the hypothalamus.[111,224] Notably, TNF-α causes alterations of skeletal transmembrane electrical potential similar to those described in hemorrhagic and septic shock.[225] These membrane effects precede hemodynamic alterations, suggesting that TNF-α exerts a primary effect on cell metabolism independent of perfusion alterations. Although TNF-α appears to be of central importance in the pathogenesis of septic shock, it is also known to be elevated in CHF[226] and hemorrhagic shock.[220]

Other substances involved in the inflammatory process include the following:

IL-1β, which can potentiate the in vivo effects of TNF-α

IL-2, which can cause hemodynamic abnormalities in humans

IL-6, which is involved in the acute-phase response and has recently been implicated in septic myocardial depression

Interferon (INF)-γ, which promotes the release of other cytokines, enhances adhesion of immune cells, and promotes macrophage activation

IL-10, which is an antiinflammatory cytokine that limits macrophage generation of proinflammatory cytokines;

TGF-β, which is another antiinflammatory cytokine that, in addition to limiting macrophage proinflammatory responses,

also blocks the effects of proinflammatory cytokines on target cells

Endothelin-1, a cytokine which strongly promotes vasoconstriction, particularly in the renal vascular bed, possibly resulting in renal hypoperfusion and decreased glomerular filtration rate

PAF, which stimulates TNF-α, thromboxane, and leukotriene release; stimulates free radical formation; and alters microvascular permeability

Leukotrienes, which release other arachidonic acid metabolites, alter vascular endothelial permeability, and may mediate vascular and myocardial depression in shock

Thromboxanes, which may contribute to altered microvascular vasomotor and permeability function

Prostaglandins, which produce fever, induce vasodilatation, and inhibit thrombus formation

Complement fragments C3a and C5a, which constrict vascular smooth muscle, release histamine, and promote chemotaxis.[115,227,228]

Several newly recognized mediators/mediator groups have been shown to have important roles in shock, particularly septic shock. These include high-mobility group 1 protein (HMG-1), myocardial depressant substances, and NO/peroxynitrites. HMG-1 appears to have a key role in the late pathogenesis of sepsis[229,230] and may also have a role in traumatic/hemorrhagic shock.[224,231,232] HMG-1 is a late mediator of inflammation. Mice show increased levels of HMG-1 in serum 8 to 32 hours after endotoxin administration. Patients succumbing to septic shock also demonstrate increased serum HMG-1 levels.[229] Administration of HMG-1 to normal and endotoxin-resistant mice induces dose-dependent mortality with signs consistent with endotoxic shock.[229,230] Several anti–HMG-1 therapies are in development.[232]

A circulating myocardial-depressant substance is present in the blood of patients with septic shock who exhibit myocardial depression with biventricular dilatation and reduced ventricular ejection fractions.[233] Similar substances have been shown to be present in animal models of hemorrhagic shock.[234] Other data suggest canine MI[235] and human cardiogenic shock[236] may also be associated with a circulating myocardial-depressant substances. Serum from appropriate septic patients or animal models depresses myocardial tissue in vitro.[144,233] Myocardial depressant substances from both septic and hemorrhagic shock appear to be dependent on calcium.[237] The substance implicated in human sepsis may represents a synergistic combination of TNF-α and IL-1β that produce depression by inducing myocardial NO production.[233,238,239] TNF-α and IL-1β are both elevated in shock and cause similar depression of myocardial tissue.[238,240] Other data suggest that IL-6 may have a central role.[115,227,241]

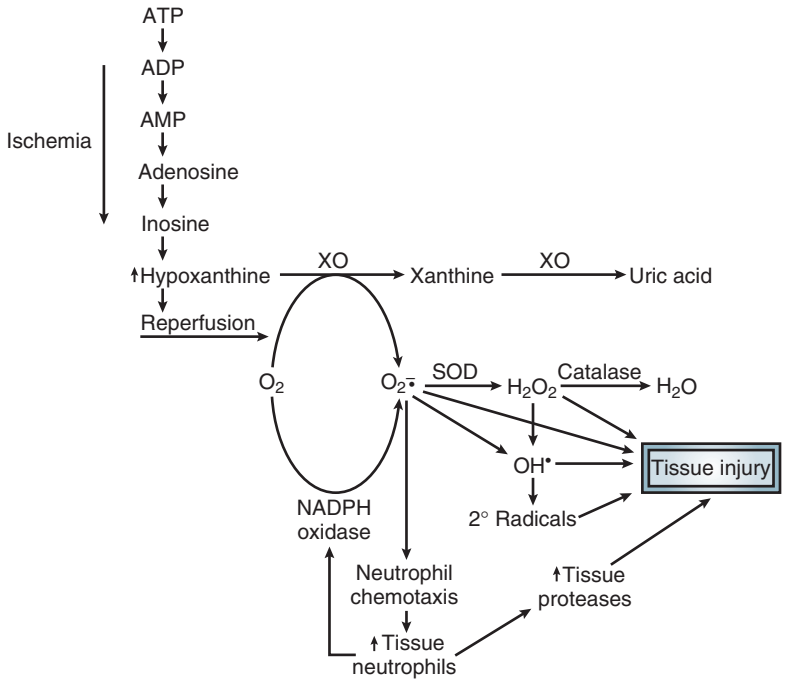
Another important mediator, NO, has a vital role in normal intracellular signal transduction.[242] Of particular importance to shock, NO is the mediator through which endothelial cells normally cause relaxation of adjacent smooth muscle.[242] Endothelial cells, through a constitutive NO synthetase, produce picomolar quantities of NO in response to a number of vasodilatory mediators such as acetylcholine and bradykinin. This NO diffuses to adjacent smooth muscle and activates guanylate cyclase to produce cGMP, which affects vascular relaxation. Nitrovasodilators bypass NO synthetase to relax smooth muscle directly though the guanylate cyclase pathway. During septic shock, an inducible NO synthetase capable of producing nanomolar quantities of NO is generated in vascular smooth muscle.[242,243] Studies have also implicated NO in late vascular dysfunction seen in hemorrhagic shock.[39] NO-mediated generation of cGMP may explain the profound loss of arterial vascular tone and venodilatation seen in septic shock[243,244] and may, in part, explain irreversible vascular collapse seen late in hemorrhagic shock.[39] A potential role for NO in inflammation-associated edema and third-spacing during shock has also been suggested.[192] The in vitro myocardial depressant effects of TNF-α, IL-1β, and serum from septic humans may be mediated by a similar NO- and cGMP-dependent pathway.[111,238]

An alternative pathway by which NO may play a role in the cardiovascular pathophysiology of shock and sepsis was described by Beckman and colleagues in 1990.[245] Peroxynitrite ($ONOO^-$), a highly reactive oxidant, is produced from the interaction of superoxide (OH^-) and NO (NO^-). It is known to react rapidly with proteins, lipids, and DNA during sepsis and shock states.[246–249] Lipids may be peroxidized and although proteins may be oxidized, nitrated, or nitrosated, the last resulting in nitrotyrosine residues.[245,250,251] Peroxynitrite inactivates mitochondrial aconitase disrupting the Kreb cycle and otherwise interferes with ATP production and utilization,[252–257] an activity similar to that described for NO.[258–260] It also generates DNA strand breaks, leading to poly-adenosine diphosphate (ADP) ribose synthetase activation that may itself have significant pathophysiologic effects.[261,262] Peroxynitrite, like NO, also activates guanylate cyclase in vascular tissues.[263,264] In the periphery, the result may be cellular energetic failure, vascular contractile dysfunction (vasodilation), and reperfusion injury.[261,265–267] Many other molecular targets of NO relevant to the cardiovascular system exist and are well reviewed elsewhere.[250,268]

It is of note that as part of the release of inflammatory mediators, immune cells, including macrophages, polymorphonuclear leukocytes, and lymphocytes, may also be activated in some forms of hypodynamic shock (e.g., hemorrhagic shock), resulting in a self-perpetuating, systemic inflammatory response (similar to that seen in sepsis). This response can contribute to vascular and parenchymal injury and culminate in MODS.

Free radical injury induced by reperfusion or neutrophil activity is another mechanism of organ injury during hemorrhagic and septic shock as well as burns and MI.[269] During tissue ischemia, oxygen deficiency leads to accumulation of ATP degradation products, including adenosine, inosine, and hypoxanthine (eFig. 22.10).[270] With resuscitation and reperfusion of ischemic areas, oxygen drives the generation of superoxide (O_2^-), the most common precursor of reactive oxidants, by xanthine oxidase in endothelial cells. Most of the superoxide is converted, either spontaneously or through superoxide dismutase to hydrogen peroxide ($H_2O_2^-$). This further reacts to produce tissue-damaging hydroxyl radicals (or other highly reactive free radicals).[269] These radicals interact with critical cell targets, such as the plasma membrane, lipid membranes of organelles, and various enzymes, resulting in cell lysis and tissue injury. Oxidant activity, directly and through endothelial damage, attracts and activates neutrophils, resulting in amplification of superoxide generation by a neutrophil dihydronicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and in further tissue damage owing to neutrophil protease release.[269] Injured tissue may release xanthine oxidase into the circulation resulting in systemic microvascular injury.[271]

A parallel process is found during reperfusion of ischemic myocardium after MI.[272] Thrombolytic therapy or balloon angioplasty results in sudden delivery of oxygen to ischemic myocardium. Although substantial salvage of myocardial function results, free oxygen radical–mediated reperfusion injury can contribute to myocardial "stunning."[273] Cardiogenic shock during this phase may resolve as the reperfusion injury settles. Free radical damage likely also plays a role in tissue damage during sepsis and septic shock. After activation by inflammatory mediators and during phagocytosis,



• **eFig. 22.10** Free radical–mediated tissue injury. Superoxide *(O_2^-)* is primarily produced in shock from hypoxanthine (a metabolite of adenosine triphosphate [*ATP*] degradation) by xanthine oxidase *(XO)* during reperfusion after ischemia. Superoxide can be converted to hydrogen peroxide *(H_2O_2)* by superoxide dismutase *(SOD)* and then to water *(H_2O)* or may be converted to the highly reactive hydroxyl *(OH^-)* that mediates tissue injury. Free radical tissue injury may be amplified by superoxide recruitment of neutrophils that secondarily produce additional superoxide through NADPH oxidase. *2°,* Second degree; *NADPH,* reduced nicotinamide adenine dinucleotide phosphate. (Adapted with permission from Girardin E, Grau GE, Dayer JM, et al. Plasma tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. *N Engl J Med*. 1989;319:397–400.)

polymorphonuclear leukocytes undergo a respiratory burst during which they consume oxygen and generate both superoxide and hydrogen peroxide through a membrane-associated NADPH-oxidase.[269] Macrophages similarly produce oxygen radicals upon activation. Activation also enhances adhesion and tissue migration of leukocytes so that both vascular endothelial and parenchymal tissue damage may result. Free radical injury may play an important role in the development of organ failure after shock.[274]

Variations in stress response genes between individuals and alteration of gene expression in immune, endothelial, muscle, and organ parenchymal cells are other important aspects of cellular dysfunction/injury in circulatory shock. Although shock can be present immediately after injury (massive trauma, hemorrhage, or endotoxin infusion) before the onset of substantial alterations of gene expression, its evolution is dependent on a combination of the ongoing nature of the insult, the genetically passive compensatory physiologic/metabolic response, the underlying genotype with respect to stress response elements, and stress-related modulation of gene expression in a variety of cells.

The clinical presentation of shock, progression of the syndrome, and final outcome may be substantially controlled by genetic factors.[275] Genetic factors have been best studied in septic shock. Studies have demonstrated that the human TNF-α promoter polymorphism, TNF-2, imparts an increased susceptibility to and mortality from septic shock.[276] Other studies suggest increased TNF-α generation, severity of sepsis, and mortality with another human TNF-α gene polymorphism.[277] A specific locus on chromosome 12 in mice has been shown to be associated with resistance to mortality owing to TNF-α–induced shock.[278] A human IL-1β receptor antagonist gene polymorphism has been linked to increased susceptibility to sepsis.[279] Several additional linked polymorphisms have been described in recent years.[280] It appears likely that gene polymorphisms may also play similar roles in other forms of shock.

Beyond the role of gene alleles in the development and clinical response to shock, the progression of irreversible circulatory shock and MODS may have its basis in genetically driven vascular or parenchymal responses. Production of cytokines by macrophages during shock requires acute expression of the genes coding for TNF-α, IL-1β, and other proinflammatory cytokines. The production of adhesion molecules by endothelial cells and inducible NO synthetase by vascular smooth muscle during shock requires active upregulation of gene expression. Both events are thought to be key to the development of MODS after shock in humans. In addition, human and animal research indicate that apoptosis, a genetically programmed process of cell autolysis, occurs in a variety of organs during shock and subsequent organ failure.[281,282] Recent data suggest that a variety of transcription factors may be activated in models of sepsis in association with the process.[283] Further research should elucidate the important link between irreversible/refractory shock/shock-associated MODS and genetically programmed cell responses to inflammatory stimulation and/or injury.

Whatever the initiating event or events, progressive cell metabolic failure occurs. Mitochondrial activity continues to deteriorate, subcellular organelles are damaged, and intracellular (and possibly, systemic) release of lysosome hydrolytic enzymes occurs, accelerating cell death and organ failure.

However, once MAP falls below about 80 to 90 mm Hg, aortic baroreceptor activity is absent. Subsequently, carotid baroreceptor response is eliminated as mean pressure falls below 60 mm Hg. As blood pressure falls further, carotid and aortic chemoreceptors, sensitive to decreased partial pressure of oxygen (P_{O_2}), increased partial pressure of arterial carbon dioxide (P_{CO_2}), and increased H^+ concentrations (decreased pH), dominate the response. These receptor complexes, active only when mean blood pressure is less than approximately 80 mm Hg, are of minimal relevance during physiologic states.[144] During shock, they make a substantial contribution to increases of sympathetic tone.

During severe shock, the most powerful stimulus to sympathetic tone is the CNS ischemic response.[144] The lower medullary chemoreceptors for this response (thought to be sensitive to increased CO_2 associated with decreased cerebral perfusion) become active when mean blood pressure falls below 60 mm Hg. Sympathetic stimulation provided by these receptors peaks at mean pressures of 15 to 20 mm Hg and results in maximal stimulation of the cardiovascular system.[144] The Cushing response to increased intracranial pressure is an example of activation of this reflex under different circumstances.

Other mechanisms also play a role in the compensatory response to shock. Vasopressin release is regulated by alterations of serum osmolality. During effective hypovolemia owing to intravascular volume loss or increased vascular capacitance, low-pressure, right atrial stretch receptors can override osmolar control of vasopressin response to effect retention of body water.[144,287] Similarly, during hypovolemia and shock, the juxtaglomerular apparatus in the kidneys respond to decreased perfusion pressure by renin release.[144]

All compensatory responses to shock, whether hemodynamic, metabolic or biochemical, support oxygen delivery to vital organs. These responses are similar (to varying extents) for different classes of shock and can be broken down into four components: (1) maintenance of mean circulatory pressure (a measure of venous pressure) by either maintaining total intravascular volume, or increasing stressed volume (i.e., increasing venous tone); (2) optimizing cardiac performance; (3) redistributing perfusion to vital organs; and (4) optimizing unloading of oxygen at the tissues (Box 22.3, see eFig. 22.3).

Mean circulatory pressure (and venous return) are sustained in early shock by a number of mechanisms. Acutely, total intravascular volume is supported by alterations of capillary hydrostatic pressure as described by Starling.[288] Sympathetic activation results in precapillary vasoconstriction. In combination with initial hypotension, this results in decreased capillary hydrostatic pressure.[288] A decrease in capillary hydrostatic pressure enhances intravascular fluid shift owing to maintained plasma oncotic pressures. Transcapillary fluid influx after removal of 500 to 1000 mL blood volumes in humans can be as high as 2 mL/min with full correction of intravascular volume by 24 to 48 hours.[289] The intravascular volume may also be supported by the osmotic activity of glucose generated by glycogenolysis. Increased extracellular osmolarity results in fluid redistribution from the intracellular to the extracellular space.

Intravascular volume is also conserved by decreasing renal fluid losses. Renal compensatory mechanisms are of limited value in acute shock but can have more impact in the subacute phase. Decreased renal perfusion associated with reduced CO and afferent arteriolar constriction results in a fall in glomerular filtration rate and urine output. In addition, decreased renal perfusion pressure, sympathetic stimulation, and compositional changes in tubular fluid[144] result in renin release from the juxtaglomerular apparatus. Renin release leads to adrenal cortical release of aldosterone (via angiotensin II), which increases sodium reabsorption in the distal tubules of the kidney in exchange for potassium or hydrogen ion.[144] Angiotensin II also exerts a powerful direct vasoconstricting effect (particularly on mesenteric vessels) while increasing sympathetic outflow and adrenal epinephrine release.[290] As noted, vasopressin (antidiuretic hormone) release occurs through activation of right atrial low pressure. Angiotensin II augments this release by increasing sympathetic outflow. The release of vasopressin from the posterior pituitary results in water retention at the expense of osmolarity. Hyponatremia can result. Vasopressin, like angiotensin II, also results in vasoconstriction, particularly of the splanchnic circulation.[290]

Finally, increased sympathetic activity and release of adrenal epinephrine results in systemic venoconstriction, particularly of the venous capacitance vessels of the splanchnic circulation. This supports mean circulatory pressure and venous return by increasing stressed volume.

Increased sympathetic nervous system activity accounts for most of the enhancement of cardiac performance during shock. Local release of norepinephrine by sympathetic nerves and systemic release of epinephrine result in stimulation of cardiac α- and β-adrenergic receptors, resulting in increases of HR and contractility that optimize CO and support blood pressure. Angiotensin II may also exert direct as well as indirect (sympathetic stimulation) inotropic effects on myocardium. Improved cardiac function also results in decreased right atrial pressure, which tends to increase venous return.

Redistribution of blood flow during shock has already been discussed. Increased sympathetic vasoconstrictor tone, systemic release of epinephrine from the adrenals, vasopressin, endothelin, and angiotensin II cause vasoconstriction in all sensitive vascular

• BOX 22.3 Cardiovascular/Metabolic Compensatory Responses to Shock

1. Maintain mean circulatory pressure (venous pressure)
   - Volume
     - Fluid redistribution to vascular space (increased total vascular volume) from interstitium (Starling effect) from intracellular space (osmotic)
     - Decreased renal fluid losses
     - Decreased glomerular filtration rate
     - Increased aldosterone
     - Increased vasopressin
   - Pressure
     - Decreased venous capacitance (increased stressed volume) increased sympathetic activity
     - Increased circulating (adrenal) epinephrine
     - Increased angiotensin
     - Increased vasopressin
2. Maximize cardiac performance
   - Increase contractility
   - Sympathetic stimulation
   - Adrenal stimulation
3. Redistribute perfusion
   - Extrinsic regulation of systemic arterial tone
   - Dominant autoregulation of vital organs (heart, brain)
4. Optimize oxygen unloading
   - Increased RBC 2,3-DPG
   - Tissue acidosis
   - Pyrexia
   - Decreased tissue P_{O_2}

2,3-DPG, *2,3-Diphosphoglycerate;* P_{O_2}, *partial pressure of oxygen.*

beds, including skin, skeletal muscle, kidneys, and splanchnic organs.[145] Dominant autoregulatory control of blood flow spares brain and heart blood work from these effects. Redistribution of flow to these vital organs is the effective result.

The effects of decreased delivery of oxygen to the tissues during shock can be attenuated by local adaptive responses. Hypoperfusion and tissue ischemia result in local acidosis as the result of decreased clearance of CO_2 and anaerobic metabolism. Local acidosis results in decreased affinity between oxygen and hemoglobin at the capillary level.[144] The resultant rightward shift of the oxyhemoglobin dissociation curve allows greater unloading of oxygen from hemoglobin for a given P_{O_2}. Tissue ischemia is also accompanied by decreased tissue P_{O_2} (relative to normal), which further augments unloading of oxygen. Pyrexia associated with sepsis may also contribute to a rightward shift of the oxyhemoglobin dissociation curve, whereas hypothermia is associated with a leftward shift. For that reason, maintenance of normothermia during resuscitation from shock is helpful in optimizing oxygen unloading.

Organ System Dysfunction Owing to Shock (Table 22.3)

Central Nervous System

CNS neurons are extremely sensitive to ischemia. Fortunately, the CNS vascular supply is highly resistant to extrinsic regulatory mechanisms. Although cerebral perfusion is clearly impaired in shock, flow remains relatively well preserved until the later stages.[291,292] Absent primary cerebrovascular impairment, cerebral function is well supported until MAP fall below approximately 50 and 60 mm Hg.[293] Eventually, irreversible ischemic injury may occur to the most sensitive areas of the brain (cerebral cortex). Before this fixed injury, an altered level of consciousness, varying from confusion to unconsciousness, may be seen depending on the degree of perfusion deficit. Disturbances of acid/base/electrolytes may also contribute. Electroencephalographic recordings demonstrate nonspecific changes compatible with encephalopathy. Sepsis-related encephalopathy may occur at higher blood pressures (owing in part to the effects of circulating inflammatory mediators) and is associated with increased mortality.[294]

Heart

The major clinically apparent manifestations of shock on the heart are due to sympathoadrenal stimulation. Increased HR, in the absence of disturbances of cardiac conduction, is almost universally present. Vagally mediated paradoxical bradycardia may be seen on occasion in severe hemorrhage.[41] In patients predisposed to myocardial ischemia or irritability, catecholamine-driven supraventricular tachycardias and ventricular ectopy with ischemic electrocardiographic (ECG) changes are not common. Like the brain, the blood supply to the heart is autoregulated. This, in combination with the resilient nature of myocardial tissue, renders it resistant to sympathetically driven vasoconstriction and shock-related hypoperfusion injury. Overt necrosis does not typically occur, although evidence of cellular injury may be present.

Most forms of shock are associated with increased contractility of healthy myocardium. Despite this, shock can have substantial impact on myocardial contractility and compliance. Hypotension during cardiogenic (and other forms of shock) is associated with decreased coronary artery perfusion pressure. In patients with coronary artery disease (CAD) and/or increased filling pressures, decreased coronary artery perfusion pressure may lead to overt ischemia. Further, circulating myocardial-depressant substances contribute to myocardial depression in septic[233] and hemorrhagic[234] shock. This has been linked to decreased β-adrenoreceptor affinity and density as well as potential defects of intracellular signal transduction involving NO, G proteins, cyclic adenosine monophosphate (cAMP), and cGMP.[111] Circulating depressant substances may also be present during cardiogenic shock.[236]

TABLE 22.3 Organ System Dysfunction in Shock

Central nervous system	Encephalopathy (ischemic or septic) Cortical necrosis
Heart	Tachycardia, bradycardia Supraventricular tachycardia Ventricular ectopy Myocardial ischemia Myocardial depression
Pulmonary system	Acute respiratory failure Acute respiratory distress syndrome
Kidney	Prerenal failure Acute tubular necrosis
Gastrointestinal system	Ileus Erosive gastritis Pancreatitis Acalculous cholecystitis Colonic submucosal hemorrhage Transluminal translocation of bacteria/antigens
Liver	Ischemic hepatitis "Shock" liver Intrahepatic cholestasis
Hematologic system	Disseminated intravascular coagulation Dilutional thrombocytopenia
Metabolic	Hyperglycemia Glycogenolysis Gluconeogenesis Hypoglycemia (late) Hypertriglyceridemia
Immune system	Gut barrier function depression Cellular immune depression Humoral immune depression

Respiratory System

Early alterations of pulmonary function seen during acute circulatory shock are primary related to changes in central drive or muscle fatigue. Increased minute volume occurs as a result of augmented respiratory drive owing to peripheral stimulation of pulmonary J receptors and carotid body chemoreceptors as well as hypoperfusion of the medullary respiratory center. This results in hypocapnia and primary respiratory alkalosis.[144,295] With increased minute volume and decreased CO, the ventilation-perfusion ($\dot{V}/\dot{Q}$) ratio is increased. Unless arterial hypoxemia complicates shock, pulmonary resistance is initially unchanged or minimally increased. Coupled with an increased workload, respiratory and diaphragmatic muscle impairment related to hypoperfusion (manifested by decreased transmembrane electrical potential) may lead to early respiratory failure.[296] ARDS owing to inflammatory or free radical injury to the

alveocapillary cell layers after established shock may develop as a late cause of respiratory failure.

Kidney

ARF is a major complication of circulatory shock with associated mortality rates between 35% and 80%.[297] Although initial injury manifested by decreased urine output occurs, other clinical manifestations of renal dysfunction (increased creatinine, urea, and potassium) may not be noted for 1 to 3 days. Once hemodynamic stabilization has been achieved, it becomes apparent that urine output does not immediately improve and both serum creatinine and urea continue to rise. The single most common cause of ARF is renal hypoperfusion resulting in ATN. The most frequent cause of renal hypoperfusion is hemodynamic compromise from septic shock, hemorrhage, hypovolemia, trauma, and major operative procedures. ATN that occurs in the setting of circulatory shock is associated with a higher mortality than in other situations.

Part of the reason for the kidney's sensitivity to hypoperfusion relates to the nature of its vascular supply. The renal vascular bed is moderately autoregulated. Increases of efferent arteriolar tone can initially maintain glomerular perfusion despite compromise of renal flow.[298] Renal hypoperfusion does not become critical until relatively late in shock when maximal vasoconstriction of renal preglomerular arterioles[298] results in cortical, then medullary, ischemic injury.

Decreased urine output in shock can pose a diagnostic dilemma because it can be associated with both oliguric ATN and hypoperfusion-related prerenal failure without ATN. Indices suggestive of the latter include a benign urine sediment; urine sodium concentration less than 20 mEq/L; fractional urine sodium excretion less than 1%; urine osmolality greater than 450 mOsm/L; and urine/plasma creatinine ratio greater than 40. Useful markers of ARF owing to ATN include hematuria and heme granular casts; urine sodium concentration to more than 40 mEq/mL; fractional excretion of urine sodium to more than 2%; urine osmolarity less than 350 mOsm/L; and urine:plasma creatinine ratio less than 20.[299] Of note, ATN caused by circulatory shock may be associated with urine sodium less than 20 mEq/L and fractional excretion less than 1% if the acute renal injury is superimposed on chronic effective volume depletion as may be seen with cirrhosis and CHF.[300]

Gastrointestinal System

The gut is relatively sensitive to circulatory failure. The splanchnic vasculature is highly responsive to sympathetic vasoconstriction. Typical clinical gut manifestations of hypoperfusion, sympathetic stimulation, and inflammatory injury associated with shock include ileus, erosive gastritis, pancreatitis, acalculous cholecystitis, and colonic submucosal hemorrhage. Enteric ischemia produced by circulatory shock and free radical injury with resuscitation may breach gut barrier integrity with translocation of enteric bacteria and antigens (notably endotoxin) from the gut lumen to the systemic circulation, resulting in propogation and amplification of shock and MODS.[301,302]

Liver

Like the gut, the liver is highly sensitive to hypotension and hypoperfusion injury. "Shock liver," associated with massive ischemic necrosis and major elevations of transaminases, is atypical in the absence of extensive hepatocellular disease on very severe insult.[303] Centrilobular injury with mild increases of transaminases and lactate dehydrogenase is more typical. Transaminases usually peak within 1 to 3 days of the insult and resolve over 3 to 10 days. In either case, early increases in bilirubin and alkaline phosphatase are modest. Despite the production of acute-phase reactants in early circulatory shock, synthetic functions may be impaired with decreased generation of prealbumin, albumin, and hepatic coagulation factors. After hemodynamic resolution of shock, evidence of biliary stasis with increased bilirubin and alkaline phosphatase can develop even though the patient is otherwise improving. Postshock MODS involves similar hepatic pathology.

Hematologic System

Hemotologic manifestations of circulatory shock tend to be dependent on the nature of shock. Disseminated intravascular coagulation (DIC), characterized by microangiopathic hemolysis, consumptive thrombocytopenia, consumptive coagulopathy, and microthrombi with tissue injury, is most commonly seen in association with septic shock. Because it is due to simultaneous systemic activation of coagulation and fibrinolysis cascades, it can be differentiated from the coagulopathy of liver failure by determination of endothelial cell–produced factor 8 (normal or increased with hepatic dysfunction). In the absence of extensive tissue injury/trauma, hemorrhagic shock is rarely associated with DIC.[304] Dilutional thrombocytopenia is the most common cause of coagulation deficits after resuscitation for hemorrhage.[305]

Metabolic Alterations

Metabolic alterations associated with shock occur in a predictable pattern. Early in shock, when hemodynamic instability triggers compensatory responses, sympathoadrenal activity is enhanced. Increased release of adrenocorticotropic hormone, glucocorticoids, and glucagon and decreased release of insulin results in glycogenolysis, gluconeogenesis, and hyperglycemia.[287,306] Increased release of epinephrine results in skeletal muscle insulin resistance, sparing glucose for use by glucose dependent organs (heart and brain). Late in shock, hypoglycemia may develop, possibly owing to glycogen depletion or failure of hepatic glucose synthesis. Fatty acids are increased early in shock but fall later as hypoperfusion of adipose-containing peripheral tissue progresses. Hypertriglyceridemia is often seen during shock as a consequence of catecholamine stimulation and reduced lipoprotein lipase expression induced by circulating TNFα.[306] Increased catecholamines, glucocorticoids, and glucagon also increase protein catabolism resulting in a negative nitrogen balance.[306]

Immune System

Immune dysfunction, frequent during and after circulatory shock and trauma, rarely has immediate adverse effects but likely contributes to late mortality. Underlying mechanisms of immune dysfunction that induce dysfunction of the cellular and humoral immune system include ischemic injury to barrier mucosa (particularly of the gut), leading to anatomical breaches (colonic ulceration) and potential mucosal translocation of bacteria and bacterial products; parenchymal tissue injury owing to associated trauma, inflammation, ischemia or free radical injury; and direct ischemic or mediator (immunosuppressant cytokines, corticosteroids, prostaglandins, catecholamines, endorphins).[307,308] In particular, macrophage function is adversely affected during trauma and circulatory shock. A decrease in antigen presenting ability impairs the activation of T and B lymphocytes. Associated with this defect are a decrease in Ia antigen expression, decrease in membrane IL-1β receptors, and the presence of suppressor T lymphocytes. Phagocytic activity of the reticuloendothelial system is also compromised, partially because of an acute decrease in fibronectin levels.

Suppression of T-lymphocyte immune function is manifested by decreased responsiveness to antigenic stimulation and a decreased helper:suppressor ratio. Decreased production of IgG and IgM suggests B-cell suppression. Nonspecific immune suppression is expressed as decreased neutrophil bactericidal function, chemotaxis, opsonization, and phagocytosis.

Resuscitation agents used in shock may also substantially depress immune function. For example, red blood cell transfusion used in traumatic hemorrhagic shock and in support of oxygen transport in septic shock[309] has been shown to suppress immune function, leading to increased infections (and improved allograft survival).[310,311] Similarly, dopamine, used for hemodynamic support in shock, has been shown to suppress pituitary production of prolactin (required for optimal immune function), resulting in suppression of T-cell proliferative responses.[312] Thus dopamine may contribute, along with stress-induced increases in immunosuppressive glucocorticoids, to T-cell anergy seen in critically ill patients.

These factors may contribute to the propensity of critically ill patients to develop ongoing organ system dysfunction as well as a variety of infections during the postshock phase. It is notable that one-third to one-half of patients with shock die late in their course after resolution of the acute-shock phase.

Diagnostic Approach and Evaluation

Shock is always a life-threatening emergency. Diagnosis, evaluation, and management must often occur virtually simultaneously. The diagnosis must be made as early as possible while shock is well compensated. Once marked hypotension and hypoperfusion are present, mortality is increased. Because early recognition and treatment are key to survival, the diagnosis is primarily a clinical one. Laboratory and imaging studies are useful for confirmation of the diagnosis and determination of the specific shock etiology. Elevated lactate might help identify patients for whom the diagnosis of shock is not obvious clinically. However, therapy of shock should never be delayed to accommodate these studies. The initial diagnosis of shock can and should be made strictly on clinical signs and symptoms. Because shock is the common endpoint of a variety of insults, evaluation and management for all forms of shock involves a common approach (Box 22.4).

Clinical Evaluation

Impending shock is characterized by the typical compensatory response to cardiovascular stress. Tachycardia, tachypnea, and oliguria (<0.5 mL/kg per hour) are usually present. Cool extremities are seen in hypovolemic, cardiogenic, and obstructive shock. The blood pressure may be elevated or normal with maximal sympathetic stimulation. With progression, however, blood pressure falls while pulse pressure narrows (except in the case of distributive shock). Frank hypotension (MAP <60–65 mm Hg in adults) may ensue. The chronic level of blood pressure must be considered. Normotension in a normally hypertensive patient may denote a critical degree of hypoperfusion. With further progression anuria may develop, extremities may become mottled and dusky (except in distributive shock), and the sensorium may become clouded. It is important to note that clinical parameters can underestimate initial resuscitative requirements in critically ill subjects including those with septic shock.[313–316]

Other clinical manifestations of shock are useful in attempting to attempt to differentiate the etiology. Hypovolemic shock is characterized by decreased jugular venous pressure. Cardiogenic shock may evidence elevated jugular venous pressure with hepatojugular reflux, an S_3, an S_4, and regurgitant heart murmurs. Obstructive shock signs are usually dependent on the nature of the obstruction. Pulmonary embolus may be characterized by dyspnea and right-sided evidence of heart failure. Cardiac tamponade may demonstrate the Kussmaul sign, a pulsus paradoxus, and distant heart sounds. Septic shock in the absence of neutropenia usually exhibits a focus of infection along with fever, chills, and warm extremities. Patients with septic shock and neutropenia often have no clinically apparent focus. Elderly patients may present with little more than unexplained hyperventilation and hypotension.

• BOX 22.4 General Approach to Shock: Initial Diagnosis and Evaluation

- Clinical (primary diagnosis)
  - Tachycardia, hypotension (systolic blood pressure <90 mm Hg) tachypnea, oliguria, encephalopathy (confusion), peripheral hypoperfusion (mottled extremities), cyanosis
- Laboratory (confirmatory)
  - Hemoglobin, WBC, platelets
- Prothrombin time/partial thromboplastin time
  - Electrolytes, arterial blood gases, Ca, Mg, BUN, creatinine, serum lactate
  - ECG
- Monitoring (continuous ECG and respiratory monitors)
  - Pulse oximetry
  - Urinary catheter (urine output)
  - Point-of-care ultrasonography (heart, lung, abdominal, and major vessels)
  - Arterial pressure catheter
  - Central venous pressure monitor (uncomplicated shock)
  - Pulmonary artery flotation catheter
    - Cardiac output
    - Pulmonary artery occlusion pressure
    - Central and/or mixed venous oxygen saturation (intermittent or continuous)
  - Oximetry[a]
- Imaging (chest x-ray)
  - X-ray views of abdomen[a]
  - Computed tomographic scan: abdomen or chest[a]
  - Formal transthoracic and/or transesophageal echocardiogram[a]

[a]*Optional.*

BUN, *Blood urea nitrogen;* Ca, *calcium;* ECG, *electrocardiogram;* Mg, *magnesium;* WBC, *white blood cell.*

Laboratory Studies

Laboratory data are used to confirm the diagnosis of shock and to help clarify the etiology. Leukocyte count is frequently elevated early in shock owing to demargination of neutrophils. Leukopenia may be found in sepsis and late shock. Hemoglobin concentration is variably affected depending on the etiology of shock. For example, nonhemorrhagic hypovolemic shock and septic shock with extravasation of intravascular water to the interstitium may result in an apparent erythrocytosis. Platelet count increases acutely with the stress of circulatory shock, but with progression of sepsis or resuscitation of massive hemorrhage, thrombocytopenia may occur. Arterial blood gases and electrolytes may demonstrate a nonanion gap acidosis if hypovolemic shock is associated with excessive diarrhea and metabolic alkalosis if associated with vomiting. An anion gap acidosis, often caused by elevated levels of lactic acid, usually reflects prolonged inadequate tissue perfusion. Serum

creatinine and blood urea nitrogen are rarely changed after the acute onset of shock even if renal injury is present. With slower onset of shock—for example, in sepsis—increased creatinine is common and early resolution is an excellent marker of effective resuscitation and survival. Markers of renal function can also be helpful diagnostically. An isolated increased blood urea nitrogen with anemia and normal creatinine may suggest gastrointestinal bleeding. An arterial blood gas analysis will help to determine adequacy of oxygenation and give evidence of acid-base disturbances. An ECG is critical for diagnosis of ischemic cardiac injury either as a primary cause of cardiogenic shock or secondary to hypotension associated with shock of another etiology.

Lactate levels (particularly serial determinations) are useful in assessment of prognosis. Substantial data suggest that lactate levels, as a marker of tissue oxygen debt, can predict outcome in shock.[46,47,317–321] The utility of lactate assessment is limited by the fact that it is a relatively late marker of tissue hypoperfusion.[322,323] Significant tissue ischemia and injury are present by the time it is elevated. In addition, lactate is cleared primarily by the liver. Liver failure may markedly increase elevated lactate levels during hypoperfusion. Conversely, normal hepatic clearance may obscure limited lactate production by ischemic tissues. Glycolysis and alkalosis will also nonspecifically increase lactate levels.[324,325] However, because in the appropriate setting, arterial lactate levels beyond 2 mEq/L are associated with increased mortality,[47,51,319,320,326] such levels should be considered to represent tissue ischemia in the absence of another clearly defined etiology. The adequacy of resuscitation of shock can also be assessed using serial changes of systemic lactate.[321,326,327] A protocol of resuscitation using a goal of lactate clearance greater than or equal to 10% versus a target of central venous oxygen saturation ($cSvO_2$) greater than or equal to 70% was found to be noninferior.[328] Therefore reduction in lactate concentration after initial management is a reassuring indicator of adequacy of resuscitation and serial lactate measurement can replace more invasive monitoring for certain cases.

$cSvO_2$ can also be used to assess prognosis and efficacy of resuscitation in shock states including septic shock.[309,316,329,330] However, central venous saturation, which has been suggested to represent a reliable marker of resuscitation efficacy in sepsis,[309] does not appear to correlate well with lactate clearance in some sepsis studies, perhaps reflecting elements other than oxygen debt in those conditions.[327] Poor correlation with mixed venous oxygen saturation has also been noted in septic shock.[331] Achievement of central venous saturation of 70% or higher was less predictive of good outcome in septic shock compared with lactate clearance of 10% or higher.

Imaging

A chest radiograph is useful in ruling out pneumonia as a source of septic shock, pulmonary edema as a manifestation of cardiogenic shock, tension pneumothorax, pericardial tamponade, and so on. Although abdominal views may be helpful on occasion, intra-abdominal processes resulting in shock are usually clinically apparent. Computed axial tomograms may be helpful in directing management in specific instances (occult internal hemorrhage, aortic dissection, pulmonary embolus). Similarly, transthoracic and transesophageal echocardiography can diagnose specific repairable cardiac or aortic lesions associated with shock with great accuracy and can be highly suggestive of other important diagnoses, including hemodynamically significant pulmonary embolus. Other imaging modalities have less of a role in the evaluation of acute shock.

Invasive Hemodynamic Monitoring

All patients suspected of having circulatory shock should have an indwelling arterial pressure catheter placed. Although there are no randomized controlled trials showing benefit of arterial pressure catheters, we believe there are reasonable grounds to use them in shock.[332] Blood pressure assessment by manual sphygmomanometry or automated noninvasive oscillometric techniques may be inaccurate during shock owing to marked peripheral vasoconstriction.[333] In addition, neither technique supplies continuous monitoring of the rapidly changing hemodynamic status of unstable patients. Further, an arterial catheter allows ready access for arterial blood gas samples and other laboratory tests. In most cases, a peripheral site, such as the radial artery, is used. However, given the potential for disparity of pressures between central and peripheral sites,[334] if marked peripheral vasoconstriction caused by either sympathetic stimulation or exogenous catecholamines obscures the peripheral pulses, a central site such as the femoral artery may be preferred.

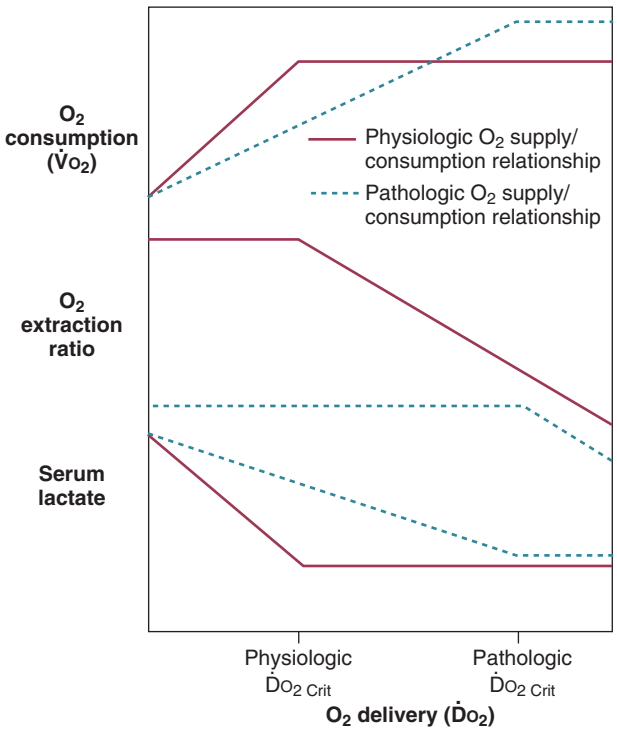
CVP monitoring is frequently used during the perioperative period for assessment of intravascular volume status in patients without critical illness. Because of the relatively stable hemodynamic status of these patients and the questionable benefit of pulmonary artery catheterization in such patients, such an approach is adequate. Similarly, CVP monitoring for otherwise healthy patients being resuscitated for hypovolemic shock may provide useful data. In the appropriate clinical context, CVP monitoring may also occasionally be useful in differentiating between different forms of shock (e.g., low CVP in hypovolemic shock, high CVP in cardiac tamponade). As a rule, though, CVP monitoring is inadequate for the hemodynamic assessment of critically ill patients, particularly those with shock. A number of studies have conclusively shown that CVP does not accurately estimate left ventricular preload in critically ill patients.[335,336] In fact, data suggest that static measures of CVP do not correlate with right or left ventricular volumes in normal volunteers.[337]

The use of the flow-directed balloon-tipped pulmonary artery catheters (PACs) with thermodilution CO determination capability has been the standard of practice for the hemodynamic assessment of circulatory shock. Their use is supported by a number of studies that demonstrate that experienced physicians cannot accurately determine cardiac filling pressures or CO based on clinical evaluation alone.[338,339] In addition to CO determination, PACs provide continuous monitoring of central venous and pulmonary artery waveforms and pressures. Pulmonary artery occlusion pressure (as an estimate of left ventricular end-diastolic pressure and volume) and waveform can be obtained intermittently. Although substantially supplanted by the increased availability of bedside echocardiography in developed nations, waveform analysis may be useful in cardiovascular diagnoses of cardiac tamponade, restrictive cardiomyopathy, CHF, ventricular hypertrophy, and mitral or tricuspid regurgitation if echocardiography access is limited. In addition, PACs can demonstrate evidence of right heart and pulmonary artery oxygen saturation step-ups for the diagnosis of left-to-right shunts associated with cardiac anatomic abnormalities such as ventricular septal defect. These devices also allow withdrawal of blood from the pulmonary artery enabling determination of MvO_2 to verify sufficient oxygen delivery during hypodynamic shock. In shock, the flow-directed balloon-tipped PAC is useful for etiologic classification, determination of optimal management, and to follow the response to therapy. Typical hemodynamic profiles of different forms of shock have been described in Table 22.1.

The utility of pulmonary artery catheterization has been questioned over the past decade. A case-matched study suggested increased resource utilization and mortality associated with the use of PACs in the ICU.[340] A series of randomized studies performed since then have reported on the role of the PAC in the setting of major non-cardiac surgery,[341] CHF,[342] sepsis and ARDS,[343] acute lung injury,[344] and in the general ICU setting.[345,346] In the perioperative management of patients undergoing major noncardiac surgery, the use of a PAC did not impact mortality and was associated with a greater incidence of pulmonary embolism.[341] In critically ill patients diagnosed with CHF, management directed with the use of a PAC did not influence mortality but resulted in more in-hospital adverse events.[342] Another study comparing the use of PAC versus central venous monitoring in acute lung injury found no difference in organ failure or mortality.[344] A large trial evaluating the role of the PAC in the management of patients with ARDS secondary to sepsis also found no significant differences in mortality if a PAC was used or not.[343] Two randomized studies of general ICU patients similarly concluded that the use of PACs among critically ill patients neither increased nor decreased mortality.[345,346] Most, although not all, meta-analyses have shown no consistent benefit with PACs.[347–350] These studies failing to show a lack of clinical benefit have been paralleled by other studies questioning some of the basic premises of PAC utility. Several studies have shown a lack of correlation between PAOP/CVP and ventricular volumes in the critically ill.[351,352] One study has even demonstrated that PAOP and CVP fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal volunteer subjects.[337] Despite these data, no studies have examined the use of PACs in cases of shock specifically. Nonetheless, the use of PACs in the United States has decreased dramatically over the past 20 years.[353]

Given the lack of evidence of benefit of PACs and alternative diagnostic and monitoring tools such as bedside ultrasonography, we believe that PACs should not be routinely inserted in shock. However, there is still room for PACs in cases of mixed shock, right ventricular failure, or in instances when the diagnostic evaluation including bedside ultrasonography cannot reveal the cause of the shock.

Another parameter provided by a PAC is mixed venous oxygen saturation. Compared with $cSvO_2$, which reflects mixed oxygen saturation from the superior vena cava, MvO_2 reflects a global picture of oxygen extraction. This measure may provide an assessment of adequacy of resuscitation of low output states before the presence of anaerobic metabolism (as signified by increased lactate). MvO_2 rises with increases of perfusion above requirements and falls, with increasing oxygen extraction ratio, as perfusion becomes inadequate (see Fig. 22.3). Normal MvO_2 falls within the 65% to 75% range. During MI saturations of less than 60% are found with CHF and less than 40% with cardiogenic shock.[330] Lactate accumulation and supply-dependent oxygen consumption begin to appear as saturation levels fall below 30% to 40%.[354,355] MvO_2 is especially useful in determining whether low COs indicate supply-dependent oxygen consumption (MvO_2 low) or normally depressed metabolic demands (normal MvO_2). Owing to the maldistribution of perfusion in distributive shock (or substrate utilization defect in septic shock) and left-to-right shunting in cardiogenic shock associated with ventricular septal defects, MvO_2 is not useful in assessment in those conditions. Recently $cSvO_2$ has been proposed as an alternate method to examine adequacy of resuscitation, although correlation with MvO_2 is imperfect in septic shock.[309,316,331]



• **Fig. 22.3** Oxygen supply–dependent oxygen *(O_2)* consumption in shock. Physiologic supply-dependent oxygen consumption is characterized by a biphasic relationship between oxygen delivery *($\dot{D}O_2$)* and oxygen consumption *($\dot{V}O_2$)*. The inflection point defines the physiologic critical oxygen *delivery ($\dot{D}O_{2crit}$)*. Below this $\dot{D}O_{2crit}$, $\dot{V}O_2$ is linearly dependent on $\dot{D}O_2$, the oxygen extraction ratio is maximal, and lactate (indicating anaerobic metabolism) is produced. Above the physiologic $\dot{D}O_{2crit}$, $\dot{V}O_2$ is independent of $\dot{D}O_2$, the oxygen extraction ratio varies to maintain a constant $\dot{V}O_2$, and lactate is not produced.

Oxygen delivery and oxygen consumption variables can also be determined using PAC-derived data. Although such global perfusion data appear to have prognostic significance for large groups of the critically ill, their utility is limited when applied to individual patients.

Recent modifications to the standard pulmonary artery flotation catheter allow continuous monitoring of MvO_2 or determination of right ventricular ejection fractions and volumes. Although both innovations have been used for clinical research purposes and each theoretically offers unique insights into shock, they have no defined role at this time in clinical shock management.

Ancillary Monitoring Techniques

Oximetry

Because oxygen delivery is dependent on arterial oxygen saturation, pulse oximetry should, in theory, provide useful data during circulatory shock. However, limitations of the technique include the fact that ambient light sources, dyhemoglobinemias (methemoglobin, carboxyhemoglobin), lipemia, and hypothermia can affect results.[356] Motion artifact may generate a false signal.[357] Shock-associated vasoconstriction also impairs signal acquisition. One study has shown that a CI less than 2.4 L/min per m^2 is associated with signal loss.[358] Although these problems limit the utility of pulse oximetry in the acute management of circulatory shock, the technique may be more helpful during postresuscitation monitoring.

At this time, sequential arterial blood gases provide more reliable data during acute shock.

Ultrasound/Echocardiography

The application of point-of-care (POC) ultrasound in the ICU environment as diagnostic and intermittent monitoring tools may represent one of the most exciting developments in critical care management. A number of factors have hastened this development. These include questions regarding the safety and efficacy of routine PAC utilization; the availability of relatively inexpensive, portable echocardiography systems; the application of advanced software algorithms to analysis of data; and the development of new, high-resolution echocardiographic techniques, including transesophageal and contrast echocardiography. The confluence of these factors has resulted in a substantial increase in use of echocardiography in the ICU for assessment of hemodynamic instability and shock. In addition to its long-recognized ability to detect anatomic lesions (pericardial tamponade, pericardial effusion, septal defects, valvular disease, aortic dissection), new techniques allow assessment of CO, SV, preload (ventricular volumes), intravascular volume status (inspiratory inferior caval collapse), pulmonary artery pressures, systolic contractility (ejection fraction), diastolic function, and regional motion abnormalities at baseline and under stressed conditions.[359] Utility for diagnosis of hemodynamically significant pulmonary embolism has also been established.[360] The widespread dissemination of echocardiographic skills among the next generation of intensivists has allowed for a substantial reduction in use of invasive monitoring techniques including pulmonary artery catheterization. Multiple different algorithms have been developed for the use of POC ultrasound in shock, including Rapid Ultrasound for Shock and Hypotension (RUSH) and Abdominal and Cardiac Evaluation with Sonography in Shock (ACES).[361,362]

As part of these algorithms, heart, lungs, abdomen, and large vessels are usually examined. Views of the heart are examined to look for signs of pericardial effusion and tamponade. The overall size and contractility of the right and left ventricles are appreciated. Left ventricle hypokinesis is suggestive of cardiogenic shock, and the presence of regional wall motion abnormalities should raise the suspicion of a coronary artery lesion. Right ventricular dilatation and hypokinesis may suggest pulmonary embolism or right ventricular infarction. The size of the inferior vena cava as well as respiratory variation can give an estimation of CVP as well as fluid responsiveness. Lung ultrasound can be used to identify pneumothorax with the absence of lung sliding and lung pulse and presence of a lung point. It is also useful to identify B-lines that represent interstitial fluid, which could represent pulmonary edema or pneumonia. Evaluation of the pleural space is more accurate with ultrasound than with standard chest radiography. Abdominal ultrasound is useful to identify free fluid in the peritoneum that might be the source of hypovolemic shock, for example, in trauma. Evaluation of the abdominal aorta is very accurate to identify abdominal aortic aneurysm. Finally, compression ultrasonography of the femoral veins can quickly identify proximal deep venous thrombus.

A POC ultrasonography examination of heart, lung, abdomen and great vessels should take only a few minutes and can often quickly diagnose the cause of shock. It can be repeated after therapeutic interventions (fluid bolus, inotropes). It should be remembered that ultrasonography is very operator dependent. Thus clinicians should ensure they are competent in POC ultrasound before basing their clinical decision on their ultrasound findings.[363] If there is a suspicion of a diagnosis not easily seen on POC ultrasound, such as valvular abnormalities or intracardiac shunt, formal transthoracic or transesophageal echocardiography should be obtained.

Management and Therapy

Patients in whom circulatory shock is suspected should be managed in an ICU with continuous ECG monitoring and close nursing support. Those whose etiologic diagnosis is in doubt, whose hemodynamic instability does not quickly resolve with IV fluids, or whose conditions are medically complicated should undergo invasive hemodynamic monitoring with arterial and central venous catheters or PACs. POC ultrasonography should generally be performed. Laboratory tests as mentioned earlier should be performed at or before admission.

Management of shock can be divided into specific therapy for the triggering injury and general therapy of the shock syndrome. Examples of specific therapy include antibiotics for infections causing septic shock, blood transfusion for hemorrhagic shock, thrombolysis for acute MI or massive pulmonary embolus, and pericardial aspiration for pericardial tamponade. Specific therapy for different etiologies of shock is discussed in Chapters 23 and 26.

Aims

Because the shock syndrome shares many characteristics across different etiologies, the general management of shock is similar in all cases. The basic goal of circulatory shock therapy is the rapid restoration of effective perfusion to vital organs and tissues before the onset of cellular injury. Effective tissue perfusion is dependent on both sufficient CO and adequate driving pressure. Consequently, ideal therapy of shock requires early reestablishment of both an appropriate CI and mean blood pressure (Box 22.5). However, because for brief periods marked hypoperfusion is better tolerated than severe hypotension, the first specific resuscitative aim—support of blood pressure (>60–65 mm Hg in a baseline normotensive

• BOX 22.5 General Approach to Shock: Immediate Goals

General
- Find cause of shock and apply specific treatment (examples: antibiotics for sepsis or pericardiocentesis for tamponade)

Hemodynamic
- MAP >65 mm Hg (higher in the presence of coronary artery disease or chronic hypertension)
- CVP = 8–12 mm Hg/PAOP = 12–15 mm Hg (may be higher for cardiogenic shock)[a]
- CI >2.1 L/min per m^2[a]

Optimization of oxygen delivery
- Hemoglobin >7–9 g/dL; >7 g/L after shock is sufficient
- Arterial saturation > 92%
- Mvo_2 > 60%, sCV02 > 70%*
- Normalization of serum lactate (to <2.2 mM/L)

Reverse organ system dysfunction
- Reverse encephalopathy
- Maintain urine output >0.5 mL/kg per hour

[a]*Optional.*

CI, *Cardiac index;* CVP, *central venous pressure;* MAP, *mean arterial pressure;* Mvo_2, *mixed venous oxygen saturation;* PAOP, *pulmonary artery occlusion pressure.*

patient)—may initially take priority over the second specific aim—maintenance of CI. The blood pressure goal target has traditionally been MAP greater than 65 mm Hg. A recent randomized controlled trial in septic shock failed to show benefit for a MAP goal of 80 to 85 mm Hg versus 65 to 70 mm Hg with more atrial fibrillation in the higher MAP goal. For patients with chronic hypertension, a higher MAP goal was associated with less renal replacement therapy but similar mortality.[364] Based on these data, a MAP greater than 65 mm Hg for most patients is reasonable. Finally, maintaining perfusion sufficiently high that arterial lactate concentration remains below 2.2 mmol/L is a generally accepted approach to avoiding anaerobic metabolism and ischemic tissue injury (Box 22.5).

The practice of targeting oxygen delivery to specified supranormal oxygen delivery goals or to evidence of supply-independent oxygen consumption in the ICU has been substantially discredited by clinical studies.[365–368] In an earlier study, early targeting (<6 hours after presentation) to a $cSvO_2$ of greater than 70% using a defined protocol with fluids, blood transfusion, and dobutamine support has been shown to improve outcome in severe sepsis and septic shock.[309] However, three more recent randomized controlled trials have shown that this protocol is not superior to standard treatment.[369–371]

The reasons for the discrepancy between the initial study by Rivers and the latest three randomized controlled trials are not totally clear.[309] However, it appears that the standard of care for septic shock has shifted in recent years to earlier recognition and aggressive early management, which might have decreased the relative benefit of the early goal-directed therapy protocol.

One of the major achievements in shock therapy in the past decade has been the recognition that speed of implementation of supportive and specific therapies may be critical to improvement in outcomes. This concept of a "golden hour" has long been recognized in the context of specific and resuscitative therapy of trauma-induced hypovolemic shock with blood products and surgical management[372,373] and then cardiogenic shock owing to MI with emergent primary angioplasty or thrombolysis.[374] In recent years, a similar rapid treatment paradigm has been established for thrombolytic therapy for obstructive shock caused by a massive pulmonary embolus.[81,82,375] Similarly, rapid fluid resuscitation (<6 hours)[309] and antimicrobial therapy (<1 hours)[376–378] have been shown to be key to maximizing survival in severe sepsis and septic shock. Accelerated provision of effective therapy probably accounts for reports of improved clinical outcomes with medical emergency response teams.[379–381] The variation in baseline provision of effective therapy likely accounts for the inconsistent results seen with such teams.[382] The importance of early aggressive resuscitative and specific therapy of all shock states cannot be sufficiently emphasized.

Resuscitation

The universal basics of resuscitation underlie the initial management of circulatory shock. Because many patients with circulatory shock may have accompanying trauma and/or decreased level of consciousness, the ventilatory status of the patient must be secured. This may involve tracheal intubation and/or mechanical ventilation, if necessary. Oxygen should be provided at a sufficiently high concentration to provide an arterial oxygen saturation of greater than 90% to 92%. Unintubated patients may require high-flow (30–45 L/min) or rebreathing oxygen delivery systems because many patients have unusually high minute ventilation volumes. Intubated patients should initially receive full ventilatory support to decrease systemic oxygen demand. Given that pulmonary infiltrates (aspiration, pneumonia, or ARDS) are common, positive end-expiratory pressure may be necessary to ensure adequate oxygenation. Potential adverse hemodynamic effects from positive-pressure ventilation (related primarily to decreased venous return) may be seen but can be minimized by fluid loading so that the patient is euvolemic or modestly hypervolemic.

Depending on the clinical situation, pain management may be necessary. Again, potential adverse hemodynamic effects may be seen if intravascular volume is inadequate because all measures result in some degree of venodilation either directly or by decreasing sympathetic tone. Two- to 4-mg boluses of IV morphine are recommended. During circulatory shock clearance of morphine by the liver may be impaired owing to hepatic hypoperfusion. In addition to relieving pain, analgesia should also decrease systemic oxygen consumption.

Management of lactic acidosis that develops during circulatory shock is problematic. Bicarbonate therapy may have adverse effects on intracellular pH even while improving the pH of the extracellular fluid. Further, even when pH is extremely low, bicarbonate therapy does not improve systemic hemodynamics in shock associated with acidosis.[383] In addition, increasing serum pH may adversely affect the oxyhemoglobin dissociation relationship. The optimal approach to the management of lactic acidosis is to improve organ and systemic perfusion so that anaerobic metabolism is limited and the liver and, to a lesser extent, kidneys can clear the accumulated lactate. If this is not effective, restricting the use of sodium bicarbonate to situations in which pH is less than 7.1 to 7.15 may be appropriate.

Initial management of circulatory shock should almost always include a crystalloid fluid challenge. In the absence of invasive monitoring with a PAC, the only practical exception is if clinical evidence strongly suggests ventricular filling pressures are already elevated. This is usually limited to clinical situations involving cardiogenic shock and marked pulmonary edema. Even then, if pulmonary edema is manageable, crystalloid challenge may be appropriate. The volume of the challenge is variable. Large volumes, on the order of 1 to 2 L given rapidly (0.5–1.0 L every 10–15 minutes) are frequently used in hemorrhagic and septic shock. Boluses of 100 to 200 mL may be used during cardiogenic shock. If shock does not resolve promptly after the initial fluid challenge, patients should undergo more detailed invasive (central venous catheter) and/or noninvasive (echocardiographic) assessment. As previously discussed, a central role for pulmonary artery catheterization in shock is now highly questionable.

Although aggressive fluid resuscitation is well accepted in the therapy of shock, emerging data support more limited resuscitation in some contexts. Resuscitation to the lower limit of normal targets (target systolic blood pressure 90–100 mm Hg) has been recommended in hemorrhagic shock resulting from penetrating trauma based on data showing improved survival using this approach.[378,384] In addition, a limited fluid resuscitation protocol for 7 days has been shown to improve the number of ventilator- and ICU-free days in acute lung injury without increasing the prevalence of shock or the mortality rate.[385] A more limited early fluid resuscitation has also been shown to be associated with improved survival in children with shock associated with infection in underresourced settings.[386]

Although fluid is generally given as the first treatment, reassessment of fluid is needed throughout the resuscitation. Multiple static and dynamic predictors of fluid responsiveness have been used. CVP of 8 to 12 mm Hg has traditionally been a target in

shock management, but CVP is not a great predictor of fluid responsiveness and many factors influence the CVP value. Response to rapid infusion of fluid or passive leg raise seems to predict fluid responsiveness better than CVP, but the sensitivity of the test is better if CO is monitored rather than simply blood pressure or pulse pressure. In passive mechanically ventilated patients, pulse pressure variation and systolic pressure variation can be used. POC measurement of inferior vena cava (IVC) can be helpful with IVC variation of 50% or greater in unintubated patients and 12% to 18% and more in intubated patients associated with fluid responsiveness.[387,388]

In addition, substantial controversy exists regarding the appropriate use of crystalloid and colloid fluids after initial resuscitation attempts. The basis of this controversy lies with the differing oncotic properties of the fluids. Crystalloid fluids (such as normal saline solution and lactated Ringer solution) contain sodium chloride in a quantity that closely matches extracellular fluid. No large molecules are present. Thus such fluids distribute into the extracellular space. Colloids, in addition, contain albumin or large osmotically active carbohydrates (hydroxyethylstarch, dextran) that may be held within the intravascular space, resulting in an increase of the plasma oncotic pressure. It has been suggested that in shock associated with microvascular changes of permeability (such as sepsis), colloid fluids remain in the intravascular space, leading to decreased tissue edema and noncardiogenic pulmonary edema.[389] However, the limited human studies available suggest that although radiographic infiltrates may appear more severe with crystalloid resuscitation of sepsis, gas exchange is comparable to colloid resuscitation.[42]

More importantly, it has been proposed that colloids may provide better outcomes in the resuscitation of shock because of the rapidity and persistence of volume expansion compared with crystalloid infusion.[42,390] However, clinical studies for the most part have not supported this contention. For the most part, meta-analyses have failed to demonstrate clinical outcome superiority of crystalloids compared to either albumin or synthetic colloids.[391] In fact, one meta-analysis of randomized controlled studies examining the effect of fluid administration in critically ill patients with burn injury, hypovolemia, or hypoalbuminemia suggested increased mortality in patients treated with colloids.[392] In one large randomized study of albumin versus normal saline solution, there was no benefit to albumin. A trend toward improved outcomes with albumin in severe sepsis and saline solution in trauma failed to reach significance in that study.[393] A more recent study of albumin versus crystalloid in severe sepsis also failed to show any benefits to albumin. More recently, a substantial body of literature has shown that synthetic colloids increase the risk of renal injury and death, particularly in sepsis and septic shock.[394–396] An increased risk of renal injury/dialysis requirement and risk of death was shown for hydroxyethylstarch versus Ringer solution therapy in two large randomized trials of sepsis.[394,395] Some data, however, suggest colloid resuscitation may clear lactate more quickly and result in less renal injury than crystalloid in penetrating trauma.[397] Given the much higher costs of colloids and higher risk of renal injury and death with synthetic colloids, resuscitation of shock should generally focus on crystalloid solutions. Albumin can be considered in septic shock for volume replacement in patients who need substantial amount of crystalloid.[398]

During hemorrhagic shock, fluid resuscitation should consist mostly of blood products. Crystalloids are only acceptable if blood products are unavailable. Controversy exists on the exact ratio of packed red blood cells, fresh frozen plasma, and platelets. Observational studies suggested that a ratio of 1:1:1 was superior.[399] A recent randomized controlled trial of a 1:1:1 versus 1:1:2 transfusion ratio of platelets:plasma:packed red blood cells showed no significant differences in mortality at 30 days. However, more patients achieved hemostasis and fewer died of exsanguination in the 1:1:1 group.[400]

With respect to hemoglobin, one randomized trial has suggested that a hemoglobin level of 70 g/L is sufficient for most patients in the ICU (other than those with high severity of illness or acute coronary syndrome[401,402]). Although several other studies have noted the potential risks associated with blood transfusion in the ICU setting,[311,403–405] no study has directly examined hemoglobin requirements during shock. The only study to (indirectly) examine blood transfusion in shock suggested that early augmentation of hematocrit to more than 30% during septic shock as part of a protocol to drive $cSvO_2$ to more than 70% was associated with improved survival.[309] For that reason, it is reasonable to recommend that a hemoglobin level of 90 to 100 g/L be maintained during acute shock.

Once intravascular volume is optimized, the next line of therapy of circulatory shock usually involves inotropes and vasopressors. Alternately, vasopressors may be occasionally required for brief periods of blood pressure support in extremely hypotensive patients before initiation of fluid infusion.

Three major classes of agents are used clinically for inotropic or vasopressor support in critically ill patients: sympathomimetics, phosphodiesterase inhibitors, and vasopressin (antidiuretic hormone) (Table 22.4). Sympathomimetics (catecholamines) may activate cardiac β_1- and α-adrenoreceptors, peripheral vascular α- or β_2-receptors, and vascular dopaminergic receptors. Cardiac β_1-adrenoreceptors augment HR and myocardial contractility by increasing activity of adenylate cyclase, resulting in increased generation of c AMP.[406] α-Receptors act through phospholipase C production of inositol triphosphate and diacylglycerol.[407–409] Peripheral vascular α-receptors cause vasoconstriction, whereas peripheral β_2-adrenoreceptors induce a mild vasodilatation. Cardiac α-adrenoreceptors contribute to increased contractility (but not HR) when stimulated.[407,409] Dopaminergic adrenoreceptors, mediating dilatation, are found in the arterial vessels supplying vital organs (including the heart, brain, kidneys, and splanchnic organs).[410] Phosphodiesterase inhibitors such as amrinone and milrinone augment cardiac contractility by inhibition of cAMP degradation. They also relax vascular smooth muscle.[411] Despite a long history of digitalis use in the management of CHF and older data suggesting potential hemodynamic benefit in sepsis,[412] cardiac glycosides are rarely used for the acute management of circulatory shock because of their narrow therapeutic index and long half-life. Recent uncontrolled studies have shown that endogenous vasopressin concentrations may be relatively deficient in shock states and that infusion of vasopressin (which has little effect in healthy, normotensive subjects), can have a profound pressor effect during vasodilatory shock.[413–416]

Norepinephrine, an endogenous catecholamine, exerts both powerful inotropic (cardiac alpha and β_1-adrenoreceptors) and peripheral vasoconstriction effects (α-adrenoreceptors). It is currently the favored catecholamine for initial management of shock. It can be used for persistent hypotension despite high-dose dopamine during septic and obstructive shock. It should generally be used only transiently in cardiogenic shock because it may drastically reduce forward flow. Similarly, it should not be required during hemorrhagic shock except for extremely brief periods of blood pressure support pending volume infusion. Infusion rates of 2 to 20 μg/min are commonly used, but if necessary higher rates may be tried. Suggestions that there is clinical utility in the concomitant use of "low"-dose dopamine with norepinephrine to generate

TABLE 22.4 Relative Potency of Intravenously Administered Vasopressors/Inotropes Used in Shock[a]

		CARDIAC		PERIPHERAL VASCULATURE			
Drug	Dose	Heart Rate	Contractility	Vasoconstriction	Vasodilation	Dopaminergic	Typical Clinical Use
Dopamine	1–4 μg/kg/min 5–10 μg/kg/min 11–20 μg/kg/min	1+ 2+ 2+	1–2+ 2+ 2+	0 1–2+ 2–3+	1+ 1+ 1+	4+ 4+ 4+	All shock
Norepinephrine	0.01–0.3 μg/kg/min	2+	2+	4+	0	0	Refractory shock
Dobutamine	1–20 μg/kg/min	1–2+	3+	1+	2+	0	CHF; cardiogenic, obstructive and septic shock
Dopexamine[b]	0.5–6 μg/kg/min	2+	1+	0	3–4+	4+	CHF; cardiogenic shock
Epinephrine	0.05–0.2 μg/kg/min	4+	4+	4+	3+	0	Refractory shock or anaphylactic shock
Phenylephrine	0.1–1 μg/kg/min	0	1+	4+	0	0	Neurogenic or septic shock
Isoproterenol	1–8 μg/min	4+	4+	0	4+	0	Cardiogenic shock (bradyarrhythmia), torsades de pointes, ventricular tachycardia
Vasopressin	0.02–0.04 U/min	0	0	4+	0	0	Vasodilatory (e.g., septic) shock
Milrinone	37.5–75 μg/kg bolus over 10 min; 0.375–0.75 μg/kg/min infusion	1+	3+	0	2+	0	CHF; cardiogenic shock

[a]The 1 to 4+ scoring system represents an arbitrary quantitation of the comparative potency of different vasopressors/inotropes.
[b]Not clinically released in the United States.
CHF, Congestive heart failure.

sparing of pressor and shock-associated renal injury has been refuted.[417–419]

Dopamine has fallen out of favor as the initial vasopressor used for circulatory shock. A central and peripheral nervous system neurotransmitter and the biologic precursor of norepinephrine, dopamine stimulates three different receptors; vascular dopaminergic, cardiac β_1, and vascular α. In addition, part of dopamine's myocardial effects are mediated by release of endogenous norepinephrine. Dose-dependent maximal stimulation of each of each of dopamine's target receptors has been suggested to result in different typical hemodynamic responses at different infusion rates. At infusion rates of less than 4 to 5 μg/kg per minute, dopaminergic effects have been said to dominate, but studies suggest this has little clinical relevance (although in the past it was the theoretical basis for use of low-dose dopamine for renal protection).[417,418] Vascular dopamine 2 receptors vasodilate the renal, mesenteric, myocardial, and cerebral vascular beds. In addition, renal dopamine 1 receptors mediate a mild natriuresis.[420] β-Adrenoreceptor–mediated cardiac inotropic effects have been suggested to dominate at doses below approximately 10 μg/kg per minute with α-adrenoreceptor vasopressor effects more prominent at doses above 10 μg/kg per minute.[410] It is important to note, however, that dopaminergic and cardiac adrenergic effects are not suppressed at higher doses but rather that additional effects are seen. In addition, there is substantial interindividual variation in response, with some showing substantial vasopressor or inotropic responses at low infusion rates. For management of circulatory shock, dopamine is often started at 5 μg/kg per minute and increased rapidly (5 μg/kg per minute every 2 or 3 minutes) to a maximum of 20 μg/kg per minute until the target blood pressure is reached. If vasopressor effects are inadequate at these infusion rates, norepinephrine infusion is begun. In a randomized controlled trial in patients with shock, norepinephrine and dopamine were similar in regard to mortality. Dopamine was associated with more adverse effects including tachyarrhythmias and subgroup analysis suggested higher mortality for dopamine in the cardiogenic shock subgroup.[421]

Dobutamine, which is structurally derived from isoproterenol, is a racemic mixture of two synthetic stereoisomers. In combination, the stereoisomers result in increased myocardial contractility through α and β_1 cardiac adrenoreceptors.[422,423] Weak arteriolar vasodilatory effects are mediated through dominance of β_1-adrenoreceptor–mediated vascular relaxation over α-adrenoreceptor–mediated vasoconstriction in the arterial circulation. Evidence suggesting that dobutamine induces vasoconstriction in the systemic venous bed (resulting in increased mean circulatory pressure and augmentation of venous return/CO) implies that α-adrenoreceptor–mediated effects may be dominant in small capacitance vessels.[162,422,423]

Although its hemodynamic effects are otherwise similar to isoproterenol, dobutamine has been reputed to exert minimal chronotropic effects.[422,424] This attribute has been questioned in recent studies[425] and may have been based on the selection of CHF patients with β-adrenoreceptor downregulation and other potential alterations of adrenoreceptor signal transduction.[424,426] Dobutamine's powerful inotropic effect is due to a combination of its direct effect on myocardial contractility, its afterload reducing effect, and α-adrenoreceptor–mediated venoconstriction.[422,424] In contrast to dopamine, it causes a reduction in filling pressures and a greater increase in CO at equivalent doses.[427,428] In addition, although it increases myocardial oxygen demand (like dopamine), myocardial perfusion is also augmented (in contrast to dopamine).[429] The most well-accepted use of dobutamine in circulatory shock relates to cardiac etiologies.[422,424] Once blood pressure is corrected, dobutamine may be used to increase cardiac performance and decrease elevated ventricular filling pressures associated with cardiogenic pulmonary edema. In this setting dobutamine may in fact increase blood pressure. Alternatively, if myocardial damage is extensive, vasodilatory properties may dominate, resulting in hypotension. Dobutamine may also be of use in obstructive shock pending definitive intervention and can be used for augmentation of low CI occasionally seen in fluid-resuscitated septic shock. Our own experience suggests that a somewhat hypervolemic state (a PAOP of at least 15 mm Hg if a PAC is used) is required during dobutamine infusion to avoid hypotension in patients with septic shock. The use of dobutamine for routine augmentation of oxygen delivery in septic shock has been substantially rejected.[430,431]

Epinephrine is occasionally used when other inotrope/vasopressors have failed to support blood pressure and/or CO in circulatory shock. It is the first-line agent for management of anaphylactic shock. In addition, it is used to support myocardial contractility after cardiopulmonary bypass.[432] Epinephrine stimulation of α, β_1-, and β_2-receptors results in increases of myocardial contractility that are more pronounced than with any other inotrope. Infusion rates in nanograms per kilogram per minute result in significant increases in CO.[432] Epinephrine is also frequently used in septic shock refractory to other inotropes/vasopressors. Effects attributable to impaired myocardial perfusion (chest pain, arrhythmias, ST depression) in patients with known CAD are usually limited to patients receiving more than 0.1 μg/kg/min.[433] Although the usual infusion rate is 0.05–0.2 μg/kg/min higher rates can be used with the potential for increasing toxicity.

Milrinone, a bipyridine phosphodiesterase inhibitor, increases intracellular concentrations of cAMP by blocking cAMP breakdown.[411] Although some controversy has existed regarding the relative contributions of increased myocardial contractility and decreased vascular tone with respect to the apparent inotropic properties of phosphodiesterase inhibitors, recent data confirm the presence of substantial increases of myocardial contractility[434]; these agents also produce substantial vasodilatation. The most accepted use for milrinone in the ICU is in the management of CHF, cardiogenic shock, and postcardiopulmonary bypass myocardial dysfunction.[411] Experimental animal studies suggest phosphodiesterase inhibitors may exert beneficial hemodynamic effects in sepsis by augmenting CO and increasing oxygen delivery without increasing consumption.[435] Occasional clinical reports suggest a potential management role in catecholamine-refractory septic shock.[436]

Phenylephrine is a synthetic catecholamine that is unique in its almost pure α-adrenergic agonist effects. Its most common uses are intraoperatively to counteract the vasodilatory effects of anesthetics and in septic shock, in which its lack of β-adrenergic activity may help limit deleterious increases in HR seen with other agents. Isoproterenol is another synthetic catecholamine with dominant β_1 and β_2 activity. Its previous indications for use have largely been supplanted by dobutamine. Because of its powerful chronotropic effects, it can be useful in the management of bradyarrhythmias and torsades de pointes ventricular tachycardia (for overdrive pacing), but otherwise it has no specific role in the management of circulatory shock.

In recent years, vasopressin levels in septic shock have been shown to be significantly suppressed.[416] Studies have shown that IV infusion of vasopressin into patients with septic shock results in a profound pressor response.[415] This profound pressor response occurs despite the absence of such an effect with even larger amounts of vasopressin in normotensive patients. Investigators have also documented efficacy in other vasodilatory shock states with refractory hypotension, including milrinone-induced shock in severe heart failure,[437] postcardiotomy vasodilatory shock,[438] unstable brain-dead organ donors,[439] and late-phase hemorrhagic shock.[413] Vasopressin (0.1–1.0 U/mL in normal saline solution or 5% dextrose in water) may be initiated at 0.02 to 0.04 U/min. Few patients respond with higher doses and the dose should rarely, if ever, be higher than 0.04 U/min for an extended period of time. In large doses, vasopressin may produce bradycardia, minor arrhythmias, premature atrial contraction, heart block, peripheral vascular constriction or collapse, coronary insufficiency, decreased CO, myocardial ischemia, and MI. In patients with CAD, even small doses of the drug can precipitate angina. At the upper end of dosing, a significant subset of patients may develop digital, mesenteric, or myocardial ischemia; thus it is imperative to use the minimal amount of vasopressin possible to achieve desired blood pressure goals. Published data suggest vasopressin can be used for up to 4 to 6 days if necessary. A randomized, blinded study of vasopressin treatment of septic shock has shown that the addition of low-dose vasopressin (vs. norepinephrine) to open-label vasopressors offered no overall advantage.[440] A recent randomized controlled trial showed that vasopressin as a first-line vasopressor was safe but did not provide any advantages over norepinephrine.[441] Because of the limited experience with this compound and the relatively longer half-life of the drug, vasopressin should be used only after hemodynamic stabilization with standard agents (catecholamines) has been attempted.

Another agent in a totally different class that could be used as vasopressor is angiotensin II. In a recent randomized controlled trial, angiotensin II as an add-on to norepinephrine showed that it could increase MAP compared with placebo without significant adverse effects. The role of this agent in management of shock is still to be defined.[290]

Conclusion

Although the syndrome of shock ultimately involves common late pathologic elements, the early pathophysiologic processes underlying different conditions resulting in circulatory shock are both diverse and complex. Our concepts of shock, which once focused on broad cardiovascular physiologic mechanisms, have more recently centered on issues of microvascular function and cellular metabolism. In the future, this focus may evolve toward questions of altered cellular gene expression and metabolomics in a variety of tissues. Advances in therapy have developed in parallel to these changes in our

understanding of shock pathophysiology. Early work on therapy of shock concentrated on correction of hemodynamic derangements through the use of vasopressors and inotropes. Clinical trials over decades have centered on anticytokines such as anti–TNF-α and various novel resuscitative compounds. The most advanced experimental therapies being examined today involve direct manipulation of gene expression via antisense oligonucleotides and transcription factor inhibitors. Despite these advances, many questions remain. Only ongoing basic research and clinical trials will answer them.

Key Points

- Shock is the final pathway through which a variety of pathologic processes lead to cardiovascular failure and death.
- Shock is the state in which profound and widespread reduction of effective tissue perfusion leads to cellular injury. The inability of cells to obtain and/or use oxygen in sufficient quantity to optimally meet their metabolic requirements is common to all forms of shock. Hypotension alone does not define shock.
- Based on hemodynamic characteristics, shock is categorized as hypovolemic, cardiogenic, extracardiac obstructive, or distributive.
- Although one hemodynamic categorization dominates, most forms of clinical shock involve some cardiovascular characteristics of several categories.
- The clinical picture of shock is dependent on the etiology, the magnitude of the injury or insult, and the degree of physiologic compensation. Physiologic compensation is determined by the time course of development of shock and the preexisting cardiovascular reserve.
- The systemic hemodynamic aspects of shock can be described by the interactive contributions of cardiac and vascular function to blood pressure and CO.
- Physiologically, blood pressure is dependent on CO and vascular resistance; CO is not dependent on blood pressure.
- Failure to maintain the blood pressure required for autoregulation during hypodynamic circulatory shock indicates a severe reduction in CO.
- In a closed cardiovascular circuit, CO (as determined by HR, preload, afterload, and contractility) equals venous return (as determined by venous pressure [mean circulatory pressure]), right atrial pressure, and venous resistance. Total systemic perfusion is therefore dependent on cardiac and vascular interactions.
- In addition to sufficient CO at sufficient pressure, effective perfusion requires normal local and systemic microvascular function, resulting in appropriate distribution of CO.
- During hypovolemic and other forms of hypodynamic shock, extrinsic blood flow regulatory mechanisms overwhelm the autoregulatory response of most vascular beds. Blood flow to vital organs such as the heart and brain is relatively well preserved owing to dominant autoregulatory control.
- During distributive shock, particularly septic shock, organ blood flow is disturbed at higher MAPs, suggesting a primary defect of microvascular function.
- Cellular dysfunction and organ failure in shock involves the interactions of cellular ischemia, circulating or local inflammatory mediators, and free radical injury.
- All compensatory responses to shock support oxygen delivery to vital tissues. The mechanisms include support of venous pressure, maximization of cardiac function, redistribution of perfusion to vital organs, and optimization of oxygen unloading.
- Circulatory shock may be associated with encephalopathy, ARDS, ATN, ischemic hepatitis or intrahepatic cholestasis, thrombocytopenia, immunosuppression, and MODS.
- Because early recognition and treatment is key to improved survival, the diagnosis of shock is primarily based on clinical criteria. Laboratory and radiologic data are used to confirm the diagnosis and to help clarify etiology.
- Clinically, shock is characterized by physiologic compensatory responses, including tachycardia, tachypnea, oliguria, and by signs of physiologic decompensation, particularly hypotension.
- Shock should be managed in an ICU with continuous monitoring and close nursing support. Those patients whose etiologic diagnosis is in doubt, whose hemodynamic instability does not quickly resolve with IV fluids, or whose conditions are medically complicated should undergo noninvasive (echocardiographic) and/or invasive hemodynamic monitoring with arterial and centrally placed catheters. PACs remain a reasonable option in some cases.
- The basic goal of therapy of circulatory shock is the restoration of effective perfusion to vital organs and tissues before the onset of cellular injury.
- The speed with which effective perfusion is established and the underlying cause of hemodynamic instability is definitively addressed are critical determinants of survival in shock.
- The specific aims of resuscitation of shock include support of mean blood pressure above 60 to 65 mm Hg, maintenance of CI greater than 2.1 L/min per m^2, and restriction of arterial lactate concentrations to less than 2.2 mmol/L.

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Review Questions

1. A 33-year-old woman is brought to the intensive care unit (ICU) for dyspnea and acute hepatic dysfunction. Her symptoms began 2 weeks ago with an apparent upper respiratory tract infection, cough, and fever. She subsequently developed complaints of progressive fatigue, weakness, and dyspnea. Overnight decompensation continues with increasing dyspnea and hypoxemia, requiring endotracheal intubation. She becomes hypotensive and oliguric despite repeated intravenous fluid boluses. The electrocardiogram (ECG) shows sinus tachycardia, with nonspecific ST-segment changes. Transaminase levels are elevated: aspartate aminotransferase, 689 U/L; alanine aminotransferase, 580 U/L. Pulmonary artery (PA) catheterization is performed; right atrial (RA) pressure is 14 mm Hg; PA pressure is 43/26 mm Hg; pulmonary capillary wedge pressure is 22 mm Hg; cardiac index 1.3 L/min/m^2; and systemic vascular resistance is 1250 dyne/sec/cm^{-5}. What is her likely diagnosis?

a. Pulmonary embolism
b. Septic shock
c. Acute myocardial infarction
d. Acute myocarditis
e. Anaphylactic shock

Answer: d. This patient experienced a viral infection that progressed to acute viral myocarditis with cardiogenic shock. Her mild transaminase elevation was secondary to a low cardiac output state. PA catheter findings in pulmonary embolism (PE) include a depressed cardiac output/index, with elevated RA pressures, and an elevated PA diastolic to pulmonary capillary wedge pressure (PCWP) gradient (classically >10 mm Hg). In PE-induced shock, the PCWP would be decreased because it only produces hypotension by decreasing left ventricular (LV) filling. Anaphylaxis and sepsis are both forms of distributive shock. These "hyperdynamic" forms of shock typically present with an elevated cardiac output/index. Central venous pressure (CVPs) and PCWPs are often low because of the intravascular volume depletion resulting from profound capillary leak, and systemic vascular resistance (SVR) is markedly reduced from arteriolar vasodilatation. Hypovolemic shock usually presents with reduced cardiac index (CI), reduced CVP and PCWP, and very high SVR. Cardiogenic shock presents with reduced cardiac indices, elevated CVP and PCWP, and elevated SVR as seen in this patient. However, there is no ST-segment elevation or Q-wave suggesting an acute infarct in this case.

2. Which of the following correctly defines oxygen consumption (Q = cardiac output; CaO_2 = arterial oxygen content; CvO_2 = mixed venous oxygen content; Hb = hemoglobin concentration; PaO_2 = arterial partial pressure of oxygen; SaO_2 = arterial oxygen consumption; SvO_2 = venous oxygen saturation)?

a. $Q \times CaO_2$
b. $SaO_2 - SvO_2/SvO_2$
c. $Q \times (CaO_2 - CvO_2)$
d. $(1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$

Answer: c. Systemic oxygen delivery is defined as the product of cardiac output and the total oxygen content of arterial blood ($Q \times CaO_2$). Oxygen content can be defined as the oxygen bound to arterial or venous hemoglobin ($1.34 \times Hb \times S[a \text{ or } v]O_2$ plus the amount of oxygen dissolved in blood ($0.0031 \times P[a \text{ or } v]O_2$). Oxygen consumption therefore can be defined as a difference between oxygen delivery and oxygen demand ($Q \times [CaO_2 - CvO_2]$). Calculating the oxygen extraction ratio represents another way to define oxygen consumption. Simply put, this is the ratio of oxygen consumption to oxygen delivery, or $SaO_2 - SvO_2/SvO_2$. The normal extraction ratio is approximately 0.25:0.33, which reflects a mixed venous saturation of 65% to 70%.

3. Match each of the following clinical scenarios with the best choice of vasoactive medication (a–d) listed below.

Scenario 1: A 58-year-old man with a history of hypertension and diabetes is brought to the ICU after successful angioplasty in the setting of acute myocardial infarction. The cardiac index is markedly low (1.5 L/min/m^2). His blood pressure is 120/70 mm Hg and his heart rate is 115 beats/min.

Scenario 2: A 24-year-old woman without medical history presents with septic shock and is still hypotensive despite adequate cardiac filling pressures and a high rate of dopamine infusion.

Scenario 3: A 67-year-old man presents in shock after a motor vehicle collision in which he has spinal cord impingement at the C4-C5 vertebrae.

a. Dopamine
b. Norepinephrine
c. Milrinone
d. Phenylephrine

Answers: Scenario 1: c; Scenario 2: b; Scenario 3: d. Dopamine stimulates dopaminergic, β-adrenergic, and α-adrenergic receptors. At low doses, dopamine receptor stimulation leads to improved renal perfusion. At moderate doses (5–10 μg/kg/min), β_1-adrenergic stimulation augments cardiac function. At high doses (10–20 μg/kg/min) α-adrenergic receptor stimulation causes peripheral vascular constriction. The β_1 effects of dopamine can cause significant tachycardia. Therefore norepinephrine, which strongly stimulates α-adrenergic receptors (with lesser β-adrenergic receptor stimulation), may increase blood pressure without the chronotropic effects of dopamine. Phenylephrine, which exclusively stimulates α-adrenergic receptors, can be used as a venous and arterial vasoconstrictor for pure vasodilatory shock states such as neurogenic or anaphylactic shock. Milrinone inhibits cyclic adenosine monophosphate (cAMP) degradation. The overall effects of milrinone include increased cardiac contractility and peripheral and pulmonary vasodilation. Similar to dobutamine, the vasodilation associated with milrinone may precipitate arterial hypotension; thus this agent must be used with caution in patients with marginal blood pressure.

The first scenario is low cardiac output state with normal blood pressure and thus milrinone is the correct choice as the use of dopamine may exacerbate tachycardia. In the second scenario, norepinephrine would be the best choice to achieve an acceptable mean arterial pressure. The third scenario is "spinal shock"; a pure vasoconstrictor (phenylephrine) is the best choice.

4. Which of the following is most correct regarding issues of invasive hemodynamic monitoring?

a. Many studies have proven that PA catheters improve mortality.
b. Manual sphygmomanometry or automated blood pressure cuffs are relatively accurate in shock states.
c. Monitoring CVP can be helpful to accurately estimate left ventricle preload in the critically ill.
d. Serum lactate will be elevated at mixed oxygen saturation levels below 30% to 40%.

Answer: d. Invasive hemodynamic monitoring may provide the clinician with a great deal of important physiologic information. Arterial catheters should be used for blood pressure measurement in shock states. Manual and automated blood pressure measurement techniques have been found to be inaccurate in hypotensive patients. CVP can be used to monitor volume status. A markedly low CVP correctly identifies a hypovolemic state. However, a normal or high CVP value does not necessarily ensure adequate cardiac filling, because the value for CVP can be influenced by valvular heart disease or intrathoracic pressure. PA catheters can provide data reflecting left venctricular preload (PCWP) and can measure cardiac output via thermodilution techniques. Data from the PA catheter can be diagnostic (differentiating shock states) or used to guide therapy. However, no study has linked PA catheter utilization with improved outcomes. PA blood can be obtained to measure SvO_2. In assessing oxygen supply dependency in shock, an SvO_2 of 65% to 70% suggests that global tissue oxygen supply is meeting tissue oxygen demands. Tissue oxygen extraction would be increased in this condition. Lactate accumulation and supply-dependent oxygen consumption reliably occur at SvO_2 levels below 30% to 40%. However, lactate levels may be elevated at higher levels of SvO_2 if regional (rather than global) hypoperfusion is occurring.

23

Cardiogenic Shock

STEVEN M. HOLLENBERG AND JOSEPH E. PARRILLO

CHAPTER OUTLINE

Definition

History

Incidence

Etiology and Epidemiology

Pathogenesis
- Systemic Effects
- Myocardial Pathology
- Reversible Myocardial Dysfunction

Clinical Assessment and Initial Management
- Evaluation
- Invasive Hemodynamic Monitoring
- Initial Management

Therapy
- Fibrinolytic Therapy
- Intraaortic Balloon Pumping
- Revascularization
- Coronary Artery Bypass Surgery

Other Causes of Cardiogenic Shock
- Right Ventricular Infarction
- Acute Mitral Regurgitation
- Ventricular Septal Rupture
- Free Wall Rupture
- Myocardial Dysfunction After Cardiopulmonary Bypass
- Myocarditis

Mechanical Support

Conclusion

Cardiogenic shock is the syndrome that ensues when the heart is unable to deliver enough blood to maintain adequate tissue perfusion. Acute myocardial infarction (MI) is the leading cause, but other potential etiologies need to be considered.[1,2] Without prompt diagnosis and appropriate management, morbidity and mortality remain substantial.[2–4] Rapid evaluation and prompt initiation of supportive measures and definitive therapy in patients with cardiogenic shock may improve both early and long-term outcomes.

Definition

Cardiogenic shock is defined clinically by decreased cardiac output with evidence of tissue hypoxia in the presence of adequate intravascular volume. The diagnosis of circulatory shock (Box 23.1) is made at the bedside by the presence of hypotension along with a combination of clinical signs indicative of poor tissue perfusion, including oliguria, clouded sensorium, and cool, mottled extremities. Hemodynamic criteria include sustained hypotension (systolic blood pressure [SBP] <90 mm Hg for at least 30 minutes, or requiring vasopressor support to maintain SBP >90 mm Hg) and a reduced cardiac index (<2.2 L/min per m^2) in the presence of elevated filling pressures (pulmonary capillary occlusion pressure >15 mm Hg).[5] Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion or correction of extrinsic factors such as hypovolemia, hypoxia, and acidosis.

History

Pump failure caused by cardiogenic shock has long been known to carry a high mortality rate. The seminal article outlining prognosis after MI was a single-center series of 250 patients reported by Killip in 1967.[6] Killip divided patients into four classes as follows:

Killip class I: no evidence of congestive heart failure
Killip class II: presence of an S_3 gallop and/or bibasilar rales
Killip class III: pulmonary edema (rales greater than halfway up the lung fields)
Killip class IV: cardiogenic shock.

Nineteen percent of the 250 patients were in class IV at presentation and their mortality rate was 81%.[6]

With the advent of right heart catheterization, Forrester and Swan defined hemodynamic subsets after MI analogous to the clinical subsets outlined by Killip.[5]

Subset I: Normal pulmonary capillary wedge pressure (PCWP) and cardiac output
Subset II: Elevated PCWP and normal cardiac output
Subset III: Normal PCWP and decreased cardiac output
Subset IV: Elevated PCWP and decreased cardiac output.

These subsets correspond with the Killip classes, and mortality was markedly increased in the subset with hemodynamics indicative of cardiogenic shock.[7]

Despite advances in management of heart failure and acute MI, the mortality rate of patients with cardiogenic shock has remained high.[2,8–10] Data suggest an increase in survival in the 1990s coincident with the use of reperfusion strategies.[9–11] More recent registry data, however, suggest that in-hospital mortality in

• BOX 23.1 Diagnosis of Cardiogenic Shock

Clinical Signs

Hypotension
Oliguria
Clouded sensorium
Cool and mottled extremities

Hemodynamic Criteria

SBP <90 mm Hg for >30 min
Cardiac index <2.2 L/min per meter squared
PAOP >5 mm Hg

PAOP, *Pulmonary artery occlusion pressure;* SBP, *systolic blood pressure.*

• BOX 23.2 Causes of Cardiogenic Shock

Acute Myocardial Infarction

Pump failure
- Large infarction
- Smaller infarction with preexisting left ventricular dysfunction
- Infarct extension
- Reinfarction
- Infarct expansion

Mechanical complications
- Acute mitral regurgitation caused by papillary muscle rupture
- Ventricular septal defect
- Free wall rupture
- Pericardial tamponade
- Right ventricular infarction

Other Conditions

End-stage cardiomyopathy
Myocarditis
Myocardial contusion
Prolonged cardiopulmonary bypass
Septic shock with severe myocardial depression
Left ventricular outflow tract obstruction
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy

Obstruction to left ventricular filling
- Mitral stenosis
- Left atrial myxoma

Acute mitral regurgitation (chordal rupture)
Acute aortic insufficiency

patients treated with percutaneous coronary intervention (PCI) for cardiogenic shock may be rising a bit, from 27.6% in 2006 to 30.6% in 2013, perhaps owing to exclusion of fewer extremely ill patients in the cohort of patients receiving PCI.[12] Cardiogenic shock still remains the most common cause of death in hospitalized patients with acute MI.

Incidence

Accurate determination of the precise incidence of cardiogenic shock is difficult because patients who die of MI before reaching the hospital generally do not receive this diagnosis.[8,13–16] Nonetheless, estimates from a variety of sources have been fairly consistent. The Worcester Heart Attack Study,[8] a community-wide analysis, found an incidence of cardiogenic shock of 7.5%, an incidence that remained fairly stable from 1975 to 1997.[8,11] The incidence was similar in the randomized Guangzhou Uptake of Surgery Trial (GUSTO) trial (7.2%),[17] in other multicenter thrombolytic trials,[13–15] and in patients with ST-elevation MI in the National Registry of Myocardial Infarction (NRMI) database from 1995 to 2004 (8.6%).[9] Although the Worcester Heart Attack Study reported a decrease from 8% to 6% from 1975 to 2005,[3] a more contemporary report from the National Inpatient Sample actually showed an increase in cardiogenic shock incidence from 6.5% in 2003 to 10.1% in 2010, with an increasingly complex profile of patients owing to higher rates of comorbidities.[4]

Etiology and Epidemiology

The most common cause of cardiogenic shock is left ventricular (LV) failure in the setting of an extensive acute MI, although a smaller infarction in a patient with previously compromised LV function may also precipitate shock. Cardiogenic shock can also be caused by mechanical complications—such as acute mitral regurgitation, rupture of the interventricular septum, or rupture of the free wall—or by large right ventricular (RV) infarctions. In a report of the SHOCK (*Sh*ould we emergently revascularize *O*ccluded *C*oronaries for shoc*K*) trial registry of 1160 patients with cardiogenic shock,[2] 78.5% of patients had predominant LV failure, 6.9% had acute mitral regurgitation, 3.9% had ventricular septal rupture, 2.8% had isolated RV shock, 1.4% had tamponade or cardiac rupture, and 6.5% had shock resulting from other causes.

Other causes of cardiogenic shock include myocarditis, end-stage cardiomyopathy, myocardial contusion, septic shock with severe myocardial depression, myocardial dysfunction after prolonged cardiopulmonary bypass (CPB), valvular heart disease, and hypertrophic obstructive cardiomyopathy (Box 23.2). An important consideration is that some cardiogenic shock may have an iatrogenic component. Early diagnosis of impending shock or of patients at high risk for development of shock is essential, both to speed intervention and to avoid therapies that may worsen hemodynamics. In many cases of cardiogenic shock in the setting of MI, the diagnosis is not made until the patient has undergone triage and has been admitted to an inpatient setting. Patients may have received early β-blockade and/or angiotensin-converting enzyme inhibition, therapies that may affect hemodynamic substantially.

Only one-fourth of patients with cardiogenic shock have shock at initial presentation; the median delay in the SHOCK trial registry was 7 hours.[2] This suggests that early treatment may potentially prevent shock, and some data indicate that early thrombolytic therapy may decrease the incidence of cardiogenic shock.[18] Comparison of the clinical characteristics of patients with early and late shock shows a similar demographic, historical, clinical, and hemodynamic characteristics, but shock tends to develop earlier in patients with single-vessel coronary artery disease (CAD) than in those with triple-vessel disease.[19] This finding suggests that early shock in the setting of acute MI may be more likely to resolve after revascularization of the culprit vessel, whereas shock developing later may require more complete revascularization.

Risk factors for the development of cardiogenic shock in MI generally parallel those for LV dysfunction and the severity of CAD. Epidemiologic and historical factors that predict the development of shock include advanced age, diabetes, previous MI or decreased ejection fraction, peripheral vascular disease, and cerebrovascular disease.[20,21] Analysis from the GUSTO-3 trial has identified age, lower systolic blood pressure, heart rate, and Killip

class as significant predictors of the risk for development of cardiogenic shock after presentation with acute MI.[22] Use of predictive scoring systems may be useful in identifying patients at high risk for the development of cardiogenic shock and targeting such patients for closer monitoring.[22]

Cardiogenic shock is most often associated with anterior MI.[2,23] Angiography most often demonstrates multivessel CAD (left main occlusion in 20% of patients, three-vessel disease in 64%, two-vessel disease in 23%, and one-vessel disease in 13% of patients).[24] The high prevalence of multivessel CAD is important because compensatory hyperkinesis normally develops in myocardial segments that are not involved in an acute MI, and this response helps maintain cardiac output. Failure to develop such a response, because of previous infarction or high-grade coronary stenoses, is an important risk factor for cardiogenic shock and death.[25]

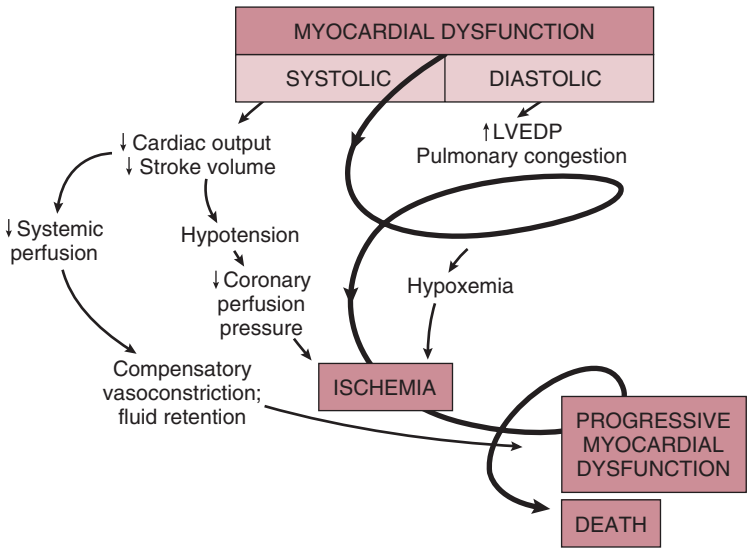
Clinical and hemodynamic data can be used to predict in-hospital mortality in patients with cardiogenic shock. Multivariate models derived from the SHOCK trial have shown that eight clinical risk factors—advanced age, previous coronary artery bypass grafting (CABG), noninferior MI, creatinine elevated above 1.9 mg/dL, decreased systolic blood pressure, shock on admission, anoxic brain injury, and clinical evidence of end-organ hypoperfusion—can divide patients into strata with mortality ranging from 12% to 88%.[26] This model can be refined by adding hemodynamic variables: stroke work and ejection fraction less than 28%.[26] Interestingly, the effect of early revascularization did not differ by risk group in the SHOCK trial, suggesting that all patients have the potential to benefit.[26]

Pathogenesis

Systemic Effects

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by MI or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward cascade[27] (Fig. 23.1). Myocardial dysfunction reduces stroke volume, cardiac output, and blood pressure, compromising myocardial perfusion, which depends on the gradient between systemic and LV diastolic pressure. Pump failure, which increases LV diastolic pressures and further reduces coronary perfusion pressure and also increases LV wall stress and myocardial oxygen requirements, further worsens ischemia. Elevation of left atrial pressure owing to pump failure can lead to pulmonary congestion and hypoxemia, with exacerbation of myocardial ischemia and impaired ventricular performance. Decreased cardiac output can also compromise systemic perfusion.

When myocardial function is depressed, several compensatory mechanisms are activated, including sympathetic stimulation to increase heart rate and contractility and renal fluid retention to increase preload. These compensatory mechanisms may become maladaptive and can actually worsen the situation when cardiogenic shock develops. Increased heart rate and contractility increase myocardial oxygen demand and exacerbate ischemia. Vasoconstriction to maintain blood pressure increases myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. This increased demand, in the face of inadequate



• **Fig. 23.1** The downward spiral in cardiogenic shock. Cardiac dysfunction is usually initiated by myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward cascade. Myocardial dysfunction reduces stroke volume, cardiac output, and blood pressure, compromising myocardial perfusion, which depends on the gradient between systemic and left ventricular (LV) diastolic pressure. Pump failure, which increases LV diastolic pressures and further reduces coronary perfusion pressure and also increases LV wall stress and myocardial oxygen requirements, further worsens ischemia. Elevation of left atrial pressure owing to pump failure can lead to pulmonary congestion and hypoxemia, with exacerbation of myocardial ischemia and impaired ventricular performance. Decreased cardiac output can also compromise systemic perfusion. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock. *LVEDP,* Left ventricular end-diastolic pressure. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* 1999;131:47–50, with permission.)

perfusion, can worsen ischemia and begin a vicious cycle that will end in death if not interrupted (Fig. 23.1). The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock.

Not all patients fit into this classic paradigm. In the SHOCK trial, the average systemic vascular resistance (SVR) was not elevated, and the range of values was wide, suggesting that compensatory vasoconstriction is not universal. Some patients had fever and elevated white blood cell counts along with decreased SVR, suggesting a systemic inflammatory response syndrome.[28] This has led to an expansion of the paradigm to include the possibility of the contribution of inflammatory responses to vasodilation and myocardial stunning, leading clinically to persistence of shock (Fig. 23.2).[28] Supporting this notion is the fact that the mean ejection fraction in the SHOCK trial was only moderately decreased (30%), suggesting that mechanisms other than pump failure were operative.[28] Immune activation appears to be common to a number of different forms of shock. Activation of inducible nitric oxide synthase with production of nitric oxide and peroxynitrate has been proposed as one potential mechanism.

Myocardial Pathology

Cardiogenic shock is characterized by both systolic and diastolic myocardial dysfunction.[29,30] Progressive myocardial necrosis has been observed consistently in clinical and pathologic studies of patients with cardiogenic shock.[29,31] Patients who develop shock after admission often have evidence of infarct extension, which can result from reocclusion of a transiently patent infarct artery, propagation of intracoronary thrombus, or a combination of decreased coronary perfusion pressure and increased myocardial oxygen demand.[20,21] Myocytes at the border zone of an infarction are more susceptible to additional ischemic episodes; therefore these adjacent segments are at particular risk.[32] Mechanical infarct expansion, which is seen most dramatically after extensive anterior MI, can also contribute to late development of cardiogenic shock.[20,33]

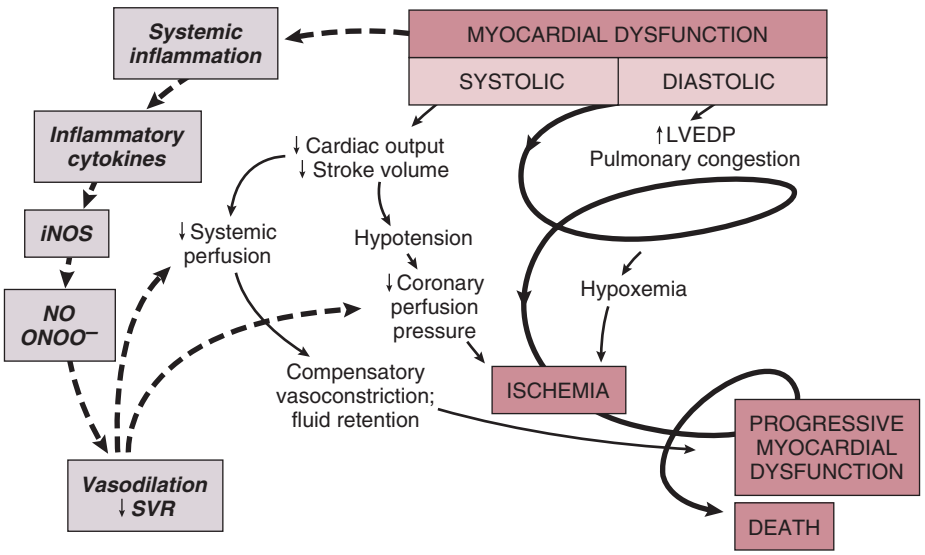
Ischemia remote from the infarct zone may be particularly important in producing systolic dysfunction in patients with cardiogenic shock.[25,34] Patients with cardiogenic shock usually have multivessel CAD,[2,29] with limited vasodilator reserve, impaired autoregulation, and consequent pressure-dependent coronary flow in several perfusion territories.[35] Hypotension and metabolic derangements thus have the potential to impair the contractility of noninfarcted myocardium in patients with shock.[36] This can limit hyperkinesis of uninvolved segments, a compensatory mechanism typically seen early after MI.[25,34]

In addition to abnormalities in myocardial performance, valvular abnormalities can contribute to increased pulmonary congestion. Papillary muscle dysfunction caused by ischemia is common and can lead to substantial increases in left atrial pressure; the degree of mitral regurgitation may be lessened by afterload reduction. This mechanism is distinct from complete rupture of the papillary muscle, a mechanical complication that presents dramatically, with pulmonary edema and cardiogenic shock.

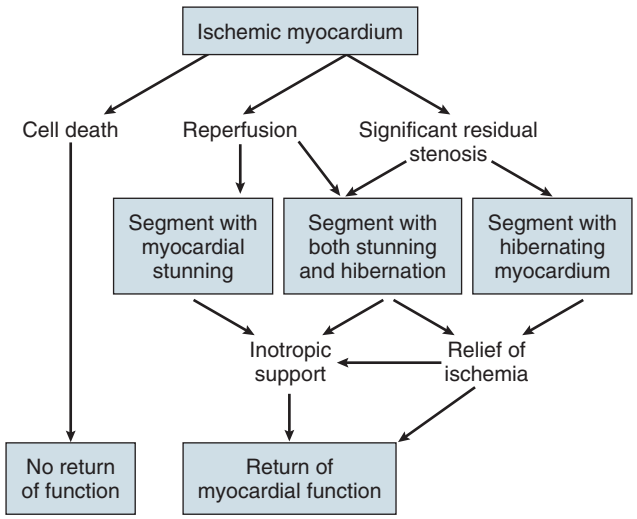
Reversible Myocardial Dysfunction

A key to understanding the pathophysiology and treatment of cardiogenic shock is to realize that large areas of nonfunctional but viable myocardium can cause or contribute to the development of cardiogenic shock in patients after MI (Fig. 23.3). This reversible dysfunction can be described in two main categories: stunning and hibernation.

Myocardial stunning represents postischemic dysfunction that persists despite restoration of normal blood flow; myocardial performance eventually recovers.[37] Originally defined in animal models of ischemia and reperfusion,[38] stunning has been recognized



• **Fig. 23.2** Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. Inhibition of nitric oxide, however, has not been shown to be beneficial in patients with cardiogenic shock.[114] *iNOS,* Inducible nitric oxide synthase; *LVEDP,* left ventricular end–diastolic pressure; *NO,* nitric oxide; $ONOO^-$, peroxynitrite; *SVR,* systemic vascular resistance. (Modified from Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation.* 2003;107:2998–3002, with permission.)



• **Fig. 23.3** Possible outcomes after myocardial ischemia. After myocardial ischemia, either necrosis or reversible dysfunction may occur. Myocardial stunning represents postischemic dysfunction that persists despite restoration of normal flow. These segments respond to inotropes and will recover function if supported. Hibernating myocardium is a state of persistently impaired myocardial function at rest owing to residual stenosis; function can be restored to normal by relieving ischemia. Repetitive episodes of stunning can coexist with and/or mimic myocardial hibernation. The concept that stunned or hibernating segments can recover contractile function emphasizes the importance of measures to support hemodynamics in patients with cardiogenic shock. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* 1999;131:47–50, with permission.)

in patients on the basis of postreperfusion myocardial dysfunction with subsequent improvement.[37] Direct evidence for myocardial stunning in humans has been found using positron emission tomography scanning in patients, with demonstration of persistent wall motion abnormalities after angioplasty for acute coronary syndromes with normal perfusion measured simultaneously by ^{13}N-ammonia.[39] The pathogenesis of stunning has not been conclusively established but appears to involve a combination of oxidative stress,[40] perturbation of calcium homeostasis, and decreased myofilament responsiveness to calcium.[41–43] The intensity of stunning is determined primarily by the severity of the antecedent ischemic insult.[43]

Myocardial hibernation represents segments with persistently impaired function at rest as the result of severely reduced coronary blood flow, with improved function after restoration of blood flow.[44] Hibernation can be seen as an adaptive response to reduce contractile function of hypoperfused myocardium and restore equilibrium between flow and function, thereby minimizing the potential for ischemia or necrosis.[45] Revascularization of hibernating myocardium can lead to improved myocardial function,[46] and improved function appears to translate into improved prognosis.[47,48]

Although hibernation is conceptually and pathophysiologically different from myocardial stunning, the two conditions are difficult to distinguish in the clinical setting and may coexist.[43,48] Repetitive episodes of myocardial stunning can occur in areas of viable myocardium subtended by a critical coronary stenosis, mimicking myocardial hibernation.[37,43,49,50] Consideration of myocardial stunning and hibernation is vital in patients with cardiogenic shock because of their therapeutic implications. Hibernating myocardium improves with revascularization, and stunned myocardium retains inotropic reserve and can respond to inotropic stimulation.[43] The potential for myocardial recovery provides a rationale for coronary revascularization and also emphasizes the importance of measures to support hemodynamics and thus minimize myocardial necrosis in patients with cardiogenic shock.

Clinical Assessment and Initial Management

Evaluation

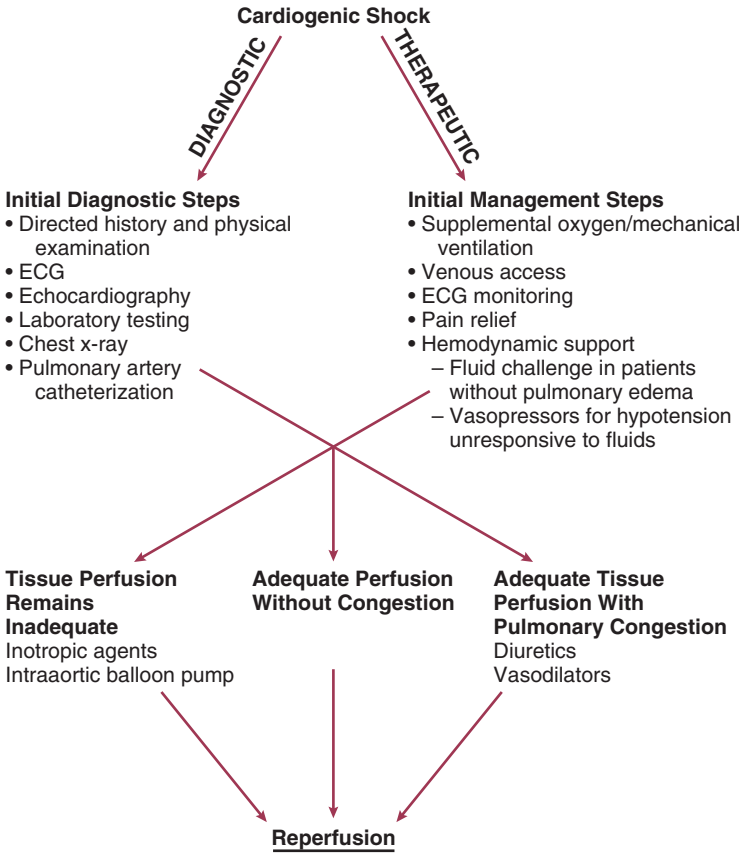
Cardiogenic shock is an emergency. The clinician must initiate therapy before shock irreversibly damages vital organs; at the same time, he or she must perform the clinical assessment required to understand the cause of shock and to target therapy to that cause. A practical approach is to make a rapid initial evaluation on the basis of a limited history, physical examination, and specific diagnostic procedures (Fig. 23.4).[27] Exclusion of alternative causes of hypotension and documentation of myocardial dysfunction is essential for the diagnosis of cardiogenic shock.

The majority of patients with cardiogenic shock present "wet" and "cold." Patients with shock are usually ashen or cyanotic, and they have cool skin and mottled extremities. Cerebral hypoperfusion may cloud the sensorium. Pulses are rapid and faint, and may be irregular in the presence of arrhythmias. Jugular venous distention and pulmonary rales are usually present, although their absence does not exclude the diagnosis. A precordial heave resulting from LV dyskinesis may be palpable. The heart sounds may be distant, and third and/or fourth heart sounds are usually present. A systolic murmur of mitral regurgitation or ventricular septal defect may be heard, but either complication may occur without an audible murmur.

An electrocardiogram (ECG) should be performed immediately. In cardiogenic shock caused by acute MI, the ECG most commonly shows ST elevation, but ST depression or nonspecific changes are found in 25% of cases. If RV infarction is suspected, ST elevation in modified right-sided leads may be diagnostic. The ECG may also provide information on previous MIs and rhythm abnormalities. A relatively normal ECG or one showing only diffuse, nonspecific changes in a patient with clinical cardiogenic shock should suggest myocarditis, especially if the patient has arrhythmias. In end-stage heart failure, the ECG may show Q waves and/or bundle branch block, indicative of extensive disease.

Other initial diagnostic tests include a chest radiograph, complete blood cell count, and measurement of arterial blood gases, electrolytes, and cardiac biomarkers. A high-quality chest film can assess signs of pulmonary edema and is helpful when signs suggest an alternative diagnosis, such as a widened mediastinum indicative of aortic dissection.

Echocardiography is an indispensable tool for confirming the diagnosis of cardiogenic shock and ruling out other causes of shock (Box 23.3) and should be performed as early as possible, preferably with color flow Doppler. Echocardiography provides information on overall and regional systolic function, and can rapidly diagnose mechanical causes of shock such as papillary muscle rupture and acute mitral regurgitation, acute ventricular septal defect, and free wall rupture and tamponade.[51,52] Unsuspected severe mitral regurgitation is not uncommon. In some cases, echocardiography may reveal findings compatible with RV infarction.



• **Fig. 23.4** An approach to the diagnosis and treatment of cardiogenic shock caused by myocardial infarction. Right ventricular infarction and mechanical complications are discussed in the text. *ECG,* Electrocardiogram. (Modified from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* 1999;131:47–50, with permission.)

• BOX 23.3 Role of Echocardiography in Cardiogenic Shock

Evaluate overall systolic performance
Delineate regional wall motion abnormalities
Rule out mechanical causes of shock
- Papillary muscle rupture
- Ventricular septal rupture
- Free wall rupture
- Tamponade

Diagnose right ventricular infarction

Invasive Hemodynamic Monitoring

If the history, physical examination, chest radiograph, and echocardiogram demonstrate systemic hypoperfusion, low cardiac output, and elevation of venous pressures, right heart catheterization may not be necessary for diagnosis. If there is any uncertainty, however, invasive hemodynamic monitoring can be quite useful to characterize the hemodynamics and to exclude volume depletion, RV infarction, and mechanical complications.[29,53] The hemodynamic profile of cardiogenic shock includes a PCWP greater than 15 mm Hg and a cardiac index less than 2.2 L/min per m^2.[2] It should be recognized that PCWP optimal filling pressures may be greater than 15 mm Hg in individual patients owing to LV diastolic dysfunction. Right heart catheterization may reveal an oxygen step-up diagnostic of ventricular septal rupture or a large V wave that suggests severe mitral regurgitation. RV infarction should be suspected when the PCWP is normal but right-sided filling pressures are notably elevated.[54,55]

Right heart catheterization is most useful, however, to optimize therapy in patients with cardiogenic shock. Clinical estimates of filling pressures can be unreliable, and changes in myocardial performance or therapeutic interventions can change cardiac output and filling pressures precipitously. These changes may occur after revascularization in the cardiac catheterization laboratory. Concomitant RV dysfunction is often underrecognized in patients with cardiogenic shock, and its importance underappreciated; right heart catheterization is the best and most expeditious way to assess right-sided hemodynamics in these patients. In the opinion of the authors, even if the diagnosis is not in question, in most patients undergoing left heart catheterization for cardiogenic shock, right heart catheterization should be performed and the catheter left in place, because of its utility in guiding subsequent therapy. Bedside right heart catheterization is another option.

Initial Management

Initial stabilization of the patient with suspected cardiogenic shock consists of venous access, supplemental oxygen, and continuous ECG monitoring. Many patients require intubation and mechanical ventilation, if only to reduce the work of breathing and facilitate

sedation and stabilization before cardiac catheterization. Central venous and arterial access, bladder catheterization, and pulse oximetry are routine. Electrolyte abnormalities should be corrected. Hypokalemia and hypomagnesemia are predisposing factors to ventricular arrhythmias, and acidosis can decrease contractile function. Relief of pain and anxiety with opiates can reduce excessive sympathetic activity and decrease oxygen demand, preload, and afterload. Atrial bradyarrhythmias and tachyarrhythmias and ventricular tachyarrhythmias may have major effects on cardiac output and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing. Cardiology consultation has been shown to be associated with improved outcomes in patients with MI and is strongly indicated in the setting of cardiogenic shock.[56]

If the cause is likely an acute MI, aspirin and heparin should be given immediately. Some therapies routinely used in acute MI, such as nitrates, β-blockers, and angiotensin-converting enzyme inhibitors,[57] have the potential to exacerbate hypotension in cardiogenic shock and should be withheld until the patient's condition stabilizes.

An initial assessment of fluid status and systemic perfusion should be performed. Patients are commonly diaphoretic and relative hypovolemia may be present. In the original description of hemodynamic subsets in MI, approximately 20% of patients had low cardiac index and low PCWP; most had reduced stroke volume and compensatory tachycardia.[7] Some of these patients would be expected to respond to fluid infusion with an increase in stroke volume, although the magnitude of such a response depends on the degree of ischemia and cardiac reserve. Some patients may benefit from judicious fluid replacement with 100- to 200-mL fluid boluses titrated to clinical endpoints of heart rate, urine output, and blood pressure.[58] Ischemia produces diastolic as well as systolic dysfunction, and thus elevated filling pressures may be necessary to maintain stroke volume in patients with cardiogenic shock. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with RV infarction.

Maintenance of adequate blood pressure is essential to break the vicious cycle of progressive hypotension and further myocardial ischemia. When arterial pressure remains inadequate, therapy with vasopressor agents, titrated not only to blood pressure but also to clinical indices of perfusion and mixed venous oxygen saturation, may be required to maintain coronary perfusion pressure. Norepinephrine is preferable to dopamine for hypotension in this situation. Dopamine acts as both an inotrope (particularly between 3 and 10 μg/kg per minute) and a vasopressor (10–20 μg/kg per minute). Norepinephrine (0.02–1.0 μg/kg per minute) acts primarily as a vasoconstrictor, has a mild inotropic effect, and increases coronary flow. A randomized trial comparing norepinephrine and dopamine in 1678 patients with shock found no significant difference in 28-day mortality in the overall trial, but a prespecified subgroup analysis did find increased mortality with dopamine in the 280 patients with cardiogenic shock.[59] More tachyarrhythmias were seen in the dopamine group in both the cardiogenic shock subset and the overall trial.[59] Phenylephrine, a selective α_1-adrenergic agonist, may support blood pressure when tachyarrhythmias limit therapy with other vasopressors, although it does not improve cardiac output and it is not especially potent. Vasopressin, which causes vasoconstriction, has a neutral or slightly depressant effect on cardiac output and increases vascular sensitivity to norepinephrine, may be added to catecholamines if needed.

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed (Fig. 23.4). If tissue perfusion remains inadequate, inotropic and/or mechanical support should be initiated. Dobutamine, a selective β_1-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output without markedly changing heart rate or SVR; it is the initial agent of choice in patients with systolic pressures greater than 90 mm Hg.[60–62] Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmias. Phosphodiesterase inhibitors such as milrinone increase intracellular cyclic adenosine monophosphate by mechanisms not involving adrenergic receptors, producing both positive inotropic and vasodilatory actions. Milrinone has fewer chronotropic and arrhythmogenic effects than catecholamines.[63] In addition, because milrinone does not stimulate adrenergic receptors directly, its effects may be additive to those of the catecholamines.[64] Milrinone, however, has the potential to cause hypotension and has a long half-life; in patients with tenuous clinical status, its use is often reserved for situations in which other agents have proven ineffective.[29] The standard loading dose of milrinone should not be given in patients with marginal blood pressure, which usually describes patients with cardiogenic shock. Milrinone should be given by an infusion at a low dose and titrated according to the hemodynamic response.

Mechanical circulatory support should be considered in patients in whom pharmacotherapy has failed and is be discussed in a subsequent section.

Infusions of vasoactive agents need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring can be extremely useful in allowing optimization of therapy in these unstable patients, because clinical estimates of filling pressure can be unreliable.[65] In addition, changes in myocardial performance and compliance and therapeutic interventions can change cardiac output and filling pressures precipitously. Optimization of filling pressures and serial measurements of cardiac output (and other parameters, such as mixed venous oxygen saturation) allow for titration of the dosage of inotropic agents and vasopressors to the minimum dosage required to achieve the chosen therapeutic goals. This can minimize the increases in myocardial oxygen demand and arrhythmogenic potential.[58,66] A hemodynamic assessment is mandatory in patients being considered for mechanical support.

Therapy

Fibrinolytic Therapy

Although fibrinolytic therapy reduces overall mortality rates in patients with acute MI,[13,67–69] the benefits of this therapy in patients with cardiogenic shock are less certain. Fibrinolytic therapy can reduce the likelihood of subsequent development of shock after initial presentation, but no trials have demonstrated that thrombolytic therapy reduces mortality in patients with established cardiogenic shock.[15,17,69] Rates of reperfusion are lower, suggesting reduced efficacy of lytics in this situation.[24,70] The reasons for decreased fibrinolytic efficacy in patients with cardiogenic shock include hemodynamic, mechanical, and metabolic factors. Decreased arterial pressure limits the penetration of fibrinolytic agents into a thrombus.[71] Passive collapse of the infarct artery in the setting

of hypotension can also contribute to decreased fibrinolytic efficacy, as can acidosis, which inhibits the conversion of plasminogen to plasmin.[71]

Intraaortic Balloon Pumping

An intraaortic balloon pump (IABP) reduces systolic afterload and augments diastolic perfusion pressure without increasing oxygen demand.[72,73] IABPs do not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis.[74] IABPs are thus probably not sufficiently effective to be used as an independent modality to treat cardiogenic shock but may support patients through a critical period of shock, while definitive therapy is undertaken.

Despite a convincing hemodynamic rationale for their use, randomized trials have failed to show improvement in 30-day mortality with IABP insertion in patients with cardiogenic shock undergoing early revascularization. The IABP-SHOCK trial randomly assigned 45 patients with an acute MI and cardiogenic shock to IABP + PCI versus PCI alone; it was not powered for mortality benefit, but did not show either a decrease in mortality or a significant improvement in multiorgan dysfunction score with the addition of IABP counterpulsation to standard therapy.[75] The IABP-SHOCK II study, a much larger prospective, randomized, open-label, multicenter trial enrolling 600 patients with cardiogenic shock complicating acute MI, randomly assigned patients to an IABP group or a non-IABP group. There was no significant difference in the primary endpoint of 30-day all-cause mortality (39.7% vs. 41.3%, $P = 0.69$), nor was there a significant difference in any of the subgroups in exploratory analyses. Secondary safety endpoints such as major bleeding, peripheral ischemic complications, sepsis, and stroke, did not differ between the two groups.[76] Some randomly assigned patients received an IABP when they were hemodynamically stable and might not have been expected to derive great benefit, and 10% of patients in the control group crossed over to IABP therapy.[76]

Although the IABP-SHOCK II has dampened enthusiasm for the routine use of IABP, these trial results may not be applicable to all patients. Because of its widespread availability, safety, lower cost compared with other support devices, and ease of placement in many health care facilities, the opinion of the authors is that it is reasonable to use IABP counterpulsation as adjunctive therapy in cardiogenic shock, an opinion consistent with the class IIa recommendation for insertion of an IABP for patients with hemodynamic instability in the American College of Cardiologists/American Heart Association guidelines.[77] Whether its use for this indication will be superseded by other mechanical circulatory support devices remains to be seen.

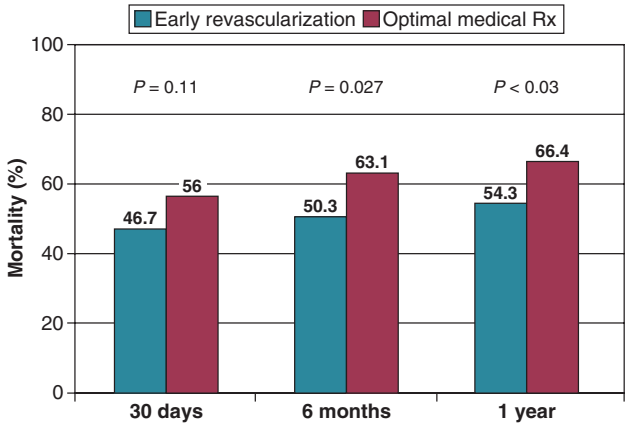
Revascularization

Supportive therapy may improve blood pressure and cardiac output in cardiogenic shock, but it does not interrupt the vicious circle of myocardial dysfunction and ischemia. Emergency percutaneous revascularization is the only intervention to date that has been shown to consistently reduce mortality rates in patients with cardiogenic shock.

Reestablishment of brisk (Thrombolysis in Myocardial Infarction [TIMI] grade 3) flow in the infarct-related artery is an important determinant of LV function and survival after MI.[70] In addition to improving wall motion in the infarct territory, increased perfusion of the infarct zone has been associated with augmented contraction of remote myocardium, possibly owing to recruitment of collateral blood flow.[25] After observational reported improved outcomes in patients with cardiogenic shock selected for revascularization,[17,78–80] a randomized trial was conducted, funded by the National Institutes of Health.

The landmark SHOCK study[81,82] was a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management—including IABP and thrombolytic therapy—or to cardiac catheterization with revascularization using cutaneous transluminal coronary angioplasty or CABG.[81] The trial enrolled 302 patients and was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates. Mortality at 30 days was 46.7% in patients treated with early intervention and 56% in patients treated with initial medical stabilization, but this difference did not quite reach statistical significance ($P = 0.11$).[81] It is important to note that the control group (patients who received medical management) had a lower mortality rate than that reported in previous studies; this may reflect the aggressive use of thrombolytic therapy (64%) and IABP (86%) in these controls. At 6 months, mortality with early intervention in the SHOCK trial was reduced significantly (50.3% compared with 63.1%, $P = 0.027$),[81] and this risk reduction was maintained at 12 months (mortality 53.3% vs. 66.4%, $P < 0.03$) (Fig. 23.5).[82] Encouragingly, this 13% absolute improvement in survival remained stable at both 3 and 6 years of follow-up.[83] In addition, most survivors had good functional status.[84]

Subgroup analysis showed a substantial improvement in mortality rates in patients younger than 75 years of age at both 30 days (41.4% vs. 56.8%, $P = 0.01$) and 6 months (44.9% vs. 65.0%, $P = 0.003$).[81] For patients older than 75 years, no benefit of revascularization was demonstrated in the SHOCK trial, although this was a small subgroup, and further analysis suggested baseline differences so that the elderly patients randomly assigned to medical therapy appeared to have been a lower-risk group.[85] In the SHOCK trial registry, elderly patients treated with early revascularization had better outcomes than those treated medically, suggesting that



• **Fig. 23.5** Mortality in the randomized SHOCK trial at 30 days, 6 months, and 1 year in the early revascularization and optimal medical management groups. (Data from Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999;341:625–634; and Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;285:190–192.)

it is possible to select elderly patients who will benefit from aggressive treatment.[86]

When the results of the SHOCK trial are put into perspective with results from other randomized, controlled trials of patients with acute MI, an important point emerges: despite the moderate *relative* risk reduction (for the SHOCK trial 0.72, confidence interval 0.54–0.95) the *absolute* benefit is substantial, with 9 lives saved for 100 patients treated at 30 days, and 13.2 lives saved for 100 patients treated at 1 year. This latter figure corresponds to a number needed to treat of 7.6, one of the lowest figures ever observed in a randomized, controlled trial of cardiovascular disease (see Fig. 23.4). In the latest American College of Cardiology/American Heart Association guidelines for the management of acute MI, primary coronary intervention was given a class I indication for patients younger than 75 years and a class IIa indication for patients older than 75 years.[77]

Coronary Artery Bypass Surgery

Analysis of the SHOCK trial helps to define the indications for CABG in the setting of cardiogenic shock. CABG should be the first line of therapy offered in cases of left main disease or triple-vessel disease as well as when the patient has sustained mechanical complications necessitating surgical repair. In patients with multivessel disease in the SHOCK trial, complete revascularization was achieved more frequently (87% vs. 23%). Long-term mortality rates were similar in the CABG and PCI groups despite worse coronary anatomy and more diabetes in the surgical group.[87]

Other Causes of Cardiogenic Shock

Right Ventricular Infarction

RV infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10%.[88] Patients present with hypotension, elevated neck veins, and clear lung fields. The diagnosis is made by identifying ST-segment elevation in right precordial leads or by characteristic hemodynamic findings on right heart catheterization (elevated right atrial and RV end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate depressed RV contractility.[55] Patients with cardiogenic shock on the basis of RV infarction have a better prognosis than those with left-sided pump failure.[88] This may be due in part to the fact that RV function tends to return to normal over time with supportive therapy,[89] although such therapy may need to be prolonged.

Supportive therapy for patients with RV infarction begins with maintenance of RV preload with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise LV filling and cardiac output.[89] Inotropic therapy with dobutamine may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect RV overdistention.[89] Maintenance of atrioventricular synchrony is also important in these patients to optimize RV filling.[55] For patients with continued hemodynamic instability, an IABP may be considered, because elevated RV pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating RV ischemia. Percutaneous axial flow pumps are now available that can provide temporary RV support, an attractive option given the potential for recovery of RV function. The small prospective RECOVER RIGHT trial has shown improved hemodynamics, with increased cardiac output and decreased central venous pressure with use of the Impella RP device (Abiomed, Danvers, MA).[90] There was no comparison group, and only 5 of 30 patients had acute MI, but outcomes with support were good and could be argued to have been better than expected.[90]

Acute Mitral Regurgitation

Ischemic mitral regurgitation is usually associated with inferior MI and ischemia or infarction of the posterior papillary muscle, which has a single blood supply, usually from the posterior descending branch of a dominant right coronary artery.[91] Papillary muscle rupture typically occurs 2 to 7 days after acute MI and presents dramatically with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of rapid equalization of pressures in the left atrium and left ventricle. More importantly, the murmur may be soft or inaudible, especially when cardiac output is low.[92]

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes afterload reduction with nitroprusside and an IABP as temporizing measures. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible since clinical deterioration can be sudden.[92,93] Although mortality is substantial, ranging from 20% to 40%, surgical results are improving,[94] and survival and ventricular function are improved compared with medical therapy.[94,95]

Ventricular Septal Rupture

Patients with ventricular septal rupture have severe heart failure or cardiogenic shock, with a pansystolic murmur and a parasternal thrill. The hallmark finding is a left-to-right intracardiac shunt (a step-up in oxygen saturation from right atrium to right ventricle). On pulmonary artery catheter tracing, it can be difficult to distinguish ventricular septal rupture from mitral regurgitation, because both can produce dramatic V waves. The diagnosis is most easily made with echocardiography.

Rapid stabilization—using intraaortic balloon pumping and pharmacologic measures followed by operative repair—is the only viable option for long-term survival. Because perforations are exposed to shear forces, the rupture site can expand abruptly. Repair can be technically difficult owing to the need to suture in areas of necrosis. Surgical mortality is 20% to 50%, especially for serpiginous inferoposterior ruptures, which typically are less well circumscribed than anteroapical ruptures.[96] RV function is an important determinant of outcome in this setting. Timing of surgery has been controversial, but guidelines now recommend that operative repair should be undertaken early: within 48 hours of the rupture.[97] Placement of a septal occluding device may be helpful in selected patients.

Free Wall Rupture

Ventricular free wall rupture usually occurs during the first week after MI; the classic patient is elderly, female, and hypertensive. The early use of thrombolytic therapy reduces the incidence of cardiac

rupture, but late use may increase the risk, particularly in older patients.[98] Free wall rupture presents as a catastrophic event with a pulseless rhythm. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair.[99]

Myocardial Dysfunction After Cardiopulmonary Bypass

Transient depression of ventricular contractility is common after CPB and can represent a significant clinical problem. The differential diagnosis includes inadequate operation, cardiac tamponade (which may be localized and difficult to detect), and increased RV afterload, but most cases likely result from myocardial stunning. The heart is rendered globally ischemic during aortic cross-clamping and then reperfused, and because demonstrable myocardial necrosis is rare, stunning can be implicated. Stunning after bypass has been documented in a study in which an ultrasonic probe was left on the epicardial surface for 2 to 3 days in 31 patients after bypass surgery; LV wall thickening fell after surgery, reached a nadir at 2 to 6 hours, and subsequently improved, usually returning to baseline by 24 to 48 hours.[100]

The degree of myocardial dysfunction after cardiac surgery is variable and may depend on the cardioplegia solution, the method of administration (antegrade or retrograde), the mode of administration (continuous or intermittent), and the temperature of the solution and of the patient during surgery.[43] In the clinical setting, transient depression of ventricular contractility is common and usually reversible within 24 to 48 hours. The depression of contractility can be severe enough to cause cardiogenic shock. In this event, therapy with inotropic agents, vasodilators, and intra-aortic balloon pumping is necessary. Occasionally, even a LV assist device may be used.[101] Better understanding of the mechanisms of post-CPB myocardial dysfunction may lead to better preventive and therapeutic approaches.

Myocarditis

Acute myocarditis can be benign and self-limited, or fulminant, with severe congestive heart failure and/or atrial and ventricular arrhythmias. Fulminant myocarditis presents with sudden onset of heart failure and can be severe enough to cause life-threatening shock. LV dysfunction is diffuse and severe, but unlike other causes of cardiomyopathy, the ventricle may not be dilated and thinned but rather thick and not dilated. Failure to dilate in the face of a low ejection fraction leads to low stroke volume. Fulminant myocarditis is a clinical rather than a histologic or etiologic diagnosis, but has classically been considered as an idiopathic lymphocytic myocarditis. In addition to clinical presentation and diffuse myocardial hypokinesis, typical patterns of late gadolinium enhancement on magnetic resonance imaging may be deemed sufficient to make the diagnosis of myocarditis.

Recent European guidelines have proposed a more granular classification of myocarditis into three broad categories: infectious, immune-mediated, and toxic/idiopathic.[102] The distinction would be made by biopsy, with viral antibodies defining infectious myocarditis, cardiac autoantibodies, or definition of an inflammatory process such as sarcoidosis in the absence of viral antibodies (thus indicating immune-mediated myocarditis), and absence of both denoting toxic/idiopathic myocarditis.[102] The question is whether the therapeutic implications of such a distinction would be sufficient to warrant myocardial biopsy. These guidelines propose consideration of antiviral and/or immunoglobulin therapy for viral myocarditis, and immunoabsorption, immunosuppressive and/or immunoglobulin therapy for immune-mediated myocarditis, but clinical trial data are limited.

Evidence exists that some patients with myocarditis benefit from immunosuppressive therapy, but the identification of which patients should be treated remains controversial. A trial initiated at the National Institutes of Health randomly assigned 102 patients with chronic dilated cardiomyopathy and ejection fraction less than 35% to receive oral prednisone or placebo.[103] The prospectively defined endpoint, an increase in radionuclide-measured ejection fraction of more than 5 percentage points, was observed in 53% of patients treated with prednisone compared with only 27% of controls at 3 months ($P < 0.05$), but the improvement did not persist at 9 months when patients were switched to alternate-day prednisone therapy.[103] Another single-center study of 85 patients with virus-negative inflammatory cardiomyopathy showed significant improvement of ejection fraction at 6 months in patients randomly assigned to immunosuppression and no improvement in those randomly assigned to placebo.[104] A randomized trial comparing intravenous immunoglobulin with placebo in patients with new-onset myocarditis, however, showed improvement of LV function in both groups to the same extent.[105]

Although it might seem that patients with fulminant myocarditis might be the best candidates for immunosuppressive therapy, the largest series confounds this notion by reporting excellent long-term survival in patients with myocarditis and a fulminant course.[106] An exception is patients with giant cell myocarditis, a rare inflammatory cardiomyopathy that usually presents in young adults, often with conduction abnormalities or arrhythmias in addition to heart failure, and for which immunosuppression is indicated, despite which outcomes are much worse than for other forms of myocarditis.[107]

Patients with fulminant myocarditis might be considered to have a more compelling rationale for myocardial biopsy than patients with more subacute presentations, particularly if information about potential infection or immune-mediated causes can be obtained from the biopsy. Further investigation is needed to identify subgroups of patients with myocarditis who might benefit from adjunctive therapies.

Mechanical Support

Mechanical circulatory support devices have the potential to interrupt the downward spiral of myocardial dysfunction, hypoperfusion, and ischemia in cardiogenic shock, allowing time for recovery of stunned or hibernating myocardium. These devices, to different extents, provide circulatory support, increasing mean arterial pressure, ventricular support, reducing LV filling pressures and afterload, and support coronary perfusion, increasing coronary perfusion pressure.

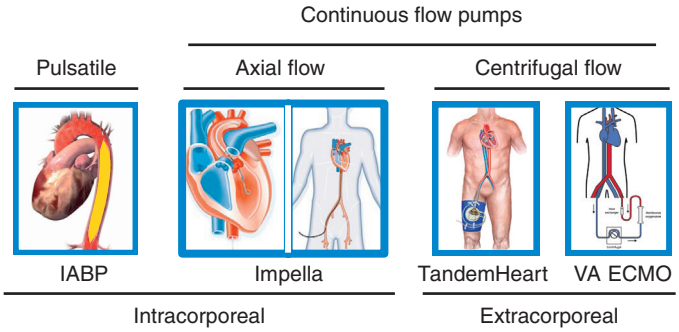
Four acute mechanical circulatory support platforms are currently available: IABP, centrifugally driven left atrial-to-femoral artery bypass (TandemHeart, Cardiac Assist, Pittsburgh, PA), centrifugally driven venoarterial extracorporeal membrane oxygenation (ECMO), and microaxial flow catheters (Impella) (Fig. 23.6). Percutaneously implanted mechanical support can be used in situations of cardiogenic shock, during high-risk percutaneous interventions, in postcardiotomy shock, and in fulminant myocarditis.

The IABP provides counterpulsation, increasing diastolic coronary perfusion pressure and decreasing afterload in systole. Counterpulsation requires pulsation, and so augmentation of cardiac

output in situations such as cardiogenic shock may be minimal, on the order of 0.5 L/min.[108]

The TandemHeart device is a bypass system with inflow of oxygenated blood from the left atrium via a transseptal catheter and outflow to the femoral artery using a centrifugal flow pump; it can increase cardiac output up to 5 L/min, depending on the size of the tubing and on left atrial volume. The TandemHeart reduces LV preload by removing blood from the left atrium but increases LV afterload because blood is returned to the aorta.[109] Since oxygenated blood is removed from the left atrium, no oxygenator is required.

ECMO provides cardiopulmonary support for both the heart and lungs and can either be venovenous or venoarterial (VA), but for patients with cardiogenic shock VA ECMO is used. ECMO involves a venous inflow catheter, a centrifugal pump, a membrane oxygenator, and an arterial return catheter. VA ECMO reduces RV and LV preload, increases blood pressure, and can provide a cardiac output up to 6 L/min.[109] VA ECMO increases LV afterload, and depending on native LV function and aortic valve disease, the LV may not eject through the AV during systole; in this case VA ECMO may increase LV diastolic pressure. Venting of the LV, using either a left atrial catheter or another assist device, may sometimes be used in this circumstance.[109]

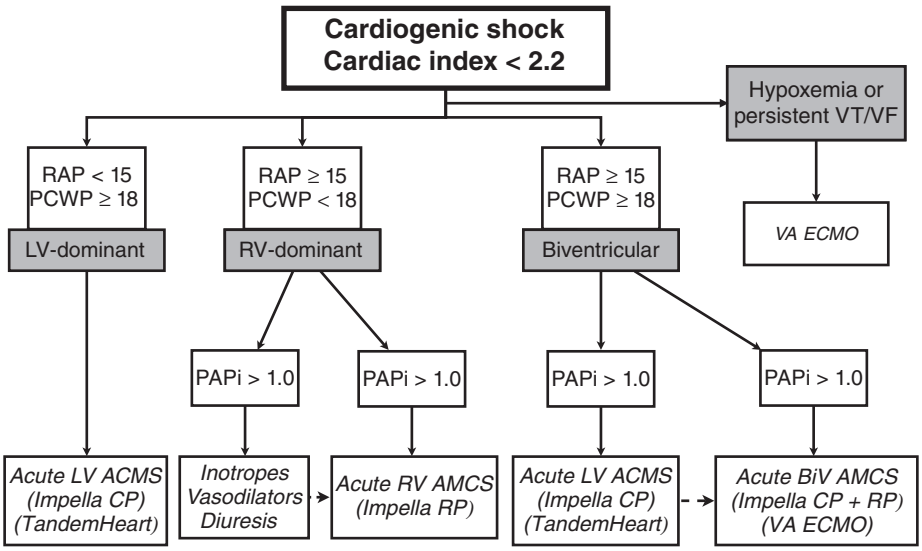


• **Fig. 23.6** Acute mechanical circulatory support devices for cardiogenic shock, classified by the type of pump and whether they are intracorporeal or extracorporeal. *ECMO,* Extracorporeal membrane oxygenation; *IABP,* intraaortic balloon pump. (Modified from Kapur NK, Esposito ML. Door to unload: a new paradigm for the management of cardiogenic shock. *Curr Cardiovasc Risk Rep.* 2016;10:41, with permission.)

The Impella device is a nonpulsatile axial flow catheter inserted retrograde across the aortic valve that pumps blood from a distal port from within the ventricle out to the ascending aorta through a proximal port of the device; there are several versions, one 12F device capable of pumping 2.5 L/min (Impella 2.5), a 21F device that can provide up to 5 L/min (Impella 5.0), and now a 14F device that can provide 3 to 4 L/min (Impella CP), although the actual flow is dependent on afterload. Impella activation increases mean arterial pressure, reduces LV diastolic pressure, increases myocardial perfusion pressure, and increases cardiac output, while decreasing myocardial oxygen demand.[109] These devices do require adequate RV function. A new device, the Impella RP, is an axial flow pump specifically designed to provide RV support by pumping blood from the right atrium into the pulmonary artery.

Two trials have compared the use of IABP to the TandemHeart for patients with cardiogenic shock,[108,110] and another compared use of the Impella to IABP therapy[111]; the results of these trials were combined in a meta-analysis that included 100 patients.[112] Hemodynamic benefits for the percutaneous LVADs compared with IABP were shown, with higher cardiac indices and mean arterial pressures as well as lower PCWPs. However, LVAD use showed no mortality benefit over IABP at 30 days.[112]

One of the key issues in choosing among mechanical support options is the function of the right ventricle. A recently proposed algorithm for acute mechanical support bases the choice on hemodynamic parameters (Fig. 23.7). Patients are divided into LV-dominant, RV-dominant, and biventricular cardiogenic shock. Among the patients with biventricular cardiogenic shock, further stratification is done using the pulmonary artery pulsatility index (PAPi), which is the pulmonary artery pulse pressure (a reflection of right-sided stroke volume) divided by RA pressure. Those with low PAPi might be considered for initial biventricular support.[113]



• **Fig. 23.7** Proposed algorithm for selection of acute mechanical support devices in patients with cardiogenic shock and low cardiac output. *ACMS,* Acute mechanical circulatory support; *LV,* left ventricle; *PAPi,* pulmonary artery pulsatility index; *PCWP,* pulmonary capillary wedge pressure; *RA,* right atrium; *RV,* right ventricle; *VA ECMO,* ventriculoarterial extracorporeal membrane oxygenation. (Modified from Kapur NK, Esposito ML. Door to unload: a new paradigm for the management of cardiogenic shock. *Curr Cardiovasc Risk Rep* 2016;10:41.)

The LV rarely fails alone for long, and assessment of RV hemodynamics with invasive hemodynamic monitoring is important to optimize mechanical support strategies.

For patients with end-stage heart failure and refractory shock, a variety of surgically placed assist devices can be used for circulatory support. These devices retrieve blood from the LV apex and use a pumping device, either continuous or pulsatile, to return the blood into the ascending aorta. Full consideration of these devices is beyond the scope of this chapter; in cardiogenic shock, they are usually used as a bridge to recovery or transplantation, although in other contexts they may be used as destination therapy.

Conclusion

Cardiogenic shock remains a prevalent and dangerous syndrome that requires accurate and efficient diagnosis. Mortality rates in patients with cardiogenic shock have improved but remain frustratingly high. Its pathophysiology involves a downward spiral in which ischemia causes myocardial dysfunction, which in turn worsens ischemia. Areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock. Expeditious coronary revascularization is crucial, and the randomized multicenter SHOCK trial[81] has provided important data that help clarify the appropriate role and timing of revascularization in patients with cardiogenic shock. The potential for reversal of myocardial dysfunction with revascularization provides the rationale for supportive therapy to maintain coronary and tissue perfusion until more definitive revascularization measures can be undertaken. Application of a thorough understanding of the essentials of pathophysiology, diagnosis, and treatment of cardiogenic shock can allow for expeditious management and improved outcomes.

Key Points

- Cardiogenic shock is a state of inadequate tissue perfusion caused by cardiac dysfunction. Acute MI is the leading cause.
- The pathogenesis of cardiogenic shock is a downward spiral in which MI or ischemia causes myocardial dysfunction and compromised myocardial perfusion, exacerbating ischemia.
- Large areas of nonfunctional but viable myocardium (either stunned, hibernating, or both) can also cause or contribute to the development of cardiogenic shock in patients after MI.
- The challenge in initial management of cardiogenic shock is that evaluation and therapy must begin simultaneously. The clinician must perform the clinical assessment required to understand the cause of shock while initiating supportive therapy before shock causes irreversible damages.
- Pathophysiologic considerations and extensive retrospective data favor aggressive mechanical revascularization for patients with cardiogenic shock caused by MI. Clinical trials support a strategy of early revascularization in most patients with cardiogenic shock.
- Other acute mechanical causes of low cardiac output must be excluded. If present, urgent surgery may be required.
- In patients with potentially reversible causes of myocardial dysfunction (including severe myocarditis), optimization of hemodynamics with a combination of inotropic agents and mechanical circulatory support may be required for hours or days to allow sufficient time for recovery.

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Review Questions

1. Which of the following describes Killip Class IV after myocardial infarction?
- **a.** Presence of an S_3 gallop and/or bibasilar rales
- **b.** Pulmonary edema (rales greater than halfway up the lung fields)
- **c.** Clear lungs with hypotension
- **d.** Pulmonary edema with hypotension

Answer: d. The Killip classification outlines prognosis after myocardial infarction by clinical presentation. The degree of heart failure was used to distinguish class II (S_3 gallop and/or bibasilar rales) from class III (pulmonary edema with rales more than half way up). Cardiogenic shock, defined as pulmonary edema with hypotension and decreased perfusion, was class IV, and had the highest mortality.

2. When should beta-blockers not be used initially in patients with acute myocardial infarction?
- **a.** Ejection fraction 40%
- **b.** Heart rate 65
- **c.** Blood pressure 105/60 mm Hg
- **d.** Pulmonary edema and heart rate 110 beats/min
- **e.** β-Blockers can be given in all of these situations

Answer: d. In patients with myocardial infarction and pulmonary edema, β-blockers can worsen heart failure and may precipitate hypotension, potentially inducing cardiogenic shock. Their use should be withheld until clinical stabilization is achieved. Left ventricular dysfunction alone is not a reason to withhold β-blockers, nor is a heart rate greater than 60 beats/min or systolic blood pressure greater than 100 mm Hg. After acute heart failure has resolved, initiation of β-blockade should be attempted.

3. Which of the findings on right heart catheterization is most consistent with acute ventricular septal rupture?
- **a.** Prominent V waves in the right atrial tracing
- **b.** Elevation and equalization of cardiac diastolic pressures
- **c.** Increased right heart pressure and decreased left heart pressure with respiration
- **d.** Oxygen step-up from right atrium to pulmonary artery

Answer: d. The hallmark finding on right heart catheterization in patients with ventricular septal rupture is a left-to-right intracardiac shunt, which is identified as an oxygen step-up in the right-sided circulation (i.e., oxygen saturation increases before the blood gets to the lungs). Prominent V waves in the right atrial tracing are suggestive of tricuspid regurgitation. Elevation and equalization of cardiac diastolic pressures suggest cardiac tamponade, which might occur in ventricular free wall rupture. Increased right heart pressure and decreased left heart pressure with respiration (Kussmaul sign) can occur during cardiac tamponade or constrictive pericarditis.

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Severe Sepsis and Septic Shock

R. PHILLIP DELLINGER, AVIRAL ROY, AND JOSEPH E. PARRILLO

CHAPTER OUTLINE

Historical Perspective and Introduction

Definitions

Epidemiology

Pathogenesis and Pathophysiology of Severe Sepsis and Septic Shock
- Role of the Immune System
- Role of Inflammation
- Alterations in Hemostasis
- Microcirculatory and Mitochondrial Dysfunction
- Multiple Organ Dysfunction

Clinical Presentation

Cardiovascular Profile of Septic Shock
- Hypovolemia and Decreased Cardiac Filling
- Myocardial Dysfunction
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Management of Severe Sepsis and Septic Shock
- Overview and Management Guidelines
- General Principles
- Antibiotic Therapy and Source Control
- Supportive Therapies
- Glucose Control
- Prophylaxis for Deep Vein Thrombosis and Stress Ulcers
- Nutrition
- Early Resuscitation and Hemodynamic Optimization
- Fluid Resuscitation
- Vasopressor Therapy
- Individual Vasoactive Agents
- Inotropic Support
- Corticosteroids
- Modulation of the Host Response

Summary

Historical Perspective and Introduction

Sepsis is a derivation of the Greek word "sepsin," which means to putrefy or "to make putrid." Sepsis was synonymous with putrefaction and pertained to the bacteria-mediated decomposition of organic matter.[1] The word was used almost unchanged for about 2700 years.[2]

The term *shock* comes from the French word "choquer," meaning "to collide with." This is particularly appropriate terminology for shock caused by sepsis, given our modern understanding of the sepsis pathophysiology, whereby the body's host defenses essentially collide with the invading microorganism, triggering a profound proinflammatory host response.

The relationship between an infection and sepsis has been well studied and recognized for many years; however, the precise mechanisms by which an infection results in organ dysfunction distant to the site of the infection continue to be unraveled. Infection-induced organ dysfunction and tissue hypoperfusion are among the deadliest of conditions known with a mortality rate of 25% to 30%.[3] The discussion in this chapter encompasses pathophysiology, assessment, hemodynamics, and management of infection-induced organ dysfunction and tissue hypoperfusion (hypotension, lactic acidosis, and oliguria). The focus is on adult patients.

Definitions

To standardize the definitions for both diagnosis and help guide future research, the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) published definitions for systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock in 1992.[4] These definitions were revisited in 2001 and no evidence was found to update these definitions with the exception of expanding the criteria for systemic manifestations of infection.[5] The Third International Consensus conference on sepsis definitions met in 2015 and published the proposed new definitions in 2016.[6] These proposed new definitions remain controversial and have not found widespread acceptance in the critical care community. In the 1992 consensus definitions, sepsis was defined as infection with two or more systemic inflammatory response syndrome (SIRS) criteria (abnormalities in temperature, respiratory rate, heart rate and white blood cell count). Severe sepsis was defined as infection-induced organ dysfunction or tissue hypoperfusion and septic shock as hypotension persisting despite reestablishing adequate intravascular volume. The second consensus conference in 2001 expanded the systemic manifestations of sepsis beyond the SIRS criteria and also included other laboratory perturbations and biomarkers as well as organ dysfunctions themselves as potential systemic manifestations of sepsis (Box 24.1). No single parameter or set of clinical or laboratory parameters has yet been shown to have high sensitivity or specificity to diagnose sepsis. The definitions of sepsis and severe sepsis remained unchanged with the 2001 document. A more refined definition for septic shock was also proposed: hypotension with a systolic blood pressure less than 90 mm Hg or a mean arterial blood pressure (MAP) less than 70 mm Hg, despite adequate fluid resuscitation.

• BOX 24.1 Diagnostic Criteria for Sepsis

Infection, documented or suspected, plus some of the following findings:
- Temperature >38.3°C or >36°C
- Heart rate >90 beats/min or >2 SD above normal value for age
- Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 in adults or <SD below normal for age)
- Mixed venous oxygen saturation (Sv_{O_2}) >70%
- Cardiac index >3.5 L/min per m^2
- Tachypnea
- Decreased capillary refill or mottling
- Altered mental status
- Significant edema or positive fluid balances
- Hyperglycemia in the absence of diabetes
- WBC count >12,000 μL or <4000 μL
- Normal WBC with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >SD above the normal value
- Hyperlactatemia (>1 mmol/L)
- Evidence of organ dysfunction:
- Arterial hypoxemia ($Pa_{O_2}/F_{I_{O_2}}$ <300)
- Acute oliguria
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or a PTT >60 s)
- Ileus
- Thrombocytopenia
- Hyperbilirubinemia

$F_{I_{O_2}}$, *Fraction of inspired oxygen;* INR, *international normalized ratio;* MAP, *mean arterial pressure;* Pa_{O_2}, *partial pressure of arterial oxygen;* PTT, *partial thromboplastin time;* SBP, *systolic blood pressure;* SD, *standard deviation;* Sv_{O_2}, *mixed venous oxygen saturation;* WBC, *white blood cell.*

TABLE 24.1 Current Definitions of Sepsis

Condition	Criteria
Systemic inflammatory response	Systemic manifestations of infection to include two or more of the traditional SIRS criteria below in addition to any systemic perturbation that might be caused by sepsis and has no other explainable cause such as hypoglycemia, elevation in CRP or PCT, or organ dysfunction SIRS criteria • White blood cell count >12,000/mm^3 or <4000/mm^3 or >10% immature bands. • Respiratory rate >20 or $PaCO_2$ <32 mm Hg • Core body temperature >38°C (100.4°F) or <36°C (96.8°F) • Heart rate >90 beats/min
Sepsis	Systemic inflammatory response + suspected or known source of infection
Severe sepsis	Sepsis and any of the following: organ dysfunction, hypotension, tissue hypoperfusion (lactic acidosis, oliguria, altered mental status)
Septic shock	Sepsis + systolic blood pressure <90 mm Hg despite adequate volume resuscitation (i.e., requiring vasopressors) along with signs of tissue hypoperfusion

SIRS, Systemic inflammatory response syndrome.

The third consensus conference in 2015 proposed redefining of sepsis terminology and for the first time used several large databases to assist in that redefining. The committee recommended abandoning the term *severe sepsis* and using *sepsis* to describe infection-induced organ dysfunction or tissue hypoperfusion. Since the 1991 consensus document, sepsis had been used to define infection with systemic manifestations of infection. Some called this "simple sepsis" as contrasted to severe sepsis. The document also recommended de-emphasizing the SIRS criteria. What was previously called *sepsis* (infection plus systemic manifestations of infection) would now simply be called *infection* with no differentiation between infection with or without systemic manifestation of infection. A SOFA score of 2 points or more was identified as being associated with increased mortality at the time of diagnosis of infection and initiation of antibiotics. Septic shock was proposed to be defined as vasopressor requirement to maintain a MAP of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia after intravascular volume repletion. These proposed new definitions have received mixed reviews, endorsed by some scientific groups and not by others and currently have no impact on International Classification of Diseases codes or Centers for Medicare and Medicaid Services quality metrics, both of which continue to use the 1991 definitions. The eventual outcome regarding the use of these proposed new definitions is unclear. The most widely accepted definitions are as shown in Table 24.1 and represent the 2001 definitions. The proposed new definitions are as shown in Table 24.2. This chapter uses the 1992/2001 definitions.

Epidemiology

Severe sepsis and septic shock continue to be a source of major morbidity and mortality worldwide. With treatment costs of about $50,000 (U.S. dollars) per patient 650,000 to 750,000 cases a year, and a mortality rate of 20% to 40%, severe sepsis and septic shock rank among the most common causes of mortality and greatest cost of illness in adults in the world. Although mortality from sepsis-related diseases has been decreasing worldwide, there has been an increase in overall rates of sepsis-related entities.[7–11] Multiple large observational studies have demonstrated an increasing overall incidence of severe sepsis with a related decrease in mortality. There has also been an overall increase in the mean age of patients admitted with severe sepsis/septic shock. The patients being admitted to the hospital also are sicker with an increased incidence of multiorgan failure and mortality among the more severe groups.[10] The increase may be attributed to increased life span, increasing use of immunosuppressive medications, use of intravascular devices and implants, and the increasing incidence and burden of chronic disease. There is a slightly higher rate for men than for women who contract sepsis-related conditions, and African American and Hispanic populations have roughly double the rate of severe sepsis as compared with the Caucasian population in the United States. The causative organisms have also gradually shifted from primarily gram-negative to primarily gram-positive organisms with an increase in rates of fungal infections. This is due in part to the increasing

TABLE 24.2 Proposed New Definitions of Sepsis

Term	Definition	Criteria	Notes
Sepsis[a] (previously severe sepsis)	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Organ dysfunction is identified as an acute change in the SOFA score ≥2 points from the baseline consequent to the infection	qSOFA (quick Sequential Organ Failure Assessment) Prolonged ICU stay or in-hospital mortality can be identified at the bedside with the qSOFA 1. Respiratory rate ≥22 breaths/min 2. Acute mental status change 3. Systolic blood pressure ≤100 mm Hg An increase in SOFA of ≥2 predicts a 10% mortality in the general hospital population Presume a baseline SOFA of 0 unless the patient has known (acute or chronic) organ dysfunction before the onset of infection
Septic shock	It is a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality	A clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain an MAP ≥65 mm Hg and having a serum lactate level ≥2 mmol/L despite adequate volume resuscitation	Septic shock portends a hospital mortality in excess of 40%

[a]Note that the proposed new definitions abandon the previous term "severe sepsis" to describe infection-induced organ dysfunction and now use "sepsis" to describe infection-induced organ dysfunction. The previous condition called "sepsis" is now just called "infection," and when infection is not associated with organ dysfunction, there is no differentiation between infection with or without systemic manifestations.
MAP, Mean arterial pressure.

use of long-term intravascular access catheters and increasing use of prosthetic hardware and devices, such as pacemakers and internal defibrillators. The more common sites of infection include the respiratory tree and intraabdominal and genitourinary tracts.

Pathogenesis and Pathophysiology of Severe Sepsis and Septic Shock

Infection-induced organ dysfunction and tissue hypoperfusion are the result of complex interactions between infecting organisms and the host response. Important components of this host response in the early phases of sepsis include the immune system, activation of the inflammatory cascade, and alterations in hemostasis. In later stages of sepsis, organ failure, immunosuppression, and apoptosis play an important pathophysiologic role. Characteristics of both the infecting organism and the host response influence the outcome of sepsis. Virulence factors, high burden of infection, and resistance to antibiotics are all organism characteristics associated with increased risk of severe sepsis. A growing body of literature suggests that host responses might be influenced by genetic polymorphisms.[12–19] This might explain why some patients develop severe sepsis to a particular pathogen and others do not. We further discuss some of the relevant components of the host response in severe sepsis.

Role of the Immune System

The immune response to infection takes place through the actions of two pathways: the innate immune system and the adaptive immune system. The goal of the innate immune system is to provide protection in the first minutes to hours after an infectious challenge. Although initially thought to be a nonspecific response, research has demonstrated that the innate immune system recognizes pathogens by means of pattern-recognition receptors (Toll-like receptors [TLRs], Table 24.3). TLRs bind to highly conserved structures on microorganisms, which are not easily altered by microbes to evade detection and are present on broad groups of organisms.[20] Our current understanding of TLRs suggests that the immune cells use different TLRs to detect several features of an organism and, based on the composite information gained,

TABLE 24.3 Toll-Like Receptors

Toll-Like Receptor	Pathogen or Disease State
TLR1	Lyme disease *Neisseria meningitidis*
TLR2	*Mycobacterium tuberculosis* Chagas disease Leptospirosis Fungal sepsis CMV viremia
TLR3	Many
TLR4	Gram-negative bacteria Septic shock *Chlamydia trachomatis* *Chlamydia pneumoniae* Certain viruses *Mycobacterium tuberculosis*
TLR5	Flagellated bacteria (e.g., *Salmonella*)
TLR7	Viral infections
TLR8	Viral infections
TLR9	Bacterial and viral infections
TLR10	Unknown

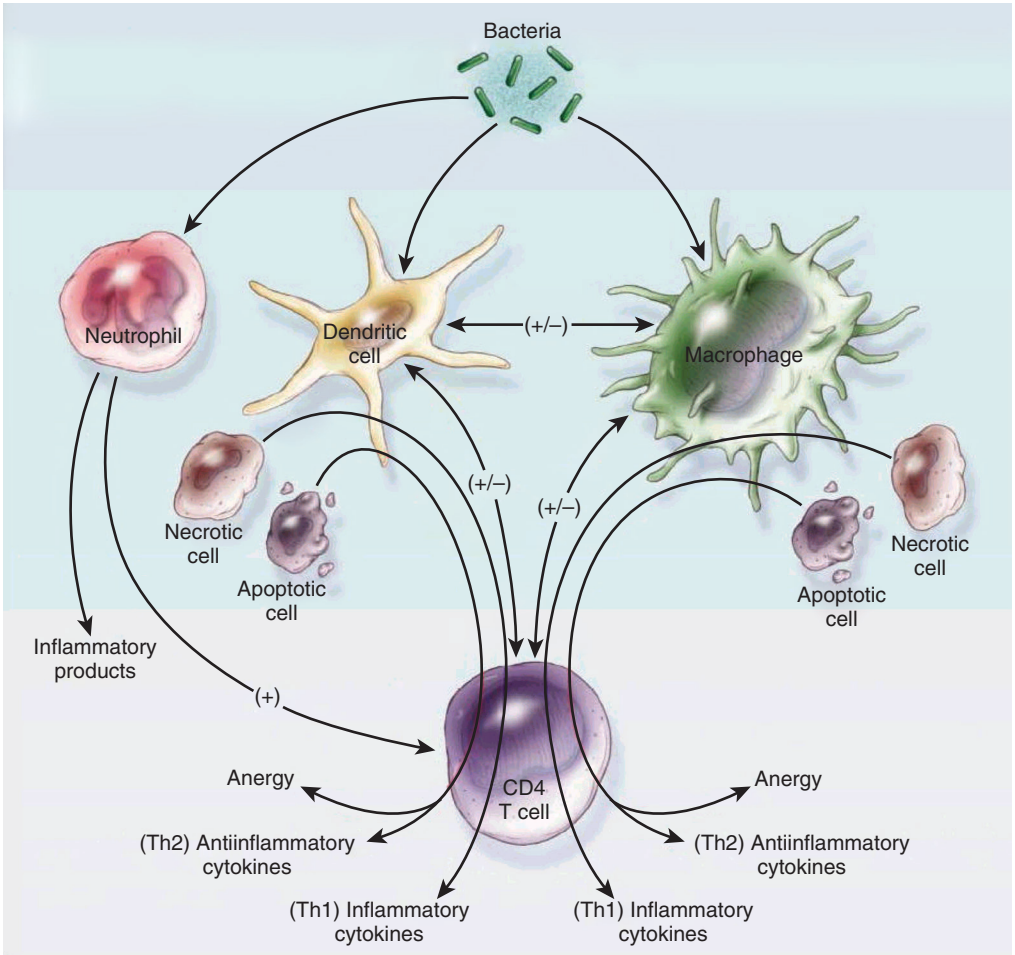
CMV, Cytomegalovirus; *TLR,* Toll-like receptor.

generate a tailored response to the invading pathogen.[20] Activation of TLRs by microorganisms stimulates signaling pathways that increase production of proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin IL 1β (IL-1β), and nuclear factor-kappa B (NF-κB), as well as antiinflammatory cytokines such as IL-10.[20,21] TLR activation also results in upregulation of microbial killing mechanisms, such as the production of reactive nitrogen species.[22] TLRs play a pivotal role in initiating the innate immune response and are important regulators of the adaptive immune response to infection. Recognition of these proteins and their functions expanded our understanding of the pathophysiology of sepsis and has provided a new target for therapeutic interventions.[22]

The adaptive immune system amplifies the response initiated by the innate immune system with a higher degree of specificity. In addition to their interactions with the innate immune system, microorganisms stimulate specific cell-mediated and humoral adaptive immune responses. Two types of lymphocytes, B cells and T cells, play an important role in the adaptive immune response. Adaptive immune responses (humoral and cellular) require days to develop. However, they are amnestic through the generation of memory T and B lymphocytes and, in the case of reexposure to the same pathogen, can elicit a faster and more robust response. CD4 T cells are divided into two types: type 1 helper T-cell (Th1) and type 2 helper T-cell (Th2). Factors such as the type of organism, site of infection, and burden of infection influence the response elicited by T cells. In general, Th1 cells secrete proinflammatory cytokines (TNF-α and IL-1β) and Th2 cells secrete antiinflammatory cytokines (IL-4 and IL-10).[23] B lymphocyte cells are responsible for releasing immunoglobulins in response to microorganisms. These immunoglobulins bind to organism-specific antigens and enhance recognition and destruction by other immune cells (natural killer cells and neutrophils). Several other cell types are involved in the adaptive immune response to infection (Fig. 24.1).

Role of Inflammation

For many years the prevailing theory has been that infection-induced organ dysfunction is the result of an uncontrolled inflammatory response.[24] This paradigm was based on extensive animal

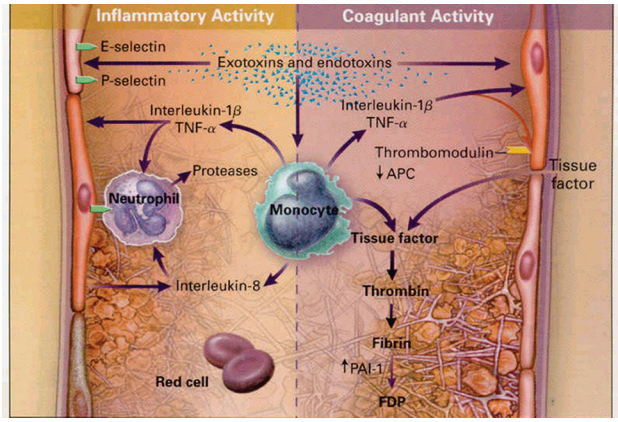


• **Fig. 24.1** Response of immune cells to infection. The immune response to pathogens involves various types of cells. Crosstalk exists among the different cell lines of the immune system (dendritic cells, macrophages, lymphocytes, and neutrophils). The plus signs represent upregulation, and the minus signs represent downregulation. Many interactions on the figure have both plus and minus signs, representing the possibility of either upregulation or downregulation, depending on a variety of factors. *Th1,* Type 1 helper T cell; *Th2,* type 2 helper T cell. (Adapted from Hotchkiss RS. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348:138–150, Figure 1, p. 140.)

experimentation with models of inflammation that may not necessarily reflect human disease. Animal models of sepsis that used large doses of endotoxin or bacteria created a "cytokine storm" that when blocked resulted in improvements in mortality. However, in human sepsis most patients have a complex host response that includes activation of both proinflammatory and antiinflammatory cascades. Early death from overwhelming inflammation is not the norm, and most patients who die develop complications related to immunosuppression, apoptosis, and multiorgan failure later in the course of the disease. These differences may partially explain why so many antiinflammatory compounds worked in animal models yet failed to improve mortality in human clinical trials. The interplay among proinflammatory cytokines, antiinflammatory cytokines, and cytokine inhibitors is a dynamic process that influences the host response to sepsis. Proinflammatory cytokines such as TNF-α and IL-1β increase early in sepsis and have overlapping and synergistic effects in further stimulating the inflammatory cascade.[24] Proinflammatory cytokines activate monocytes, macrophages, and neutrophils; stimulate neutrophil margination; and increase gluconeogenesis. In addition, proinflammatory cytokines have an important role in the development of clinical abnormalities, such as fever, hypotension, capillary leakage with decreased intravascular volume, and myocardial depression.[24] More recently, proinflammatory cytokines such as macrophage migration inhibitory factor and high-mobility group 1 protein have received attention as downstream mediators of inflammation and potential therapeutic targets.[25] The role of antiinflammatory cytokines in sepsis is still not fully understood. Current understanding suggests that sepsis-induced multiorgan failure and death may be caused in part by a shift to an antiinflammatory phenotype and by apoptosis of key immune cells.[26,27] This shift is driven in part by increased levels of antiinflammatory cytokines and results from a shift in helper T-cell populations (from Th1 to Th2).[28] Inflammation plays an important role in the host response to sepsis. It is now apparent that simple therapeutic strategies that block specific proinflammatory cytokines are insufficient to modulate this response.[29,30] Given that more patients survive the initial stage of sepsis and have progressive long-term organ dysfunction, a "proimmune" strategy using immunostimulators to boost immune function in the later stage of the disease may have some benefit. As our understanding of the intricate relationship between proinflammatory and antiinflammatory responses increases, we might become more successful in modulating these to improve patients' outcomes with demonstrable immune dysfunction.

Alterations in Hemostasis

Another important factor in the pathophysiology of sepsis is the alteration of the hemostatic balance. In sepsis this balance is altered by an increase in procoagulant factors paired with a decrease in anticoagulant factors (Fig. 24.2). Under normal conditions the intraluminal vascular surface has anticoagulant properties. During sepsis, stimulation from cytokines promotes expression of tissue factor on endothelial cells, monocytes, and neutrophils.[31,32] Tissue factor triggers the extrinsic coagulation pathway by activating factor VII. Activation of the extrinsic pathway leads to the formation of thrombin. The intrinsic pathway is triggered by activation of factor XI and leads to amplification of the coagulation cascade with further formation of thrombin. Excessive coagulation is normally counterbalanced by several anticoagulant factors. Anticoagulant factors such as antithrombin III, activated protein C, protein S, and tissue factor pathway inhibitor are decreased in sepsis, along



• **Fig. 24.2** Relationship among inflammatory and coagulation systems in sepsis. Monocytes are activated by endotoxins and exotoxins from bacteria and release tumor necrosis factor α *(TNF-α)* and interleukin-1β (IL-1β). TNF-α and IL-1β activate the inflammatory cascade via neutrophils and the production of other proinflammatory cytokines, and in combination with tissue factor, they also activate the coagulation cascade, with production of fibrin and fibrin degradation products *(FDP). APC,* Activated protein C; *PAI-1,* plasminogen activator inhibitor-1. (Adapted from Matthay MA. Severe sepsis: a new treatment with both anticoagulant and anti-inflammatory properties. *N Engl J Med.* 2001;344:759-762, Figure 1A, p. 761.)

with a decreased expression of fibrinolytic pathway by plasminogen activation factor inhibitor-1 and thrombin-activated fibrinolysis inhibitor.[33] These circumstances push the hemostatic balance toward the procoagulant state. Activation of the coagulation cascade leads to a consumption of coagulation factors. The clinical expression of this phenomenon is disseminated intravascular coagulation (DIC). DIC is characterized by a consumptive coagulopathy, which can result in an increased risk of bleeding but can also be problematic by increasing the risk of thrombosis. In sepsis the excessive formation of fibrin from thrombin compounded by the suppression of fibrinolysis and the impairment of anticoagulant pathways may be associated with microthrombi. These microthrombi may lead to microcirculatory alterations and play a role in the pathogenesis of organ failure.[34] The cutaneous and acral manifestations of DIC are systemic peripheral gangrene and purpura fulminans which may lead to limb loss in the most extreme form. Bleeding may be seen at the sites of intravenous (IV) cannula and natural orifices.[35]

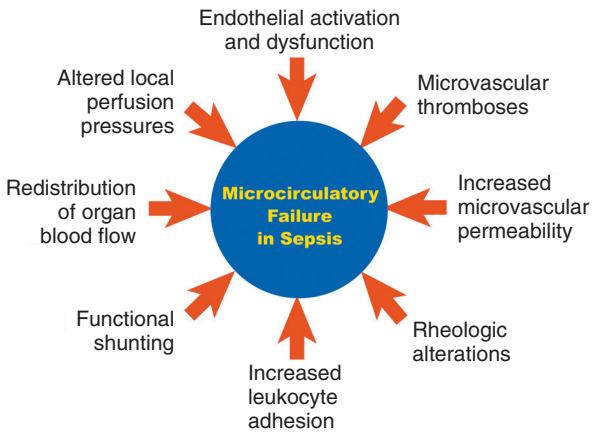
Microcirculatory and Mitochondrial Dysfunction

Microcirculatory dysfunction is a pivotal element of the pathogenesis of septic shock.[36–39] Although the macrocirculation (heart and large arteries) regulates the global distribution of blood flow throughout the body, it is the microcirculation that controls the final delivery of blood to tissues. Using intravital videomicroscopy, experimental models of sepsis have demonstrated impaired microcirculatory flow velocity, "stopped-flow" microvessels, increased heterogeneity of regional perfusion, and low density of perfused capillaries.[40–43] These derangements can cause marked alterations of oxygen transport including impaired tissue oxygen extraction.[42] With the advent of new investigational videomicroscopy techniques, it is now possible to study the microcirculatory network in human subjects with septic shock. Microcirculatory failure appears to be one of the critical pathogenic events in sepsis that is associated

with acute multiorgan dysfunction and death. As these alterations of microcirculatory flow in sepsis can occur in the *absence* of global hemodynamic perturbations (i.e., absence of low arterial pressure or low cardiac output [CO]),[36,43,44] derangements of small vessel perfusion are largely a function of intrinsic events in the microcirculation.

The causes of microcirculatory flow alterations in sepsis (Fig. 24.3) are multifactorial and include endothelial cell dysfunction, increased leukocyte adhesion, microthrombi formation, rheologic abnormalities, altered local perfusion pressures owing to regional redistribution of blood flow, and functional shunting.[40,45] The proinflammatory cytokines released in sepsis cause diffuse endothelial cell activation, which is associated with neutrophil activation, expression of endothelial adhesion molecules (i.e., integrins and selectins), and localization of white blood cells to areas of microvascular injury. Pan-endothelial cell injury increases microvascular permeability with the influx of proinflammatory cells into the tissues; this is hypothesized to be an important pathogenic step in the development of acute system organ dysfunction in sepsis. Leukocyte adhesion of white blood cells to the microvessel endothelial surface (primarily in the postcapillary venule) further impedes microcirculatory blood flow. The endothelial injury also triggers the activation of the coagulation cascade via expression of tissue factor on the microvascular endothelium, resulting in fibrin deposition and microvascular thrombosis that may further impair microcirculatory flow. All of these mechanisms collectively contribute to microcirculatory failure in septic shock.[38,40]

Although septic shock research has classically been focused on macrocirculatory hemodynamic parameters that reflect the distribution of blood flow globally throughout the body, a functional microcirculation is another critical component of the cardiovascular system that is necessary for *effective* blood flow to tissues. This conceptual framework is depicted in Fig. 24.4. Although a shift of research focus from global hemodynamic parameters to indices of microvascular perfusion could potentially be viewed as a major change of direction for septic shock research, the microcirculation likely represents a logical next frontier in the evolution of our understanding of circulatory failure in shock states.[40,45] Although there are currently no therapies to specifically target microcirculatory dysfunction in sepsis, going beyond optimization of macrocirculatory hemodynamics and developing new innovative strategies to reverse microcirculatory failure could (in the future) potentially represent a cutting edge method to augment tissue perfusion in sepsis.



• **Fig. 24.3** Causes of microcirculatory failure in sepsis. (Adapted from Spronk PE, Zandstra DF, Ince C. Bench-to-bedside review: sepsis is a disease of the microcirculation. *Crit Care.* 2004;8:462–468.)

There is strong evidence that cellular utilization of oxygen can be markedly impaired in septic shock.[46] Bioenergetic failure can occur even after effective restoration of blood flow to tissues has been achieved, and this has been termed "cytopathic hypoxia." Despite the current absence of therapies to reverse cytopathic hypoxia, this phenomenon does have some relevance for clinical practice, as impaired cellular oxygen extraction and utilization can manifest clinically with acute organ system failure in the setting of markedly elevated values for mixed (or central) venous oxygen saturation. Cytopathic hypoxia has been associated with acute organ dysfunction, but the extent to which this does or does not represent a cause-and-effect relationship has not yet been fully elucidated.

Microcirculatory and mitochondrial dysfunction likely coexist in septic shock. Both of these pathogenic mechanisms can impair tissue oxygen delivery and utilization, but the relative contribution of either mechanism is difficult to discern and may vary considerably. Fig. 24.5 demonstrates the pathogenetic sequence of events in septic shock.

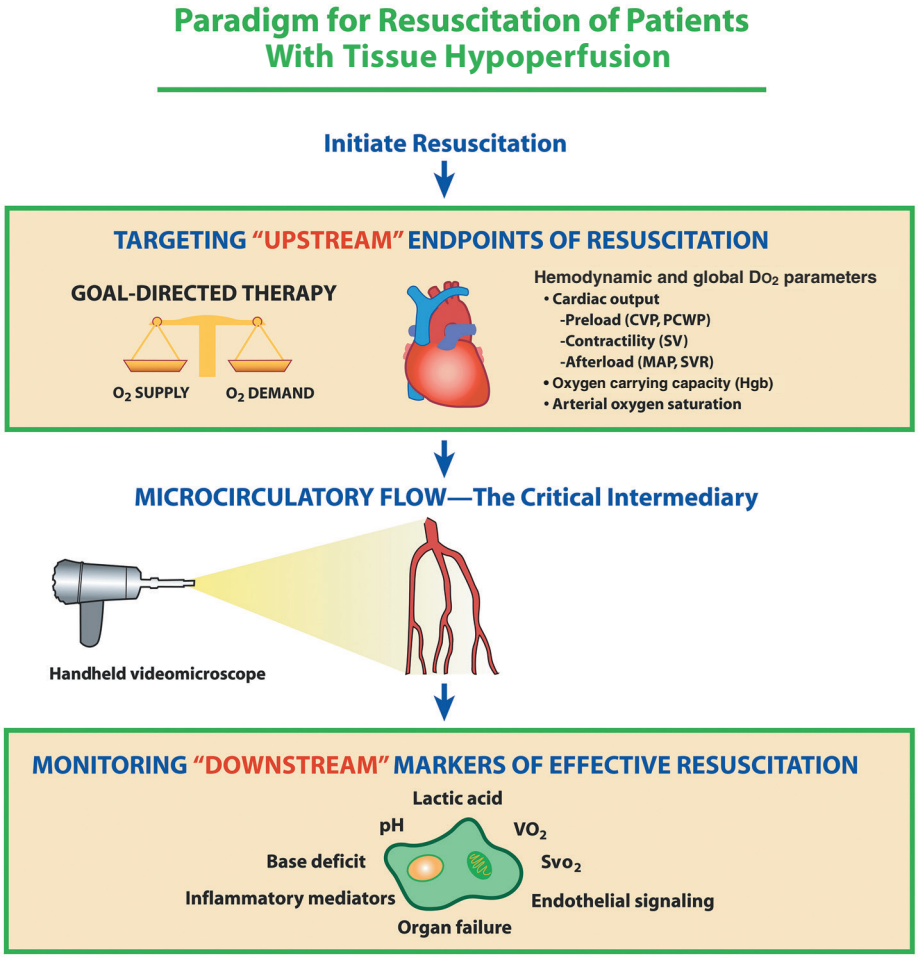
Multiple Organ Dysfunction

Multiple organ dysfunction is a common complication of sepsis. Multiple organ dysfunction syndrome (MODS) occurs when two or more organ systems fail sequentially or at the same time in a patient with sepsis. Various organs, such as the brain, heart, lung, kidney, and liver, can be affected in patients with severe sepsis. Often these organs are distant from the site of primary insult, and development of organ failure occurs as a response to complicated interactions and pathophysiologic events. These include the microcirculatory and bioenergetics failure as described previously. Metabolic and hematologic dysfunctions are also common with severe sepsis and MODS. MODS significantly contributes to higher mortality. Studies have shown that mortality in patients with severe sepsis increases in parallel with increases in number and severity of organ failures.[47,48] Russell and associates evaluated the pattern of organ dysfunction in early sepsis and its relationship with mortality.[48] In this study, clinically significant pulmonary dysfunction, although common early in sepsis, was not associated with 30-day mortality. Early dysfunction of other organs and, particularly, worsening neurologic, coagulation, and renal dysfunction over the first 3 days were associated with significantly higher 30-day mortality.

Recognition of early organ dysfunction is important because it is likely that early intervention can affect outcomes. The clinical manifestations of MODS for individual organs are summarized in Fig. 24.6. The cornerstones of treatment for MODS are based on appropriate treatment for the underlying cause (sepsis) and on early organ-specific support interventions. Early implementation of therapies directed at control of infection, hemodynamic support, and modulation of the host response are key to improving organ dysfunction and patient outcomes. Perhaps the single most important aspect relates to early and aggressive hemodynamic support. As demonstrated in the study by Rivers and colleagues, goal-directed interventions instituted in the first 6 hours of presentation to the hospital have a tremendous impact on long-term organ function and survival.[49]

Organ Dysfunction Scoring Systems

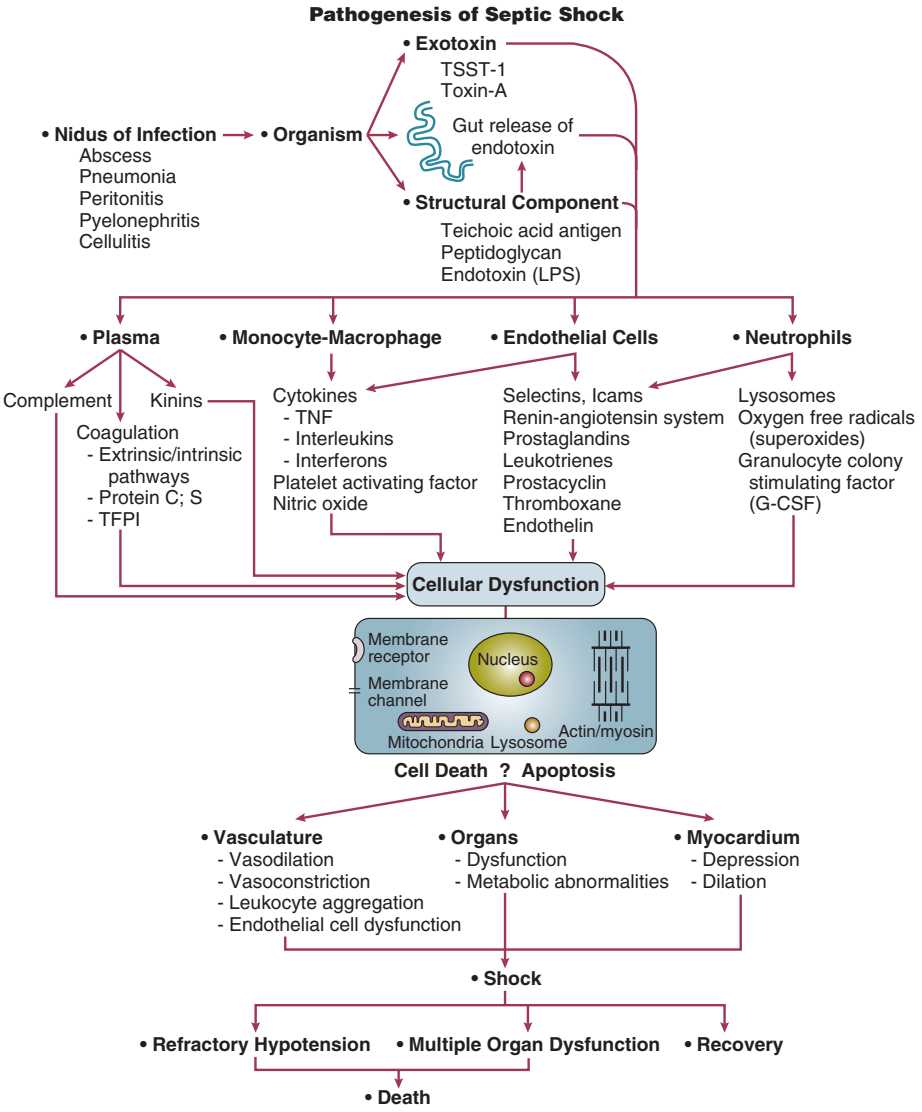
Severity of illness scoring systems have been developed and applied in the intensive care unit (ICU) to describe patient populations. These scoring systems have been useful in predicting expected



• **Fig. 24.4** New paradigm of the cardiovascular profile of septic shock featuring the importance of the microcirculation. Conventional resuscitation targets the optimization of macrocirculatory (i.e., "upstream") hemodynamic parameters, with the monitoring of "downstream" surrogates of tissue perfusion to determine the effectiveness of resuscitation. The microcirculation is the critical intermediary. Although the macrocirculation (heart and large arteries) regulates the global distribution of blood flow throughout the body, an intact and functional microcirculation is necessary for the effective delivery of blood flow to tissues. Intrinsic microcirculatory dysfunction can be a pivotal pathogenic event in the development of sepsis-associated tissue hypoperfusion. Using new videomicroscopy techniques, microcirculatory flow can now be studied in human subjects with septic shock. *CVP,* Central venous pressure; *DO_2,* oxygen delivery; *Hgb,* hemoglobin; *MAP,* mean arterial pressure; *PCWP,* pulmonary capillary wedge pressure; *SV,* stroke volume; *SvO_2,* mixed venous oxygen saturation; *SVR,* systemic vascular resistance; *VO_2,* oxygen consumption.

mortality and comparing different patient populations. The use of general outcome prediction models, such as the Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Probability Model (MPM), and the second Simplified Acute Physiology Score (SAPS), is discussed in greater detail in Chapter 67.

It is recognized that the risk of death for patients with severe sepsis is directly related to the number of dysfunctional organs. Organ dysfunction scoring systems have been developed as a tool for the clinician to characterize the severity of illness and follow the clinical evolution of patients with sepsis. The more commonly used systems are the SOFA, the Logistic Organ Dysfunction System, and the MODS. Perhaps the most commonly used is the SOFA score (Table 24.4). It was initially described by Vincent and colleagues to assess the incidence of organ dysfunction in critically ill patients.[47] Using the SOFA scores in patients with severe sepsis, these researchers found that mortality rates were lowest in patients without organ dysfunction (9%) and rose progressively with the number of organ dysfunctions (one organ, 22%; two organs, 38%; three organs, 69%; ≥four organs, 83%). The type of organ dysfunction also affects mortality. Hebert and coworkers[50] used logistic aggression analysis of the results of a simple multiple system organ failure score to determine the odds ratio for death for specific organ system dysfunctions. This study showed that the adjusted odds ratios (ORs) for covariates most predictive of mortality were hematologic (OR = 6.2), neurologic (OR = 4.4), hepatic (OR = 3.4), cardiovascular (OR = 2.6), and age (OR = 1.05). It is important to remember that there are caveats when using organ dysfunction scores for the management of individual patients with severe sepsis. Most important, organ dysfunction is not a static process and it changes over time. Levy and colleagues reported that changes in SOFA score over the first 24 hours were associated with outcomes in patients with severe sepsis.[51] Improvement in cardiovascular,

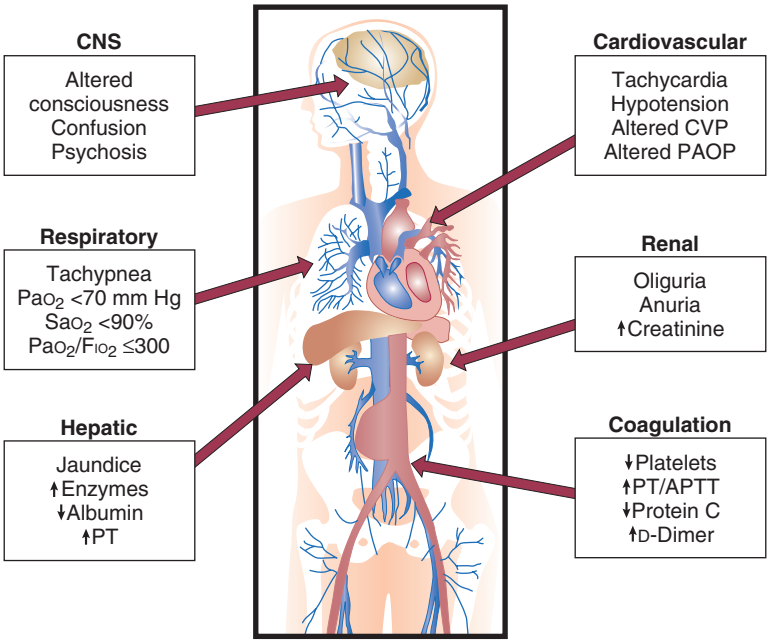


• **Fig. 24.5** Pathogenetic sequence of the events in septic shock. *G-CSF,* Granulocyte colony-forming factor; *LPS,* lipopolysaccharide; *TFPI,* tissue factor pathway inhibitor; *TNF,* tumor necrosis factor; *Toxin A, Pseudomonas aeruginosa* toxin A; *TSST-1,* toxic shock syndrome toxin 1. (Data from Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med.* 1993;328:1471–1477.)

renal, or respiratory failure over the first 24 hours was associated with lower mortality. On the other hand, worsening SOFA scores for these organ systems were associated with higher mortality (an approximately 60% mortality rate). Finally, how these scores change over time in response to therapeutic interventions is probably of greater value than an initial organ dysfunction score.

Clinical Presentation

Patients with severe sepsis and septic shock typically manifest signs of systemic inflammation, including fever or hypothermia, tachycardia, tachypnea, and elevation or reduction of the white blood cell count. Infection-induced organ dysfunction may occur in the absence of hypotension; however, the hallmark of severe sepsis is hypotension. Other signs of potential tissue hypoperfusion may include lactic acidosis, oliguria, encephalopathy, or diminished capillary refill in the extremities. Hypotension that persists after intravascular volume repletion defines septic shock. Patients with septic shock typically have other organ system dysfunctions; clinical evidence of other organ system dysfunction may range from subtle abnormalities to overt organ failure. Multiorgan system involvement in sepsis may include cardiovascular, respiratory, renal, central nervous system, hepatic, metabolic, or hematologic dysfunction. Respiratory system dysfunction manifests as acute lung injury or, in the most extreme cases, the acute respiratory distress syndrome (ARDS). Sepsis-induced renal dysfunction typically manifests with oliguria and may progress to acute renal failure requiring dialysis. Central nervous system dysfunction manifests as encephalopathy, which may range from mild cognitive impairment to overt coma. Cholestasis is a common manifestation of hepatic dysfunction in sepsis, but in the presence of severe shock, ischemic hepatitis ("shock liver") may occur. Metabolic derangements of septic shock include a loss of glycemic control (hyperglycemia or hypoglycemia) as well as metabolic acidosis. Septic shock is commonly associated with a consumptive coagulopathy, which is likely present in almost all patients at least subclinically,[34,37] but may also manifest clinically



• **Fig. 24.6** Identification of organ failure in severe sepsis. Clinical and laboratory criteria to identify organ failure are shown for each organ system. *APTT,* Activated partial thromboplastin time; *CNS,* central nervous system; *CVP,* central venous pressure; *FIO_2,* fraction of inspired oxygen; *PaO_2,* partial pressure of arterial oxygen; *PAOP,* pulmonary artery occlusion pressure; *PT,* prothrombin time; *SaO_2,* oxygen saturation of arterial blood. (Adapted from Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit Care Clin.* 2000;16:337–352.)

TABLE 24.4 The Sequential Organ Failure Assessment Score

	SCORE				
Organ System	**0**	**1**	**2**	**3**	**4**
Respiratory: Pao_2/Fio_2 ratio	>400	≤400	≤300	≤200[c]	≤100
Coagulation: platelets ($\times 10^3$ μ/L)	>150	≤150	≤100	≤50	≤20
Liver: bilirubin (mg/dL)	<1.2	1.2–1.9	2–5.9	6–11.9	>12
Cardiovascular: hypotension	No hypotension	MAP <70 mm Hg	Dop ≤5 or Dob any dose	Dop >5, Epi ≤0.1 or Nor ≤0.1	Dop ≥50, Epi >0.1, or Nor >0.1
Central nervous system: GCS	15	13–14	10–12	6–9	<6
Renal: creatinine (mg/dL) or daily urine output (mL)	<1.2	1.2–1.9	2–3.4	3.5–4.9 or <500	>5 or <200

Dob, Dobutamine; *Dop,* dopamine; *Epi,* epinephrine; *FIO_2,* fraction of inspired oxygen; *GCS,* Glasgow Coma Scale score; *MAP,* mean arterial blood pressure; *Nor,* norepinephrine; *PaO_2,* partial pressure of arterial oxygen.

Adapted from Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med.* 1998;26:1793–1800.

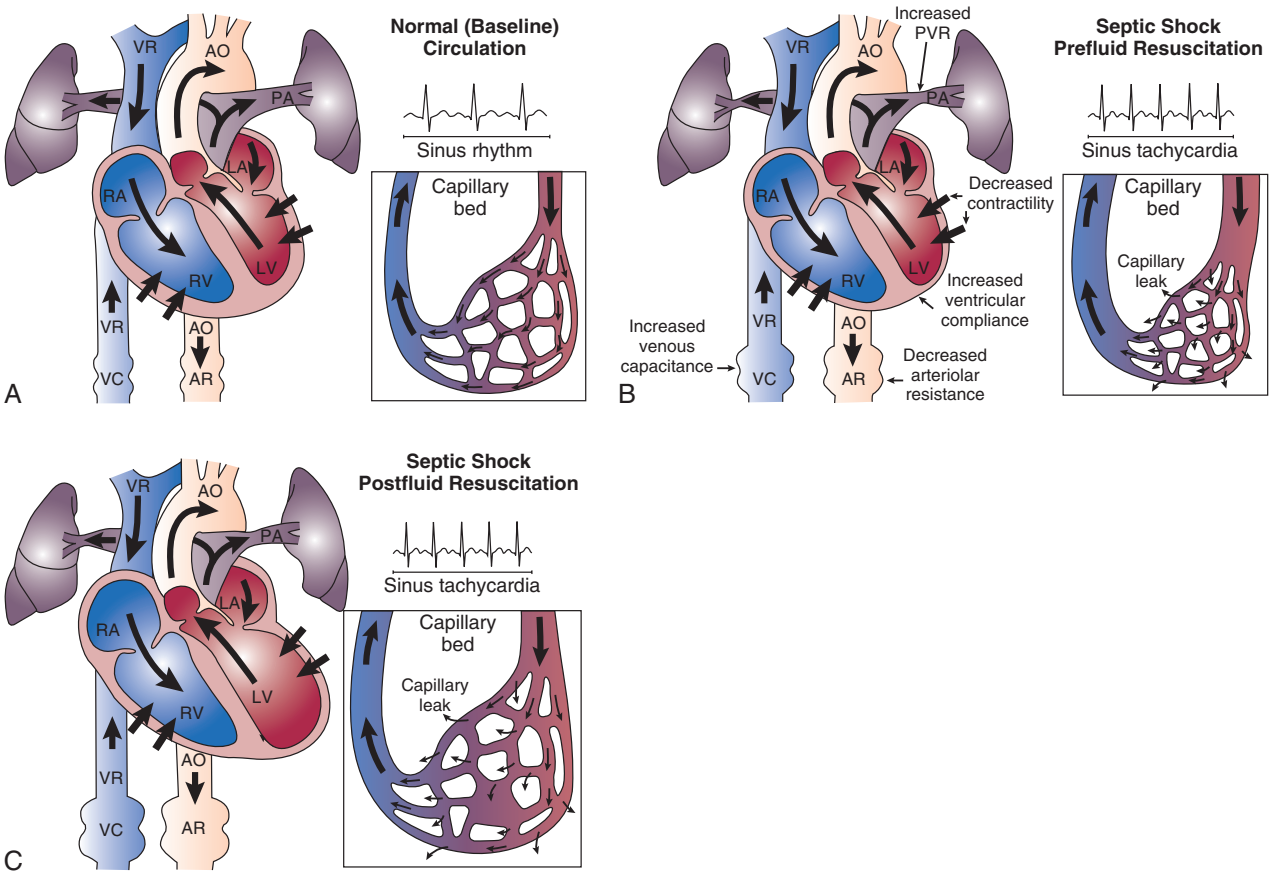
with thrombocytopenia, prolongation of the prothrombin time, or in the most severe cases, overt DIC.

Cardiovascular Profile of Septic Shock

The hemodynamic profile of septic shock is the most complex hemodynamic profile of all shock etiologies (Fig. 24.7).[52] What sets septic shock apart from other causes of circulatory shock is the fact that there may be multiple different mechanisms of circulatory shock occurring simultaneously. Septic shock may have features of (1) hypovolemic shock (poor cardiac filling secondary to systemic capillary leak and increased venous capacitance), (2) cardiogenic shock (infection-induced myocardial depression), and (3) distributive shock (arteriolar vasodilation with tissue hypoperfusion in the face of an adequate CO).

Hypovolemia and Decreased Cardiac Filling

The release of proinflammatory mediators into the circulation causes injury to the integrity of the endothelial cell surface throughout

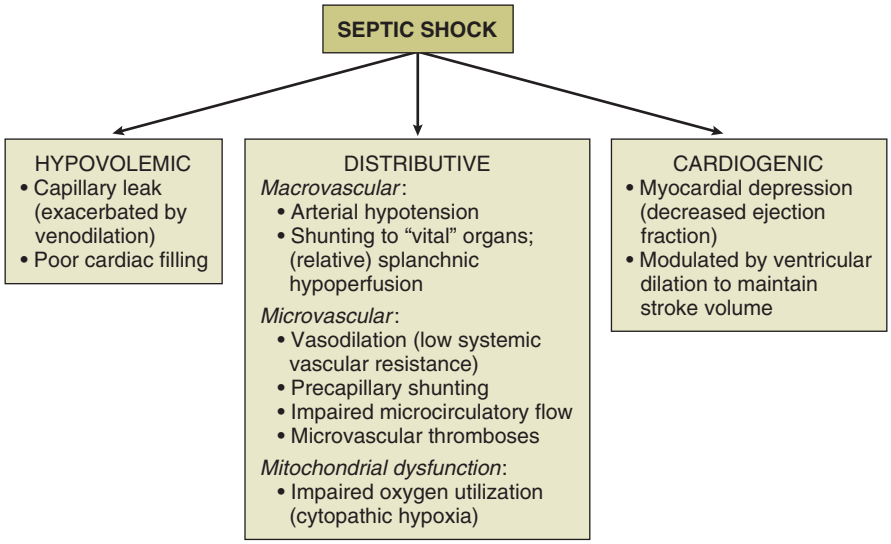


• **Fig. 24.7** Cardiovascular changes associated with septic shock and the effects of fluid resuscitation. A, Normal (baseline) state. B, In septic shock, left ventricular blood return is reduced owing to a combination of capillary leak *(inset),* increased venous capacitance *(VC),* and increased pulmonary vascular resistance. The stroke volume is further compromised by a sepsis-induced decrease in left and right ventricular *(RV)* contractility. Tachycardia and increased left ventricular compliance serve as countermeasures to combat low cardiac output, the latter by increasing left ventricular preload. However, cardiac output remains low to normal. Finally, a decrease in arteriolar (systemic vascular) resistance not only allows a higher stroke volume at any given contractility and left ventricular filling state, but also the potential for severe hypotension, despite restoration of adequate left ventricular filling. C, Aggressive fluid resuscitation compensates for capillary leak, increased venous capacitance, and increased pulmonary vascular resistance by reestablishing adequate left ventricular blood return. Decreased arteriolar resistance *(AR),* tachycardia and increased left ventricular compliance compensate for decreased ejection fraction. Ejection fraction increases as left ventricular filling increases. The net result is that after adequate volume resuscitation, most patients with severe sepsis have a high cardiac output and low systemic vascular resistance state. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *PVR,* peripheral vascular resistance; *RA,* right atrium; *VR,* venous return; ➞, blood flow (cardiac output); ⇄, contractility. (From Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med.* 2003;31:946–955.)

the systemic microvasculature, resulting in severe capillary leak and extravasation of fluid into tissues. Venodilation also compromises venous return. These are major factors in producing hypovolemia and decreased cardiac filling in the patient with septic shock. Septic shock typically has a decreased cardiac preload in the initial phase of resuscitation. Fluid resuscitation with IV volume expansion then frequently produces the hallmark increased CO–low systemic vascular resistance (SVR) hemodynamic profile of septic shock (see the later "Vasodilation" section).[41] The combination of a decreased preload and myocardial depression means that in the early phase of sepsis resuscitation—before receiving adequate volume resuscitation—patients may initially have low CO. Capillary leak is an ongoing process in the course of septic shock therapy, and therefore hypovolemia may continue to be problematic, even after adequate cardiac filling has been initially achieved. Fluid balance (input of IV fluids and output of urine) is an unreliable parameter for assessing adequacy of fluid resuscitation in septic shock.

Myocardial Dysfunction

Septic shock is associated with depression of biventricular function with a decrease in the ejection fraction. Ventricular dilation occurs as a compensatory mechanism and raises end-diastolic volume so that stroke volume (SV) can be preserved, taking advantage of the Starling principle. When myocardial dysfunction occurs, a high CO can still be achieved in many circumstances because of biventricular dilation, tachycardia, and arteriolar dilatation, as long as the patient is adequately volume resuscitated and does not have a



• **Fig. 24.8** Major components of the hemodynamic profile in septic shock. (From Trzeciak S, Parrillo JE. Septic shock. In: *Society of Critical Care Medicine 8th Adult Critical Care Refresher Course*. Chicago: Society of Critical Care Medicine; 2004.)

severe cardiac suppression (related either to previously existing cardiac dysfunction or overwhelming sepsis-induced suppression of cardiac systolic function).[53] The most important inflammatory mediators that induce myocardial depression are TNF-α, IL-1, and perhaps nitric oxide.[54,55] Coronary blood flow is typically normal or increased in septic shock.[56] Although coronary blood flow can be diminished by severe arterial hypotension that compromises coronary perfusion pressure (especially if there is preexisting coronary artery disease), myocardial ischemia does not appear to be the causative factor of the depression in myocardial performance. It has been reported that nearly half of patients with septic shock have echocardiographic evidence of some degree of depression of systolic function, even in the absence of preexisting cardiac disease.[57] However, myocardial depression is typically not the predominant feature of the septic shock hemodynamic profile.[53] For the majority of patients, aggressive intravascular volume expansion to restore adequate cardiac filling pressures is enough to achieve a reasonable CO.

Vasodilation

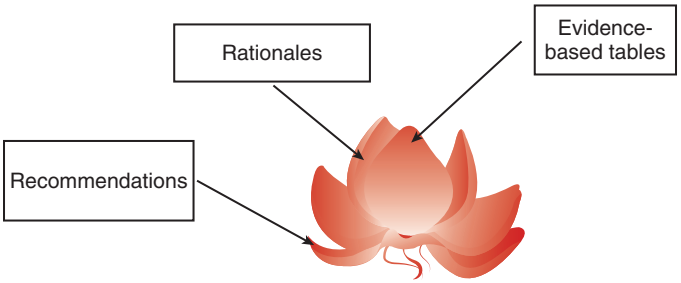
Septic shock is characterized by peripheral maldistribution of blood flow to tissues such that tissue hypoperfusion abnormalities can persist despite a normal or high CO. This is called "distributive shock."[53] This maldistribution of blood flow may occur at both microcirculatory and macrocirculatory levels. The role of microcirculatory dysfunction is discussed in detail in a separate section of this chapter. At the level of the macrocirculation, the autoregulation of blood flow within any single organ system in a normal host can typically maintain effective tissue perfusion over a wide range of systemic pressures (usually ranging from a MAP of 50 mm Hg to 150 mm Hg). However, there is heterogeneity of blood flow distribution throughout the body in septic shock owing to preferential shunting of blood flow to vital organs (e.g., the brain and myocardium). The gastrointestinal tract may be the earliest organ system to experience tissue hypoperfusion in septic shock, as blood is shunted away from the splanchnic circulation to preserve blood flow to the brain, myocardium, and skeletal muscles. Ischemic injury to the gastrointestinal tract and leakage of endotoxin into the systemic circulation may be a source of ongoing systemic inflammation in septic shock. The three components of the hemodynamic profile are displayed in Fig. 24.8.

Management of Severe Sepsis and Septic Shock

Overview and Management Guidelines

The Surviving Sepsis Campaign (SSC) first published comprehensive international consensus guidelines for sepsis management in 2004.[58] The SSC guidelines were updated in 2008 and then again in 2012 and then most recently in 2016 as the best evidence for sepsis management continues to evolve.[59,60] The critical care practitioner should be familiar with the concepts in the SSC guidelines and is referred to the most recent update for a comprehensive review, including evaluation of the strength of evidence for each recommendation. The SSC guidelines writing committee consisted of representatives from numerous medical professional societies that relate to the care of the septic patient, and these medical professional societies have endorsed the guidelines. The 2016 guidelines are 73 pages long and include 90 recommendations. A users' guide has been published that recommends differing approaches to the guidelines based on interests of the reader[61] (Fig. 24.9). A concise synthesis of the 2016 recommendations is included in the appendix presented later in this chapter.

The treatment recommendations in the SSC guidelines are intended to provide guidance for clinicians. However, treatment decisions must be individualized to the patient, and the recommendations cannot replace a clinician's decision-making capability when he or she is presented with a patient's unique set of clinical data. In addition, resource limitations in some institutions may prevent physicians from accomplishing some treatment recommendations. Thus the SSC guidelines are intended to represent "best practice" recommendations for the management of sepsis rather than standard of care. These guidelines have now been adopted by certain governments as quality indicators for the treatment of septic patients with mandatory reporting of performance.



• **Fig. 24.9** Layers of the Surviving Sepsis Campaign. The layers of an onion are paralleled to the components of the guidelines document, reflecting the depth of exploration by the user. (From Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 Surviving Sepsis Guidelines. *Intensive Care Med.* 2017;43(3):299–303.)

General Principles

The patient should be brought to a critical care area in the emergency department (ED) or ICU as quickly as possible to facilitate appropriate monitoring, rapid resuscitation, and optimal hemodynamic support. Continuous electrocardiographic monitoring and pulse oximetry are useful tools in the management of critically ill patients with severe sepsis. In addition, a variety of more invasive devices may be of use. The arterial catheter has two functions. It allows frequent blood sampling and continuous assessment of arterial pressure. Metabolic parameters to monitor the effectiveness of resuscitation and cardiovascular support are limited; however, measurement of blood lactate can provide important information. In 1964, Broder and Weil first proposed the utilization of blood lactate levels as a surrogate of adequacy of tissue perfusion and presence of anaerobic glycolysis.[62] It is important to realize, however, that elevation of blood lactate does not always indicate ineffective tissue perfusion, as hyperlactatemia can be due to metabolic derangements or drug therapy (e.g., β-agonists such as epinephrine) and can be responsible for the elevation of blood lactate observed in sepsis. However, in the great majority of cases an elevated lactate represents ongoing tissue hypoperfusion. Blood lactate levels have prognostic value in septic patients. Regardless of the cause of lactate elevation in sepsis, markedly elevated blood lactate (e.g., lactate ≥4 mmol/L) signals an increased risk of death.[63–66]

Antibiotic Therapy and Source Control

Early administration of empiric antibiotic therapy and expeditious source control to eliminate any nidus of infection are imperative in the management of septic shock. Appropriate antibiotics given early may substantially improve the likelihood of survival.[67] A choice of antibiotics is usually empiric because the organism is not yet identified when antibiotics must be delivered. Failure to include antibiotic coverage for what is later identified to be the offending organism has been associated with increased risk of death[68]; therefore broad-spectrum antibiotics are necessary as soon as septic shock is identified. Kumar and associates performed a large-scale multicenter retrospective study of patients with septic shock and found a linear association between the duration of hypotension before the first dose of antibiotic administration and risk of death.[68] One prospective ED-based study from Puskarich and colleagues found higher survival rates if antibiotics were administered before the onset of shock compared to after shock onset, but in contrast to the Kumar data the authors did not find a measurable effect of incremental time to administration of antibiotics on survival.[69] One potential reason to explain these results is that the Kumar study was a heterogeneous population and the therapeutic interventions (e.g., early resuscitation and hemodynamic support) that the patients received were not standardized, whereas all the patients in the Puskarich study were ED patients treated according to a standardized early resuscitation protocol.

The SSC currently recommends that IV antimicrobial therapy be started as soon as possible, preferably within an hour of recognition of severe sepsis and septic shock. Even though a 1-hour time window is deemed desirable, longer time frames are common in real-world clinical practice. One reason for this could be the fact that sepsis often mimics other disorders, and the diagnosis of sepsis as the cause of the illness is often not obvious at the time of initial presentation. As such, the need for antimicrobial agents in the treatment of the patient may also not be immediately obvious. Once the diagnosis is made (or strongly suspected), antimicrobial therapy should be started promptly. When multiple antibiotics are to be given, it is important to think about what the more likely organism(s) is and how long each antibiotic takes to infuse when one antibiotic is to be administered followed by another. Initial empiric antimicrobial selection should be broad enough to cover all likely pathogens based on clinical circumstances. In patients with septic shock, de-escalation or restriction of antibiotic therapy as a strategy to reduce the development of antimicrobial resistance is not recommended until after a causative organism has been identified or after the patient's condition has markedly improved.

Pertaining to source control, the SSC recommends that a specific anatomic diagnosis of infection requiring consideration for emergent source control (e.g., laparotomy for intraabdominal source) be sought and diagnosed or excluded as rapidly as possible. Thus imaging studies, if needed, should be performed as soon as possible to make the diagnosis. One important caveat to this is the inherent hemodynamic instability and overall severity of illness in septic shock that may make invasive procedures or transport of patients outside the ICU for imaging studies potentially unsafe. Balancing potential risks and benefits in that scenario is very important. When a procedure for source control is found to be necessary, the surgical drainage should be undertaken for source control as soon as feasible after successful initial resuscitation and stabilization of the patient.[70,71]

Supportive Therapies

The 2016 SSC guidelines offer a comprehensive document on recommendations as it pertains to supportive therapies for the critically ill patient that are relevant for severe sepsis/septic shock.[60] In addition, the reader is referred to other chapters in this textbook dealing with organ-specific support therapies.

Glucose Control

Hyperglycemia and insulin resistance are common in sepsis and in the critically ill patient in general. In 2001, Van den Berghe and colleagues demonstrated that intensive insulin infusions titrated to strict glycemic control (80–110 mg/dL) in critically ill surgical patients could produce a mortality reduction (2016 guidelines).[72] A second study by Van den Berghe targeted medical ICU patients and used the same strict upper threshold target of 80 to 110 mg/dL.[73] In the intention-to-treat analysis, no significant difference

was found in mortality but the incidence of acute kidney injury was decreased and earlier weaning from mechanical ventilation was shown. Hypoglycemia occurred in one of 20 patients in the strict control arm compared with one in 100 in the control group.

A multicenter randomized trial in Germany, examining the role of intensive insulin therapy in critically ill patients using a similar insulin protocol, was stopped early because of a high incidence of hypoglycemia (17.0% vs. 4.1%, $P < 0.001$) with no difference in 28-day mortality.[74]

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) was a multicenter, multinational randomized clinical trial involving 6100 subjects from 42 hospitals in Australia, New Zealand, Canada, and the United States.[75] The NICE-SUGAR study compared maintaining the glucose concentration at 180 mg/dL or lower with strict glucose control with a target glucose of 81 to 108 mg/dL. Ninety-day mortality (the primary outcome variable) was higher in the intensive glucose control group (27.5% vs. 24.9%, $P = 0.02$). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients as well as patients with sepsis versus those without sepsis. The higher mortality in the strict glucose control group occurred despite a much lower rate of hypoglycemia than previously reported in strict glycemic control protocols. The take-home message from the NICE-SUGAR trial would be that a glucose level higher than 180 mg/dL should be treated to achieve a target blood glucose concentration between 120 and 180 mg/dL.

Prophylaxis for Deep Vein Thrombosis and Stress Ulcers

Patients with severe sepsis and septic shock are at risk for thromboembolism and, in the absence of contraindications, are deserved of deep vein thrombosis prophylaxis. Low-molecular-weight heparin is preferred.[76]

Patients with severe sepsis and septic shock are at risk for gastric stress ulcers and should receive prophylaxis. The potential causes of stress ulcers include loss of mucosal protection from gastric acid, increased acid production, gastric mucosal hypoperfusion, and oxidative injury to the gastric mucosa.[77]

Risk factors for stress ulcers are shown in Box 24.2.[78,79] Proton pump inhibitors or histamine-2 receptor antagonists may be used for stress ulcer prophylaxis.

Nutrition

Although parenteral nutrition can provide targets for calories, protein, and essential fats, it is associated with complications; the primary one of concern is infection and it is not associated with the physiologic advantages of enteral feeding as it relates to mucosal health.[80] Therefore enteral feeding is preferred in patients with severe sepsis. Early parenteral nutrition should be avoided and initial low-dose (trophic/hypocaloric) enteral nutrition begun early in the course of the patients with sepsis and advanced as tolerated.[60] We do not consider septic shock a contraindication for initiation of enteral feeding and the use of prokinetic agents may facilitate tolerance.

• BOX 24.2 Risk Factors for Gastric Stress Ulcers

Coagulopathy receiving renal replacement therapy
Mechanical ventilation >48 h
More severe organ failure score
Liver disease

Early Resuscitation and Hemodynamic Optimization

One of the goals in the early management of patients with sepsis is effective resuscitation to restore adequate tissue perfusion and decrease the risk of organ system injury. A number of hypotheses have been developed to explain the relationship between shock and the development of organ failure in critical illness. One hypothesis suggests that organ failure during critical care occurs as a consequence of inadequate oxygen delivery to the organs and tissues. Based on this hypothesis, several investigators have suggested that patients should be resuscitated to supranormal goals of systemic oxygen delivery in an attempt to prevent organ failure and improve outcome. The concept of supranormal oxygen delivery refers to the use of fluid resuscitation and inotropic drugs to drive up the oxygen delivery to achieve a predefined target. Several studies have examined this concept, although it is important to recognize that some studies have been performed in heterogeneous populations of critically ill patients rather than populations of patients with sepsis. The earliest clinical trials in perioperative high-risk surgery patients demonstrated an outcome benefit.[81,82] Subsequently, however, numerous trials of supranormal oxygen delivery in critically ill patients failed to demonstrate any benefit.[83,84] A meta-analysis concluded that supranormal oxygen delivery in critically ill patients was not beneficial[85] and this concept largely fell out of favor in the 1990s.

For goal-oriented hemodynamic optimization to be beneficial, it has become clear that *timing* is critical. In contrast to the trials in perioperative high-risk surgery patients, subjects in the earlier studies were randomly assigned to treatment much later, up to 72 hours after initial presentation.[83] In a meta-analysis of critically ill patients that stratified studies by severity and the timing of interventions (early vs. late), an outcome benefit was identified in the subset of patients with a high severity of illness and early initiation of interventions.[85] A meta-analysis, this time specifically focused on patients with sepsis, found that quantitative resuscitation (i.e., early hemodynamic optimization targeting predefined quantitative endpoints of resuscitation) was associated with lower mortality rate in patient with sepsis, but only if applied early, defined as less than 24 hours after presentation.[86] These data suggest that quantitative resuscitation in the treatment of severe sepsis and septic shock can in fact be beneficial—in the right patient.

This early intervention concept was the rationale behind the study of early goal-directed therapy (EGDT) for severe sepsis and septic shock by Rivers and colleagues.[49] EGDT is a type of quantitative resuscitation for patients with sepsis that involves targeting central venous oxygen saturation ($ScvO_2$) as a monitor of the adequacy of oxygen delivery. In a single-center randomized controlled trial of 263 ED patients with severe sepsis and septic shock, Rivers and colleagues targeted predefined endpoints of resuscitation, including central venous pressure (CVP) 8 to 12 mm Hg, MAP 65 mm Hg or greater, and $ScvO_2$ 70% or greater in the ED.[49] The authors reported that the EGDT protocol was associated with a 16% absolute risk reduction for mortality rate (30.5% vs. 46.5%). This study was a landmark contribution to the literature in showing that early interventions in the resuscitation phase of therapy can be associated with a significant improvement in long-term survival

for patients with sepsis. There have now been multiple large randomized controlled trials that now show that early aggressive resuscitation without CVP and $ScvO_2$ guidance is just as effective and noninferior to early goal-directed targets of the original Rivers trial.[87–90]

A multicenter-based randomized trial by Jones and associates compared lactate clearance (defined as a decrease by ≥10% in the serum lactate concentration) versus $ScvO_2$ as an endpoint of sepsis resuscitation.[90] Among 300 patients with sepsis-induced tissue hypoperfusion, the authors found that lactate clearance was noninferior to $ScvO_2$ for the primary outcome of all-cause in-hospital deaths. These data suggest that, in addition to ensuring adequate cardiac preload and arterial blood pressure, lactate clearance has potential as a resuscitation target in sepsis-induced tissue hypoperfusion.

The data are conflicting regarding which therapeutic interventions are typically needed beyond intravascular volume expansion and vasopressor agents in the early resuscitation of patients with sepsis. In the Jones trial, after aggressive administration of IV crystalloid to achieve a CVP of 8 to 12 mm Hg and vasopressor agents to achieve an arterial pressure of 65 mm Hg or greater in a stepwise resuscitation algorithm, very few patients required additional therapies for augmentation of oxygen delivery to achieve either lactate clearance or $ScvO_2$ goals (i.e., only 7% required packed red blood cell transfusion and 3% required inotropes).[90] In contrast, 64% of patients in the EGDT ($ScvO_2$-targeted) arm in the Rivers study were treated with blood transfusions and 14% were treated with inotropic support. The Rivers data would suggest that packed red blood cell transfusions and inotropes are commonly required therapies for optimization of oxygen delivery in sepsis resuscitation, whereas the Jones trial (and multiple other recent observational clinical studies) suggests that these additional therapies are rarely required to achieve resuscitation goals. Although the optimal endpoints of quantitative resuscitation for sepsis remain controversial, it is generally accepted that the earlier the therapeutic interventions are delivered, the greater the capacity for benefit. The ProMISe (Protocolized Management In Sepsis), ARISE (Australasian Resuscitation In Sepsis Evaluation), and ProCESS (Protocolized Care for Early Septic Shock) trials compared early resuscitation of septic shock with and without use of a central venous catheter (CVC) for measurement and protocolization use of CVP and $ScvO_2$ to guide therapy.[87–89] These trials compared the original EGDT protocol as devised by Rivers et al. to "usual care" in the ICU (no use of protocolized CVC variables) and found no difference in mortality. A meta-analyses of these three studies confirmed this outcome.[91] However, at time of randomization, patients in these large studies had already received significant crystalloid fluid resuscitation before randomization and antibiotics had already been administered in the great majority despite only a short stay in the ED.[87,89] Therefore the resuscitation phase of therapy incorporating early recognition and treatment of septic shock appears to be an important window of opportunity for impact on outcome.

Currently the SSC recommends at least 30 mL/kg of initial volume resuscitation with addition volume guided by frequent reassessment of hemodynamic status. For patients who present with an elevated lactate as a marker of tissue hypoperfusion, a normalization of lactate is a therapeutic target. A target MAP is at least 65 mm Hg using vasopressors as needed in septic shock. See Chapter 67 for a discussion of the sepsis quality metrics for the first 6 hours of treatment of severe sepsis and septic shock that are mandatory for reporting by U.S. hospitals.

The SSC acknowledges limitations with using static ventricular pressure estimates (e.g., CVP) for assessing intravascular volume status in patients with septic shock. Specifically, measuring CVP in a range that is typically thought to be normal (or even high) does not necessarily exclude the possibility of preload-dependent CO, especially in patients with preexisting chronically elevated cardiac filling pressures (e.g., cardiomyopathy or pulmonary artery hypertension). However, a markedly low value for CVP can be helpful in that it can reliably indicate the presence of hypovolemia in patients with circulatory shock. Targeting dynamic measures of fluid responsiveness (e.g., pressure variation) and volumetric indices (e.g., SV variation) may be useful. Bedside cardiovascular ultrasonography has gained wide application where it is used to assess intravascular volume and cardiac filling and contractility. Inferior vena cava size and respiratory cycle variation in size in a patient with a regular heart rhythm is thought to be helpful in decision making with regard to predicting a positive response to fluids. More recent data support that the superior vena cava may provide more precise data in this regard.[92] The ability to directly assess a global estimate of cardiac filling as well as assess cardiac contractility is also valuable. The latter would assist in decision making as to adding inotropic therapy for a patient believed to have adequate intravascular volume, depressed systolic function, and persisting evidence of tissue hypoperfusion.

It is appropriate to assume that SV is proportional to arterial pulse pressure.[93] Given that assumption, pulse contour devices use the same principle and relate the contour of the arterial pressure waveform to SV and SVR.[94] With constant SVR any pulse contour variation is produced solely by changes in SV. An algorithm is used to determine SV, and CO is then determined by factoring in heart rate. Devices that use pulse contour to estimate SV and CO may be calibrated or uncalibrated. Calibrated devices directly measure CO initially and then are able to assign the pulse contour at the time of that measurement to a precise SV. The pulse contour is then tracked with an increase or decrease in the pulse contour representing increase or decrease in SV, respectively. Uncalibrated devices use proprietary formulas to convert pulse waveform analysis to SV.

A number of devices are available that use pulse contour analysis for SV calculation. The PiCCO system (Pulsion Medical Systems SE, Munich, Germany) uses a thermistor-tipped arterial line in a proximal artery to measure the arterial waveform morphology while using transpulmonary thermodilution via a CVC for CO measurement and calibration.

The Vigileo/FloTrac system (Edwards Lifesciences, Irvine, CA) uses a standard arterial catheter. SV is calculated using a proprietary algorithm to calculate specific vascular compliance based on age, height, gender, weight, and waveform characteristics. It is does not calibrate by direct measurement of CO.

The LiDCO device (LiDCO, Cambridge, UK), also uses an arterial catheter but CO is measured with lithium dilution for calibration. Although conceptually similar, the analysis of the arterial waveform is a pulse power analysis instead of a pulse contour analysis.

Although potentially useful in the resuscitation of hypoperfused patients with sepsis, pulse contour analysis monitors do have potential limitations. First, these devices rely on an optimal arterial signal. Overdamped or underdamped traces may lead to inaccuracies of SV measurement. Arrhythmias, aortic regurgitation, and the use of an intraaortic balloon pump all affect the pulse contour and have been shown to affect accuracy.[95] Changes in SVR may also lead to inaccuracies in CO measurement. Recalibration or

recalculation of the referencing constant will assist with errors based on changes in SVR. Respiratory variation of SV as measured by pulse contour analysis can also assist in predicting which patients will respond to additional fluid administration with greater SV variation representing greater likelihood of response.[96]

The pulmonary artery catheter (PAC) can provide data such as cardiac filling pressures, cardiac index, and SVR. The data gathered from the PAC can be useful for titrating vasoactive medications in septic shock. Although indications for PAC use are controversial and are often debated, it is important to recognize that the PAC represents a tool for guiding therapy rather than being a therapeutic intervention in itself. Monitoring venous oxygen saturation (either mixed venous oxygen saturation [SvO_2] or $ScvO_2$) can yield information on the oxygen supply/demand relationship, especially in the early resuscitation phase of septic shock therapy. A markedly low value for either SvO_2 or $ScvO_2$ indicates a significant imbalance in the oxygen supply/demand relationship and likely indicates a need for augmenting global oxygen delivery in most patients. Paradoxically, in patients whose cells are unable to consume oxygen (precapillary shunting or mitochondrial dysfunction) an elevated SvO_2 or $ScvO_2$ with an elevated lactate level becomes a very poor prognostic indicator and identifies patients in whom increasing oxygen delivery will not correct tissue hypoxemia.

Fluid Resuscitation

Intravascular volume expansion is another important aspect of sepsis management and is the best initial therapy for the cardiovascular instability of septic shock. The initial hypotension observed in many patients with sepsis-induced cardiovascular instability may be reversed with volume infusion alone. A reasonable approach to initial volume resuscitation in the adult patient is the rapid administration of 30 mL/kg or 2 to 3 L of crystalloid solution (e.g., 0.9% sodium chloride [NaCl] or lactated Ringer solution). If (after initial volume infusion) the hemodynamic instability has resolved, further aggressive resuscitation may be unnecessary and the patient may be relegated to a somewhat higher maintenance fluid.

Crystalloid fluid can be administered as normal saline or balanced crystalloid (Ringer lactate, Ringer acetate, Plasma-Lyte [Baxter Healthcare, Deerfield, IL]). Normal saline solution has chloride concentrations that significantly exceed those of plasma while the sodium concentration is similar. Giving large amounts of normal saline solution to patients with septic shock would narrow the strong ion gap (difference between sodium and chloride) and produce a non–anion gap hyperchloremic acidosis. Database and prehistorical and posthistorical control studies have shown an association between normal saline solution–based fluid administration compared with balanced crystalloid, and worse outcomes including increased renal replacement therapy.[97–99] A small animal study suggested that balanced crystalloids might be better for renal stress in a hemorrhagic shock model.[100] The SPLIT (Saline vs. Plasma-Lyte Fluid Therapy) trial randomly assigned 2278 patients admitted to the ICU to receive normal saline solution versus balanced crystalloids and showed no difference in outcomes. However, these were predominantly postoperative patients and the median fluid amount during the ICU stay was only 2 L.[101] The SMART study (Isotonic Solutions and Major Adverse Renal Events Trial) randomly assigned 15,802 patients admitted to the ICU to receive either balanced crystalloids or normal saline solution for the duration of the hospital stay and found a significant difference between treatment groups as to an a priori combined renal morbidity/mortality score (MAKE30 [major adverse renal events by 30 days after acute kidney injury]) that favored balanced crystalloid (14.3% vs. 15.4%).[102] Of the patients in the study, 15% had severe sepsis or septic shock. Two additional megatrials comparing normal saline solution and balanced crystalloid are also under way (one in Australia/New Zealand and one in Brazil) with a companion design offering the ability for a combined analysis. The summation of literature to date as applied to the critically ill patient population in general would favor the use of balanced crystalloid such as Ringer lactate or Ringer acetate in patients with severe sepsis/septic shock without clinically significant hyponatremia, metabolic alkalosis, or the need for hypernatremia as a therapeutic target (such as in the presence of increased intracranial pressure).

Because there is no proven benefit of colloid therapy over crystalloids in resuscitation,[103] the SSC currently recommends initiating volume resuscitation with crystalloid for patients with septic shock and suspicion of hypovolemia. The SSC-recommended volume of crystalloid is a minimum of a 30-mL/kg fluid challenge. If there is hemodynamic improvement with this initial fluid challenge, clinicians may continue repeated fluid challenges to see if further hemodynamic improvement occurs. The SSC further suggests consideration of the addition of albumin infusion to initial crystalloid resuscitation if the initial crystalloids are judged to be ineffective. The SSC recommends against the use of synthetic hydroxyethyl starches in volume resuscitation because these agents have been associated with increased risk of acute kidney injury and increased mortality.[104]

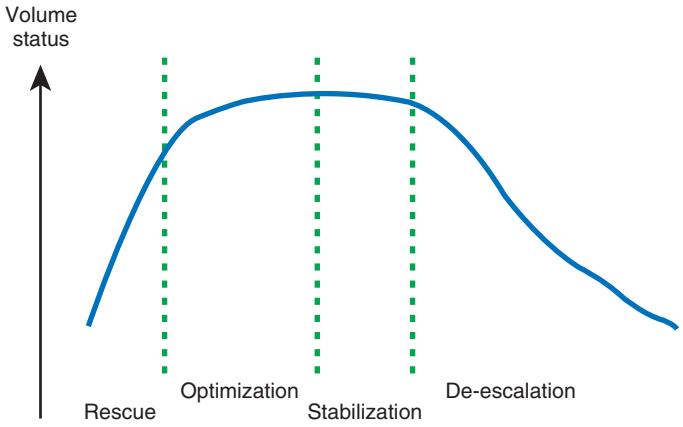
One prudent strategy of volume resuscitation (rather than targeting a predefined cardiac filling pressure) would be to continue fluid bolus administration until the cardiac index or SV fails to rise with additional intravascular volume expansion, indicating optimization of cardiac preload. This would be accomplished by directly measuring or estimating flow. With the increasing use of point-of-care ultrasonography and bedside cardiac ultrasonography, the ability to predict volume responsiveness using IVC/SVC measurements, aortic flow, and intracardiac pressures is becoming increasingly more prevalent. A high left ventricular filling pressure should be avoided because it could contribute to pulmonary capillary leak and cause impairment of oxygenation if the patient has concomitant acute lung injury. The association of poor outcome with high input-output ratios has raised concern about the potential detriment of overly aggressive fluid administration in resuscitation of septic shock.[105] However, patients with more severe sepsis (and therefore more likely to die) would be expected to have more severe venodilation and more severe capillary leak and by definition require more fluids to maintain adequate intravascular volume. The challenge is knowing the optimal intravascular volume. For each patient there is likely an optimal mix of fluid and vasopressor to maintain MAP, and the challenge for the clinician is to determine this optimal mix. A guideline recommendation for an initial fluid bolus that fits most patients is needed, particularly when directed to the practitioner who is not skilled in caring for the critically ill, hypoperfused patient with sepsis. It is likely that both underresuscitation and overresuscitation occur and influence outcome. Individualization of fluid resuscitation by those more experienced in caring for such patients is important.[106] When life-threatening hypotension is present, norepinephrine should be started early even before hypovolemia has resolved regardless of the reason for poor outcomes after fluid resuscitation. In 2017 the New York State–mandated hospital quality improvement efforts were published showing that rapid completion of the entire 3-hour bundle and rapid administration of antibiotics—but not rapid completion of

initial fluid bolus—were associated with better outcome.[107] It is possible that a sense of urgency was a confounder that correlated with patients with more severe illness and could not be accounted for in the risk adjustment. Even if early aggressive fluid resuscitation saves lives, there is likely still a price to pay downstream with the fluid that is left in the extravascular tissues once the pathogens are eradicated and the inflammation response is quenched. This fluid is typically mobilized (so-called autodiuresis) in patients with adequate renal function as capillary membranes heal during the recovery phase. Whether this diuresis could be encouraged with an IV diuretic after a patient's infection is cleared and tissue hypoperfusion no longer exists is a matter that requires more research. A conceptual model proposing four phases of IV fluid therapy has been proposed.[108,109] The four phases are rescue, optimization, stabilization, and de-escalation (Fig. 24.10). Rescue should occur within minutes and may be lifesaving. Optimization occurs over hours and maintains tissue perfusion. Stabilization occurs over days and aims for zero fluid balance while maintaining organ support. Finally, de-escalation is characterized by mobilization of fluid and autodiuresis as a sign of recovery of capillary function and organs. Of note, it has also been shown that outcomes are better when diuresis is targeted to produce lower intravascular filling pressures in patients with ARDS who are not using vasopressors and do not have an elevated lactate level.[110]

Vasopressor Therapy

In addition to fluid administration, pharmacologic support of blood pressure is frequently necessary in both the initial resuscitation and subsequent support of patients with septic shock. After administration of fluids these agents are the next most important interventions for the initial management of the hemodynamically unstable patient. Restoration of adequate arterial pressure is the endpoint of vasopressor therapy. The SSC recommends targeting a MAP of 65 mm Hg or higher; however, blood pressure does not always equate to systemic blood flow and the precise MAP to target may not necessarily be the same for all patients. LeDoux and coworkers demonstrated that in patients with septic shock treated with norepinephrine to maintain target MAP, MAPs of 65, 75, and 85 mm Hg achieved equivalent indices of tissue perfusion.[111] In an observational study of patients with septic shock Varpula and associates found that an area under the curve of 65 mm Hg was the best predictor of positive outcome and showed that among multiple hemodynamic variables, a MAP above 65 mm Hg was the best predictor of a favorable outcome.[112] A large multicenter randomized controlled trial noted that a MAP goal of 80 to 85 mm Hg has similar outcomes compared to a MAP goal of 65 to 70 mm Hg. The higher dose range was associated with an increased rate of new-onset atrial fibrillation,[113] and in patients with chronic hypertension the higher MAP target was associated with a lower need for renal replacement therapy. A MAP of 65 mm Hg may be inadequate for a patient with preexisting poorly controlled essential hypertension and associated vascular disease. Similarly, it should be recognized that in some patients it is possible to have MAPs lower than 65 mm Hg with adequate tissue perfusion. A pooled analysis of higher versus lower MAP targets for vasopressor therapy in septic/vasodilatory shock revealed increased mortality with the higher target when started more than 6 hours after initiation of vasopressors.[114] The OVATION (Optimal Vasopressor Titration) study showed better outcomes in vasodilatory shock with an MAP target of 60 to 65 mm Hg versus 75 to 80 mm Hg.[115] Thus the most appropriate MAP target in an individual patient remains elusive and likely should be judged based on history of uncontrolled hypertension and tissue perfusion parameters at the blood pressure currently chosen. It is hypotension in the presence of tissue hypoperfusion that merits therapy with vasopressor agents. Endpoints of resuscitation such as arterial pressure should be combined with assessments of regional and global perfusion. Other bedside indicators of persistent tissue hypoperfusion (besides hypotension) include oliguria, encephalopathy, poor capillary refill, and metabolic acidosis, and should also be considered as targets for blood pressure and fluid management. Thus even though the SSC recommends targeting a MAP of 65 mm Hg for most patients, the optimal MAP should be individualized based on the clinical considerations noted here.

The appropriate use of vasopressors may require accurate assessment of a patient's cardiovascular status with invasive hemodynamic monitoring. However, in the earliest stage of therapy, it is common to institute vasopressor therapy when invasive monitoring data are not immediately available if a patient remains hypotensive despite adequate intravascular volume expansion. If the MAP remains low (e.g., <65 mm Hg) with evidence of ongoing tissue hypoperfusion despite adequate fluid resuscitation, vasopressor therapy is indicated. In some circumstances, patients with sepsis may require vasopressor support even if hypovolemia has not yet been resolved. Below a threshold blood pressure, autoregulation of blood flow in vascular beds may be lost and linearly dependent on blood pressure; thus the administration of vasopressor agents to achieve a minimal perfusion pressure and maintain adequate flow is reasonable as an emergency measure in some situations while fluid resuscitation is ongoing.



• **Fig. 24.10** Patients' volume status at different stages of resuscitation. (From Acute Dialysis Quality Initiative 12. Copyright 2013 ADQI [www.ADQI.org]. From Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth.* 2014;113:740–747.)

Individual Vasoactive Agents

Multiple different vasoactive agents, including norepinephrine, epinephrine, vasopressin, dopamine, and phenylephrine, can achieve arterial pressure goals in the management of patients with septic shock. The different catecholamine agents have different effects on α- and β-adrenergic receptors. The hemodynamic actions of these receptors is well described: α-adrenergic receptors promote vasoconstriction, but β_1-adrenergic receptors increase heart rate and myocardial contractility and β_2-adrenergic receptors cause

peripheral vasodilation. Given the differential effects of vasopressor drugs on adrenergic receptors, these different agents have different effects on arterial pressure and systemic blood flow. In this context, the quintessential question as to which catecholamine is the best initial choice for treating septic shock is best framed as a question of which agent is most appropriate for a given therapeutic strategy in an individual patient, and the choice is largely dependent on that individual patient's hemodynamic status. Rather than a "one-size-fits-all" strategy, vasoactive agents should be carefully selected based on the intended goals of therapy.

Vasoactive agents and their characteristics are summarized in Table 24.5. The selection of one of these drugs over the other as a first-line agent is a controversial and an often debated subject in the field of critical care medicine. Both norepinephrine and dopamine effectively raise the blood pressure and the cardiac index, but the rise in cardiac index is greater with dopamine. Dopamine, however, may cause or exacerbate tachycardia or dysrythmias.[116] Norepinephrine is a more potent drug than dopamine in achieving a target MAP. Information from five randomized trials ($n = 1993$ patients with septic shock) comparing norepinephrine and dopamine does not support the routine use of dopamine in the management of septic shock.[117]

Epinephrine is a potent α- and β-adrenergic agent that increases MAP by vasoconstriction and also increases the cardiac index. Although epinephrine is a potent agent in raising the arterial pressure, the chief concern with the use of epinephrine has been the potential for impaired splanchnic perfusion.[118] A large-scale randomized controlled trial comparing epinephrine to norepinephrine plus dobutamine reported no difference in vasopressor withdrawal, organ failure, and mortality rate.[119] There was also no difference in the rates of serious adverse events. The authors concluded that there is no difference in efficacy and safety for epinephrine versus norepinephrine plus dobutamine in the management of septic shock.

Vasopressin is an agent that has both vasoconstriction and antidiuretic properties. Vasopressin constricts vascular smooth muscle directly via V_1 receptors and may also increase the responsiveness of the vasculature to endogenous or exogenous catecholamines.[120,121] Normally, endogenous vasopressin levels are very low and there is essentially no vasoconstriction effect in a normal host. However, in septic shock vasopressin levels are initially extremely elevated. In prolonged septic shock, a relative vasopressin deficiency can develop.[122] It has been postulated that this relative vasopressin deficiency may be the result of the depletion of the pituitary stores or the downregulation of vasopressin production by the pituitary gland via the effects of nitric oxide. Exogenous administration of low-dose vasopressin can have a dramatic hemodynamic response in this scenario, rapidly restoring arterial pressure.[123] A large randomized clinical trial compared vasopressin to norepinephrine in 776 subjects with vasopressor-dependent septic shock. Patients receiving norepinephrine to maintain MAP target in septic shock were randomized to receive vasopressin 0.03 U/min or additional norepinephrine in a blinded fashion such that either vasopressor would likely result in a downtitration of the basal norepinephrine dose. The low dose vasopressin was then continued while the norepinephrine was weaned as allowed.[124] It appears that vasopressin (up to 0.03 U/min) may be as equally safe and effective as norepinephrine in patients with septic shock after fluid resuscitation. The VANISH (Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock) trial used slightly higher doses of vasopressin, up to 0.06 U/min, before norepinephrine was initiated as initial vasopressor compared to norepinephrine alone in a randomized controlled trial.[125] This was a factorial design trial and each vasopressor arm also had either placebo or hydrocortisone. This trial was primarily targeted to detect any renal failure–sparing effect that vasopressin might offer. There was no difference in mortality or renal failure–free days between the two groups.

Phenylephrine is a pure vasoconstrictor with α-adrenergic effects alone. Although one potential advantage of using phenylephrine is that it will not cause or exacerbate tachycardia, the increase in peripheral resistance may produce a deleterious lowering of CO. It is not recommended for routine use in septic shock. Phenylephrine may be useful in select patients with severe dysrhythmias associated with catecholamine infusion because it has no β-adrenergic effects, as well as in patients with refractory hypotension in the presence of a known high cardiac index.

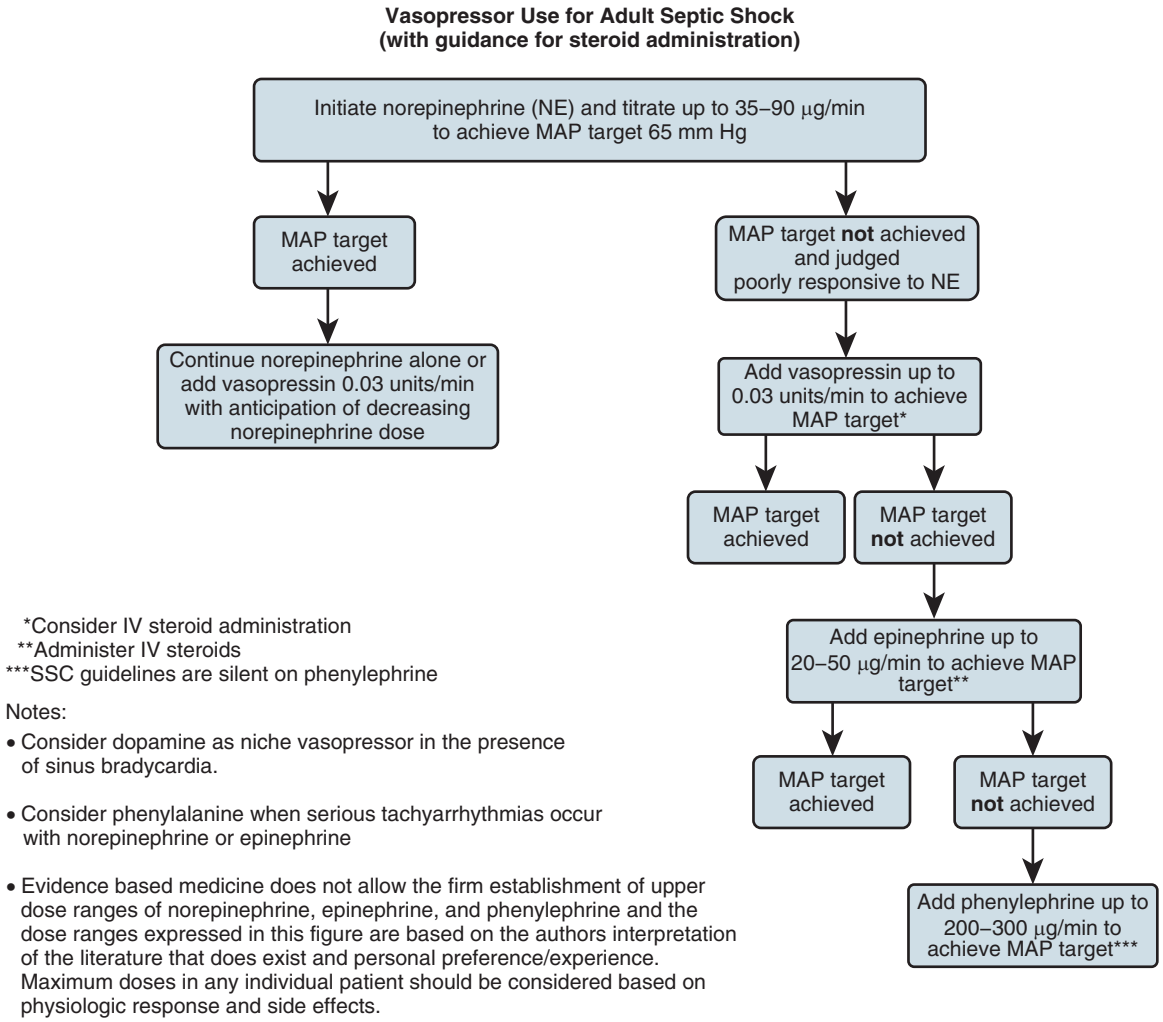
The SSC recommends norepinephrine as the first-line vasopressor agent in septic shock. The SSC further recommends the addition of either epinephrine or vasopressin (0.03 U/min) if a second vasopressor agent is needed to support the blood pressure. Fig. 24.11 offers a general guide to vasopressor selection and escalation in septic shock.

The Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) trial (randomized controlled) comparing angiotensin II with placebo in 344 patients with vasodilatory shock, 80% of whom had sepsis, was recently published. All the patients were receiving conventional vasopressor support (primarily norepinephrine) at the time of enrollment. Angiotensin II or placebo was

TABLE 24.5 Vasoactive Agents for Potential Use in the Hemodynamic Support of Septic Shock[a]

Agent	Typical Dose	Chronotropic Effects	Inotropic Effects	Vasoconstriction
Dopamine	6–20 μg/kg per minute	++	++	+/++ (dose-dependent)
Epinephrine	1–10 μg/min	++	++	++
Norepinephrine	2–50 μg/min	+	+	++
Phenylephrine	20–200 μg/min	–	–	++
Vasopressin	0.01–0.03 U/min	–	–	++
Dobutamine	2–15 μg/kg per minute	++	++	–

[a]Doses shown are common range of use. +, Low effect; ++, high effect; –, no effect.
Modified from Trzeciak S, Parrillo JE. Septic shock. In: *Society of Critical Care Medicine, 8th Adult Critical Care Refresher Course.* Chicago: Society of Critical Care Medicine; 2004.



• **Fig. 24.11** An example of how the guideline recommendations on vasopressor and steroid use can be molded into a flow diagram approach to the management of septic shock. (From Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 Surviving Sepsis Guidelines. *Crit Care Med.* 2017;45:381–385.)

added to the background vasopressor regimen.[126] The primary endpoint was an increase in blood pressure at 3 hours without an increase in background vasopressor dose. The primary endpoint was reached by more patients in the angiotensin II group than in the placebo group (69.9% vs. 23.4%, $P < 0.001$). Rates of serious adverse events were not dissimilar between groups (60.7% with angiotensin II and 67.1% with placebo). This study showed that angiotensin II is an effective agent for raising blood pressure and works by a different mechanism than previously available vasopressors. It appeared safe in the patient population enrolled in this study that targeted patients without evidence of low CO. As a pure vasopressor there would be some concern if it was used in a low-CO septic shock scenario.[127]

Inotropic Support

Inotropic support may be required for patients with septic shock. In the context of severe sepsis-induced myocardial depression, or if the patient has severe preexisting myocardial dysfunction, an inotrope may be necessary to augment CO (in combination with a drug that is supporting the MAP). The SSC recommends that dobutamine be the inotrope selected. When used beyond early quantitative resuscitation (first 6 hours of therapy), inotropic therapy is ideally guided by measurements of cardiac index. A reasonable goal for inotropic therapy would be a cardiac index of 3.0 L/min per m^2 or greater.

Corticosteroids

Administering high doses of steroids (30 mg/kg of methylprednisolone) failed to show an outcome benefit in septic shock in large-scale randomized controlled trials in the 1980s.[128,129] These studies used large doses of steroids over a short time period in an attempt to blunt the proinflammatory response of sepsis. In contrast, an alternative strategy of administering low-dose (i.e., "stress" or "physiologic" dose) steroids appeared to be promising in multiple small studies in the 1990s.[130,131] Despite the fact that patients with septic shock typically have elevated serum cortisol levels, it was identified that some patients with septic shock may have "relative adrenal insufficiency," as evidenced by failure to mount a significant elevation of serum cortisol in response to IV adrenocorticotropic hormone (ACTH) stimulation. Relative adrenal insufficiency in the context of septic shock may predispose a patient to persistent cardiovascular failure that is refractory to conventional hemodynamic

support therapies, and administration of exogenous low-dose steroids could help achieve shock reversal. On the other hand, administration of exogenous steroids could be associated with deleterious effects such as immunosuppression or myopathy.

In 2000 Annane and colleagues performed an observational study focusing on the ability to respond to an ACTH stimulation test in septic shock.[132] The highest 28-day mortality rate (75%) was observed in patients who did not increase serum cortisol level greater than 9 μg/dL. Being a "nonresponder" was a better predictor of death than an initially low cortisol value. In a randomized controlled trial by the same investigators in 2002, 300 severely ill (persistent hypotension despite fluid resuscitation and vasopressor initiation) patients with septic shock were randomly assigned to 7 days of hydrocortisone plus fludrocortisone versus placebo.[133] The study found that in the 229 nonresponders administration of low-dose steroids was associated with an improvement in time to shock reversal and mortality rate. Patients who responded appropriately to ACTH stimulation test did not demonstrate a benefit with low-dose steroids.

The concept of low-dose steroid administration was further tested in a multicenter randomized controlled trial (Corticosteroid Therapy of Septic Shock [CORTICUS]).[134] This study found no difference in the primary outcome measure of mortality rate between those treated with steroids compared to placebo. However, it is notable that (1) in contrast to the Annane study in which all subjects had vasopressor-refractory septic shock, the CORTICUS study tested a more diverse patient population with overall lower severity sepsis, and (2) randomization in the Annane study occurred within 8 hours of patients developing shock as opposed to CORTICUS, which randomly assigned subjects up to 72 hours after shock onset.

The 2016 Surviving Sepsis Campaign guidelines suggest against the use of low-dose hydrocortisone (200 mg/day) if fluid resuscitation and vasopressors are able to restore hemodynamic stability. Since the publication of these guidelines a recent *New England Journal of Medicine* study randomly assigned 3800 mechanically ventilated patients with septic shock to a continuous daily infusion of 200 mg hydrocortisone versus placebo.[135] Steroids or placebo were continued until 7 days, death, or discharge from ICU. There was no difference in mortality at 90 days, primary endpoint (steroids 27.9% vs. placebo 28.8%, $P = 0.50$) or at 28 days (steroids 22.3% vs. placebo 24.3, $P = 0.13$). There was no difference in any of the secondary endpoints with the exception of faster resolution of shock and fewer transfusions in the steroid-treated patients. There was no evidence of increase in secondary infections (bacteremia or fungemia) in the steroid group. It is noteworthy that there was no steroid signal with more severe versus less severe illness or earlier versus later treatment. Patients taking higher doses of catecholamines did have better outcomes in the steroid-treated group compared to patients using lower doses of catecholamines. This large study was stellar in design, execution, and reporting but will unlikely end the debate about utility of steroids in select patients with septic shock.

Yet another recent trial testing the potential benefit of steroids in septic shock has been published, the APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) trial.[136] In this trial of 1241 patients with septic shock receiving 0.25 μg/kg or more of norepinephrine for at least 6 hours with severe dysfunction of at least 2 organ systems, the 90-day mortality was significantly less in patients treated with hydrocortisone 50 mg IV every 6 hours and oral fludrocortisone 50 μg each morning versus placebo. The 90-day survival was significantly increased in the steroid-treated group. There was an increase in vasopressor-free days in the steroid treatment group as well as increase in hyperglycemia, the latter common to all trials of steroids versus placebo in septic shock.

Despite the fact that low-dose steroids do not consistently improve clinical outcome in clinical trials, septic shock patients receiving sustained high doses of norepinephrine or multiple vasopressors may benefit. In this group steroids should be considered.

The recommended dose of IV hydrocortisone is 200 mg/day as either 50 mg IV every 6 hours or a 50-mg IV bolus followed by a 200-mg continuous infusion over 24 hours. The ACTH stimulation test is not recommended to identify candidates for steroid therapy, but rather the use of bedside clinical criteria of severity of shock. Hydrocortisone is administered for 7 days.

Modulation of the Host Response

The toxin, primary mediator, and secondary mediator cascade thought to drive infection-induced organ dysfunction is elaborate and often redundant. A multitude of studies since the late 1980s have targeted modulation of the host response due to the premise that organ dysfunction and mortality in severe sepsis and septic shock are based on a disorganized host response to microbial toxin. Large multicenter trials have targeted endotoxin (neutralization and removal), the proinflammatory response (such as anti-TNF, anti–IL-1, anti-bradykinin), and the procoagulant response (recombinant human–activated protein C, tissue factor pathway inhibitor). All efforts to date have been unsuccessful. More recently attention has turned toward immune enhancement in select patient populations in whom organ dysfunction and secondary infections may be driven by immune suppression with resultant morbidity and mortality. Efforts continue to unravel the molecular biology of severe sepsis and the potential to leverage that knowledge for patient benefit.

Summary

The systemic changes seen in sepsis are driven initially by the proinflammatory and procoagulant responses. Organ dysfunction may result and septic shock may be a result. Septic shock is a composite of hypovolemic, cardiogenic, and vasodilatory shock with the potential for intracellular mitochondrial dysfunction. Management includes restoring intravascular volume losses, both capillary leak (absolute loss) and venodilation (functional loss). Crystalloids are preferred as the initial fluid of choice. Vasopressors may be required if blood pressure is not restored with fluid administration. The balance of fluids and vasopressors to maintain mean arterial pressure is controversial and currently more of an art than a science. Corticosteroids, although controversial, do lead to earlier shock reversal but without proven mortality benefit and may be useful in select patients with more severe shock. Despite failure to date with clinical trials testing novel interventions targeting the sepsis cascade, study continues looking for success in this area.

Appendix: Recommendations and Best Practice Statements

A. Initial Resuscitation

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS [best practice statement]).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

   Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.
4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).
5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).
6. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

B. Screening for Sepsis and Performance Improvement

1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).

C. Diagnosis

1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials (BPS).

   Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

D. Antimicrobial Therapy

1. We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence).
2. We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).
3. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).
4. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).
5. We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamics principles and specific drug properties in patients with sepsis or septic shock (BPS).
6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).
7. We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock (weak recommendation, low quality of evidence).

   Remarks: This does not preclude the use of multidrug therapy to broaden antimicrobial activity.
8. We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence).

   Remarks: This does not preclude the use of multidrug therapy to broaden antimicrobial activity.
9. If combination therapy is used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy (BPS).
10. We suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
11. We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).
12. We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intraabdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).
13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).
14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).
15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

E. Source Control

1. We recommend that a specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).
2. We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established (BPS).

F. Fluid Therapy

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).
2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

G. Vasoactive Medications

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).
2. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising mean arterial pressure to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.
3. We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).
4. We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
5. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

   Remarks: If initiated, vasopressor dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.
6. We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

H. Corticosteroids

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg/day (weak recommendation, low quality of evidence).

I. Blood Products

1. We recommend that RBC transfusion occur only when hemoglobin concentration decreases to <7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence).
2. We recommend against the use of erythropoietin for treatment of anemia associated with sepsis (strong recommendation, moderate quality of evidence).
3. We suggest against the use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (weak recommendation, very low quality of evidence).
4. We suggest prophylactic platelet transfusion when counts are $<10{,}000/mm^3$ ($10 \times 10^9/L$) in the absence of apparent bleeding and when counts are $<20{,}000/mm^3$ ($20 \times 10^9/L$) if the patient has a significant risk of bleeding. Higher platelet counts ($\geq 50{,}000/mm^3$ [$50 \times 10^9/L$]) are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).

J. Immunoglobulins

1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).

K. Blood Purification

1. We make no recommendation regarding the use of blood purification techniques.

L. Anticoagulants

1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).
2. We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.

M. Mechanical Ventilation

1. We recommend using a target tidal volume of 6 mL/kg predicted body weight compared with 12 mL/kg in adult patients with sepsis-induced acute respiratory distress syndrome (ARDS) (strong recommendation, high quality of evidence).
2. We recommend using an upper limit goal for plateau pressures of 30 cm H_2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong recommendation, moderate quality of evidence).
3. We suggest using PEEP (higher positive end-expiratory pressure) over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS (weak recommendation, moderate quality of evidence).
4. We suggest using recruitment maneuvers in adult patients with sepsis-induced, severe ARDS (weak recommendation, moderate quality of evidence).
5. We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio <150 (strong recommendation, moderate quality of evidence).
6. We recommend against using high-frequency oscillatory ventilation in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).
7. We make no recommendation regarding the use of noninvasive ventilation (NIV) for patients with sepsis-induced ARDS.
8. We suggest using neuromuscular blocking agents (NMBAs) for <48 hours in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio <150 mm Hg (weak recommendation, moderate quality of evidence).

9. We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).
10. We recommend against the use of β_2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm (strong recommendation, moderate quality of evidence).
11. We recommend against the routine use of the PA (pulmonary artery) catheter for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).
12. We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS (weak recommendation, low quality of evidence).
13. We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP (ventilator-associated pneumonia) (strong recommendation, low quality of evidence).
14. We recommend using spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning (strong recommendation, high quality of evidence).
15. We recommend using a weaning protocol in mechanically ventilated patients with sepsis-induced respiratory failure who can tolerate weaning (strong recommendation, moderate quality of evidence).

N. Sedation and Analgesia

1. We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points (BPS).

O. Glucose Control

1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose level ≤110 mg/dL (strong recommendation, high quality of evidence).
2. We recommend that blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions (BPS).
3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS).
4. We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters (weak recommendation, low quality of evidence).

P. Renal Replacement Therapy

1. We suggest that either continuous RRT (renal replacement therapy, CRRT) or intermittent RRT (renal replacement therapy) be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence).
2. We suggest using CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).
3. We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).

Q. Bicarbonate Therapy

1. We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (weak recommendation, moderate quality of evidence).

R. Venous Thromboembolism Prophylaxis

1. We recommend pharmacologic prophylaxis (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (strong recommendation, moderate quality of evidence).
2. We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (strong recommendation, moderate quality of evidence).
3. We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (weak recommendation, low quality of evidence).
4. We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).

S. Stress Ulcer Prophylaxis

1. We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence).
2. We suggest using either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence).
3. We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding (BPS).

T. Nutrition

1. We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence).
2. We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).
3. We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally (weak recommendation, low quality of evidence).
4. We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (weak recommendation, moderate quality of evidence).
5. We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock (strong recommendation, low quality of evidence).

6. We suggest against routinely monitoring gastric residual volumes (GRVs) in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, very low quality of evidence).

   Remarks: This recommendation refers to nonsurgical critically ill patients with sepsis or septic shock.
7. We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence).
8. We suggest placement of post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, low quality of evidence).
9. We recommend against the use of IV selenium to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).
10. We suggest against the use of arginine to treat sepsis and septic shock (weak recommendation, low quality of evidence).
11. We recommend against the use of glutamine to treat sepsis and septic shock (strong recommendation, moderate quality of evidence).
12. We make no recommendation about the use of carnitine for sepsis and septic shock.

U. Setting Goals of Care

1. We recommend that goals of care and prognosis be discussed with patients and families (BPS).
2. We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence).
3. We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission (weak recommendation, low quality of evidence).

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Review Questions

For questions 1 through 5 use the following clinical scenario:

A 72-year-old man is admitted to the intensive care unit (ICU) from the medical ward because of hypotension (80/40 mm Hg) and presumed severe sepsis. He was admitted to the medical floor 12 hours ago for multilobar pneumonia with a moderate oxygen requirement. His condition has progressively worsened despite broad-spectrum antibiotic coverage. He is now febrile, tachycardic, and hypotensive. The pulse oximeter reads 88% on high-flow oxygen by face mask. Physical examination is significant for confusion, a markedly increased work of breathing, and coarse breath sounds. In addition to a severe metabolic acidosis, laboratory results reveal the following: white blood cell (WBC) count, 32,000 with 47% band forms; platelet count, 105,000/mm^3; hemoglobin level, 10.8 g/dL. Two liters of normal saline solution are rapidly administered as a bolus via peripheral intravenous (IV) line, and the blood pressure improves slightly. The patient is intubated for impending respiratory failure and mechanical ventilation is initiated. After pulmonary artery catheterization is performed, the following data are available:

Arterial blood pressure (mm Hg)	90/45
Mean arterial pressure (MAP) (mm Hg)	60
Heart rate (beats/min)	105
Central venous pressure (mm Hg)	10
Pulmonary artery pressure (mm Hg)	30/18
Pulmonary capillary wedge pressure (mm Hg)	16
Cardiac index (L/min per m^2)	2.1

Use this clinical scenario to answer the next five questions about the administration of vasoactive drugs. You will be given five sets of hemodynamic parameters. Match each set of hemodynamic parameters with a corresponding vasoactive drug administered to this patient.

a. Norepinephrine
b. Dopamine at 6 μg/kg per minute
c. Dopamine at 25 μg/kg per minute
d. Dobutamine
e. Phenylephrine

Question 1 Hemodynamic parameters.

Arterial blood pressure (mm Hg)	90/45
MAP (mm Hg)	60
Heart rate (beats/min)	115
Central venous pressure (mm Hg)	8
Pulmonary artery pressure (mm Hg)	25/15
Pulmonary capillary wedge pressure (mm Hg)	12
Cardiac index (L/min per m^2)	3.3

Question 2 Hemodynamic parameters.

Arterial blood pressure (mm Hg)	110/60
MAP (mm Hg)	77
Heart rate (beats/min)	90
Central venous pressure (mm Hg)	10
Pulmonary artery pressure (mm Hg)	30/18
Pulmonary capillary wedge pressure (mm Hg)	16
Cardiac index (L/min per m^2)	1.9

Question 3 Hemodynamic parameters.

Arterial blood pressure (mm Hg)	99/55
MAP (mm Hg)	70
Heart rate (beats/min)	115
Central venous pressure (mm Hg)	10
Pulmonary artery pressure (mm Hg)	30/18
Pulmonary capillary wedge pressure (mm Hg)	16
Cardiac index (L/min/m^2)	3.1

Question 4 Hemodynamic parameters.

Arterial blood pressure (mm Hg)	118/65
MAP (mm Hg)	80
Heart rate (beats/min)	120
Central venous pressure (mm Hg)	10
Pulmonary artery pressure (mm Hg)	30/15
Pulmonary capillary wedge pressure (mm Hg)	16
Cardiac index (L/min per m^2)	3.1

Question 5 Hemodynamic parameters.

Arterial blood pressure (mm Hg)	118/65
MAP (mm Hg)	80
Heart rate (beats/min)	95
Central venous pressure (mm Hg)	10
Pulmonary artery pressure (mm Hg)	30/18
Pulmonary capillary wedge pressure (mm Hg)	16
Cardiac index (L/min per m^2)	2.4

Answers

1: d. Dobutamine is an inotrope that primarily affects β_1-adrenergic receptors, which increases inotropy, chronotropy, and cardiac output. Dobutamine has little effect on α_1-receptors and β_2-receptors, which results in overall vasodilatation and a decrease in systemic vascular resistance (SVR). These two factors produce a net effect of increasing cardiac output and decreasing SVR, and they may cause a small decrease in blood pressure owing to the overall vasodilatation. Dobutamine is best used in patients with cardiogenic shock and refractory heart failure. Note that the use of dobutamine alone in this patient without an agent to support the blood pressure resulted in worsening hypotension.

2: e. Phenylephrine is primarily a vasopressor with purely α-adrenergic agonist properties. Because it produces vasoconstriction with negligible increases in cardiac inotropy or chronotropy, the increase in SVR is mainly responsible for the increase in mean arterial pressure (MAP). This may result in a reflex bradycardia. Overall, phenylephrine increases SVR with little or no change in cardiac output. Because phenylephrine lacks β-adrenergic properties, it is useful in patients with pure vasodilatory shock with normal cardiac function. Note that the use of phenylephrine in this patient decreased the already low cardiac index by increasing afterload on the heart.

3: b. Dopamine's effects can vary with the dose of drug administered. At lower doses (1–5 μg/kg per minute), dopamine primarily acts on dopamine-1 receptors in the splanchnic bed,

which results in selective vasodilatation and increased urine output. When the dose is increased (5–10 μg/kg per minute), dopamine also has effects on the β_1-adrenergic receptors. This causes an increase in stroke volume and heart rate, which ultimately results in increased cardiac output and usually a mild increase in systolic blood pressure.

4: c. At higher doses of dopamine (>10 μg/kg per minute), the α-adrenergic receptors are predominately affected. This leads to an overall vasoconstriction and increase in SVR, as well as an increase cardiac output and systolic blood pressure through its effects on β-adrenergic receptors. At high doses of dopamine, the drug can be used as a potent vasopressor.

5: a. Norepinephrine binds to both α_1-adrenergic and β_1-adrenergic receptors, which results in both potent vasoconstriction and a slight increase in cardiac output. Norepinephrine is commonly used in sepsis because of its potency in achieving desired MAP. The expected increase in cardiac output is much less than with dopamine; therefore an additional agent for inotropic support may be required in select patients with poor cardiac contractility.

6. Which of the following statements is *most* correct regarding the use of corticosteroids in patients with septic shock?

a. Corticosteroids are contraindicated in patients with septic shock.

b. Patients with septic shock should receive hydrocortisone 100 mg IV every 8 hours.

c. Corticosteroids should be considered for patients who remain hemodynamically unstable despite aggressive fluid and vasopressor resuscitation.

d. Corticosteroids should only be used in patients who do not respond to an adrenal corticotropic hormone (ACTH) stimulation test.

Answer: c. The use of corticosteroids in septic shock has a long and controversial history. Initial use of high-dose steroids to modulate inflammation was shown to be ineffective and was abandoned in the late 1980s. More recently the concept of relative adrenal insufficiency in septic shock was proposed, leading to a resurgence of the use of corticosteroids in septic shock. Furthermore, small studies and one randomized clinical trial showed that in nonresponders to an ACTH stimulation test, the use of hydrocortisone was associated with improved mortality. However, a large multicenter study (CORTICUS) failed to show any benefit with the use of hydrocortisone in patients with septic shock. The 2016 Surviving Sepsis Campaign guidelines recommend that IV hydrocortisone not be given to patients with septic shock in whom blood pressure responds to fluids and vasopressors. However, in patients who do not respond to aggressive fluid and vasopressor resuscitation, the use of steroids (200 mg hydrocortisone continuous infusion over 24 hours a day for 7 days or until shock resolution) should be considered as an adjunct to modulate the cardiovascular response of shock. The ADRENAL study (published in 2018) randomly assigned more than 3000 patients to the hydrocortisone regimen previously described versus placebo and failed to clarify the issue with faster resolution of shock but no difference in 28-day or 90-day mortality, albeit trends favoring steroids at both time points. The APROCCHSS trial (also published in 2018) randomly assigned 1241 patients to hydrocortisone/fludrocortisone versus placebo and demonstrated a survival advantage in the steroid treated patients. Steroid therapy should be considered in the more critically ill patient requiring high doses of vasopressors.

25

Cardiac Tamponade

ZOLTAN G. TURI AND SAJJAD A. SABIR

CHAPTER OUTLINE

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- Physiology
- Pericardial Pressure
- Etiology

History and Physical Examination
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- Venous Pressure
- Cardiac and Chest Examination

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Overall Assessment

Special Syndromes in Tamponade
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- Cardiac Catheterization and Electrophysiology Laboratories
- Critical Care Units and Medical Wards

Management

Fundamentals of Tamponade

Pericardium surrounding the heart was described in antiquity by Hippocrates (460 BCE–370 BCE) who called it "a smooth mantle surrounding the heart."[1] Galen (129 CE–210 CE) was the first to note the presence of a pericardial effusion.[2] Tamponade was described in the 17th century by the Cornish clinician Richard Lower,[2] although the first known treatment was not attempted until 200 years later when the Austrian pathologist and surgeon Franz Schuh performed a successful pericardiocentesis. The term "cardiac tamponade" was coined by a German surgeon, Edmund Rose, and its hallmark, pulsus paradoxus, by Adolph Kussmaul, both in the 19th century. Claude Beck, an American heart surgeon, described his eponymous sign in 1935.[3] In 1964, Harvey Feigenbaum and colleagues demonstrated pericardial effusion by cardiac ultrasound.[4]

Cardiac tamponade is a condition characterized by an increase in pressure external to the heart, resulting in impaired filling of the cardiac chambers. In the typical scenario, as fluid in the pericardium accumulates, cardiac output falls. The diagnosis represents a continuum from mild tamponade with subtle diagnostic findings to a critical clinical setting with imminent mortality.[5] The variability in presentation, including diagnostic findings and course, and the morbidity and mortality associated with treatment make this a particularly challenging clinical problem in critical care medicine.

Pericardial Anatomy

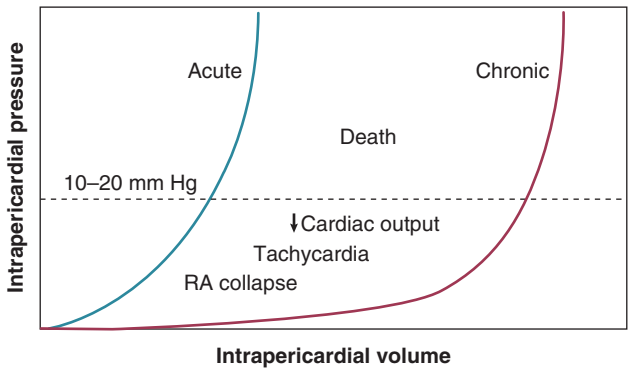
The pericardium consists of a visceral and a parietal pericardial segment, the former being composed of a single layer of cells that adhere to the cardiac epicardial surface.[6,7] The parietal pericardium is the structure responsible for the clinically relevant features of tamponade; it is a relatively noncompliant structure composed of collagen and elastin and normally is less than 2 mm thick.[8,9] The mechanical properties of the pericardium—in particular, those reflected by its pressure-volume curve (Fig. 25.1)—are responsible for the clinical features seen in cardiac tamponade.

The pericardium extends from the lower third of the superior vena cava to the apex of the heart. It is attached to the sternum, the diaphragm, and the proximal portion of the great vessels. Because it extends beyond the heart border, trauma to not only the heart but also the great vessels approaching the heart borders can lead to cardiac tamponade.[10,11] The main arterial blood supply of the pericardium is provided by the pericardiophrenic arteries which branch from the internal mammaries; the former are prominently visible when the latter have been used for bypass grafts and become occluded, and are sometimes mistaken for coronary vessels. The phrenic nerve provides sensory innervation, whereas vasomotor innervation comes from the sympathetic trunks.[12]

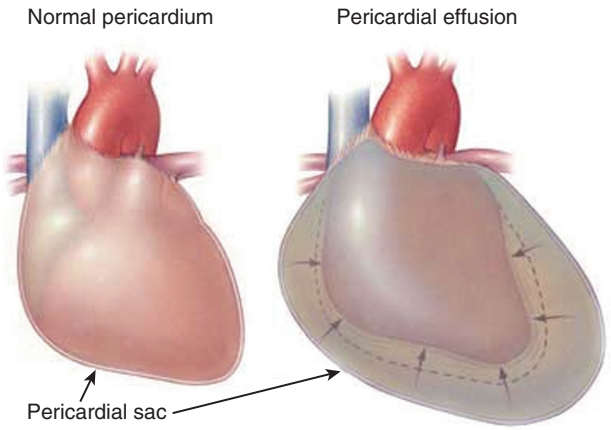
Physiology

Cardiac tamponade is a result of decreased transmural pressure (the difference between intracavitary and pericardial pressure), typically from accumulation of fluid in the pericardial space (Fig. 25.2). Other causes of "tamponade-like physiology" are related to extrinsic compression of the heart,[13] although these pathologic processes should be separated from those causing constriction rather than true tamponade. Differentiating between these two distinct physiologic entities, constriction and tamponade, is essential to diagnosis and management.

The fluid accumulating in the pericardial space can be blood, serous fluid, purulent material, clot, or rarely gas.[14] As fluid accumulates, the pericardium stretches, until it reaches a point (see Fig. 25.1) at which its degree of compliance is exhausted, so that it has become largely inelastic. At this point, any further



• **Fig. 25.1** Pressure-volume curves for normal pericardium on the *left* and compliant pericardium on the *right*. In the setting of rapid onset of effusion in the normal pericardium, low volumes, typically starting from less than 50 mL, lead to a rise in pressure that exceeds the limit of pericardial stretch, with early onset of tamponade physiology. With more compliant pericardium, a result of chronic stretching, critical extramural pressures do not result until substantially higher volumes are achieved, in some cases more than 1 L. *RA,* Right atrial.



• **Fig. 25.2** The pericardium surrounding the heart in a normal physiologic setting and in tamponade. The pericardium can be seen to extend to the proximal great vessels. Note the large amount of effusion in the image on the *right,* consistent with chronic pericardial stretch, which leads more slowly to tamponade. (Courtesy Mayo Foundation for Medical Education.)

increase in intrapericardial fluid is associated with a decrease in intracardiac chamber volume, because the total volume of pericardial fluid, heart muscle, and the cardiac chambers becomes fixed by pericardium no longer able to stretch. This in turn results in decreased filling of the heart and consequently decreased stroke volume. To maintain cardiac output, an early compensatory mechanism is an increase in heart rate. Subsequent adaptations to maintain blood flow to central end organs (heart, brain, kidneys) are venous pressure rise, peripheral vasoconstriction, increase in ejection fraction, and selective shunting of blood to preserve flow to the essential end organs. Venous pressure increase is accomplished by fluid retention and peripheral venoconstriction. In severe tamponade, equalization of right atrial, right ventricular (RV) diastolic, pulmonary diastolic, pulmonary artery wedge, and intrapericardial pressures occurs. Both pulmonary and systemic arterial and pulse pressures fall. Tamponade is a continuum, ranging from a primarily echocardiographic finding of right-sided chamber collapse to shock and pulseless electrical activity.

Pericardial Pressure

The normal pericardium contains a small amount of fluid, typically in a range of 20 to 50 mL, resulting in no more than 5 mm of separation between the visceral and the parietal pericardial surfaces. Pressure in the normal pericardium reflects intrathoracic pressure, which in turn reflects atmospheric pressure, with variation influenced by respiration. During inspiration, the pressure falls a few millimeters below atmospheric pressure (by convention, 0 mm Hg); during expiration, it increases a few millimeters above. The difference between intracardiac and intrapericardial pressures, the transmural pressure, in turn distends or compresses the cardiac chambers. Because intrapericardial mean pressure in patients breathing unassisted typically is the same as atmospheric pressure, whereas right atrial pressure is normally in the range of 2 to 8 mm Hg, the latter is the typical range of net right atrial transmural pressure. When intrapericardial pressure rises to the level of right atrial pressure, the right atrium collapses, a typical feature of early cardiac tamponade, although this nonspecific finding can be seen with hypovolemia alone.

The normal parietal pericardium, because of its limited compliance, functions to limit abrupt expansion of the heart as a whole.[15] Thus in the setting of right ventricular infarction, for example, acute dilation of the right ventricle is at the cost of left ventricular volume decrease—a ventricular interdependence phenomenon similar to that illustrated in Fig. 25.3. Acute chamber enlargement as the result of other etiologic conditions or disorders, such as abrupt volume loading or sudden onset of severe valvular regurgitation, is impeded by the constraint of pericardium that has reached the limits of its intrinsic elasticity. Because right-sided heart filling occurs preferentially with inspiration, when negative intrathoracic pressures result in increased venous return and higher right-sided chamber volume, left ventricular stroke volume, and hence systolic blood pressure, tend to fall as left atrial and left ventricular volumes are decreased. This exaggerates the normal respiratory variation, and systemic pressure falls with inspiration to a level at which pulsus paradoxus, defined by convention as a greater than 10 mm Hg decrease in systolic pressure, is seen. In addition, decreased intrathoracic pressure has a disproportionate effect on the pulmonary venous circulation, which is not exposed to the high pericardial pressures; hence a disproportionate fall during inspiration in the pulmonary vein to left atrial gradient further exacerbates the decrease in left atrial filling.[16] In fact, the fall in systolic pressure is not a paradox but rather an exaggeration of the normal respiratory variation of approximately 3%[17] with an associated inspiratory decrease in left ventricular stroke volume. With severe tamponade, total elimination of pulse pressure can be seen with individual heartbeats, as in the example in Fig. 25.4.

The inability to dilate further means that additional volume beyond the intrinsic stretch limit of the pericardium, such as from bleeding into the pericardial sac, results in increasing compression of heart chambers as volume expands in the pericardial space. Because the right-sided chambers have the lowest intracardiac pressures, in particular the right atrium, those are the first chambers to show collapse, particularly in diastole, when the tricuspid valve is open and the right atrium can decompress into the right ventricle. With progressive increase in intrapericardial pressure, compression of the right ventricle in diastole occurs during pressure equalization with the right atrium. Eventually, as intrapericardial pressure continues to rise, compression of the left-sided chambers ensues.

In contrast to acute tamponade physiology, in which hemodynamic decompensation may occur after only a modest accumulation

• **Fig. 25.3** Hemodynamic tracings from a patient with ventricular interdependence (200–mm Hg scale). With inspiration, left ventricular *(LV)* systolic pressure falls as right ventricular *(RV)* systolic pressure increases. Because of ventricular interdependence, the right ventricular and left ventricular systolic pressures trend in opposite directions (lines connecting peak systolic pressures diverge during phases of the respiratory cycle). Diastolic pressures in both ventricles are essentially identical *(green oval)*. Absence of pulsus paradoxus and preserved systolic pressure make this physiology consistent with constriction rather than tamponade. The patient had a clot in the pericardial space after prior cardiac trauma.

of fluid (generally in the range of 100–200 mL), chronic pericardial effusion results in gradual increase in distensibility of the pericardium. With increasing compliance, large amounts of fluid can accumulate at low pressure without decreasing transmural pressure or compressing the cardiac chambers (see Fig. 25.1). Even in chronic low pressure–high volume tamponade, a limit of distensibility is eventually reached that results in similar pathophysiology as with acute tamponade, in some cases only after a liter or more of fluid has accumulated. Once the steep portion of the pressure-volume curve is reached, it is important to appreciate that with accumulation of another 50 to 100 mL of pericardial fluid, hemodynamic decompensation can occur rapidly, with similar outcomes as in patients who have acute tamponade, such as is seen with penetrating trauma, coronary artery perforation, aortic dissection, or cardiac rupture.

Etiology

Pericardial effusions generally can be characterized as transudate or exudate, infectious or bloody, with tamponade occurring with variable frequency depending both on the rapidity of fluid accumulation and, to a somewhat lesser degree, on characteristics of the effusion and physiology determined by its etiology. Transudates are characteristic of congestive heart failure, radiation, and uremia; exudates are characteristic of infections, malignancy, and connective tissue disorders. Laboratory testing may help differentiate exudates from transudates; pericardial and serum protein, albumin, lactate dehydrogenase, cholesterol, and glucose should be obtained,[18] although some of the differentiating characteristics applicable to pleural effusions may not be discriminatory in pericardial effusions.[19] In addition, pericardial fluid total and differential cell count, Gram stain, aerobic and anaerobic culture, and mycobacterial and fungal evaluation should be performed along with cytology when malignancy is considered. Molecular techniques can be useful in diagnosing otherwise occult infections.[20] Amylase is reserved for cases when pancreatic disease or esophageal rupture is part of the differential diagnosis.

Conditions predisposing to slow accumulation—such as heart failure, myxedema, chronic renal failure, and connective tissue disorders in general—are less likely to cause acute tamponade, whereas those associated with rapid development, such as malignancy, infection (including bacterial, fungal, and human immunodeficiency virus–related), or particularly hemorrhage, commonly result in abrupt hemodynamic deterioration. The effect of

• **Fig. 25.4** Hemodynamic tracing of systemic pressure in cardiac tamponade, 100–mm Hg scale. Systolic pressure variation is nearly 40 mm Hg, and pulse pressure is markedly reduced during inspiration. Note the complete obliteration of the systemic pressure during deep inspiration in the beat highlighted by the *arrow.* Because of low stroke volume, cardiac output is being maintained to some extent by a high heart rate (146 beats/min).

inflammation in decreasing compliance of the pericardium exacerbates the hemodynamic effects of effusions associated with pericarditis.[21] The potential etiologic disorders are highly variable, with significant influence of demographics and geography, so that tamponade secondary to tuberculous pericardial effusion in immune-compromised patients is a not uncommon presentation in Africa,[22] whereas in industrialized nations malignant effusions are a far more common cause.[23] Large and usually benign pericardial effusions are seen frequently after heart transplantation, possibly immune-mediated.[24] Large pleural effusions can cause sufficient compression of the heart such that tamponade physiology occurs.[25] The most common etiologic disorders are listed in Table 25.1; more detailed discussion of the various causes is presented later in the chapter, organized by the hospital setting in which presentation typically is seen.

History and Physical Examination

Dyspnea is the most common symptom of tamponade, although its etiology sometimes is unexplained and it usually is not associated with significant concomitant pulmonary vascular congestion. It is likely to be secondary to decreased cardiac output and encroachment on lung volume by the expanding pericardium as well as any simultaneous pleural effusions. The patient may describe a sensation of fullness in the chest or abdomen and dysphagia, associated with venous engorgement and passive congestion, stretching of the richly innervated pericardium, and occasionally vagal stimulation.[26] Occasionally hoarseness and hiccups may be noted owing to the involvement of the recurrent laryngeal nerve and the phrenic nerve, respectively.[14] Because most patients with tamponade have comorbid conditions accounting for their effusion, additional signs and symptoms are likely to be related to pericarditis, malignancy, or other concomitant conditions.

The hallmarks of cardiac tamponade on physical examination relate to features associated with venous hypertension, low cardiac output, and effects of the layer of fluid between the heart and the chest wall. In patents with tamponade, the general appearance changes substantially during progressive increase in pericardial pressure. Because tamponade represents a continuum, some patients with early tamponade physiology look well, whereas patients with more advanced tamponade show features of a low-output state, with clinical manifestations reflecting the high catecholamine levels required to maintain cardiac output. They become progressively more anxious and agitated and less communicative and may be struggling to breathe. Patients may complain of chest pain associated with pericardial irritation, not infrequently radiating to the neck, jaw, or shoulder[27]; if venous congestion is acute, patients may experience pain from stretching of Glissen's capsule around the liver.

Pulsus Paradoxus

The physical examination in significant tamponade can include Beck's triad, composed of jugular venous distention, decreased

TABLE 25.1 Etiology of Cardiac Tamponade

Causative Disorder/Condition	Frequency (%)
Most common[a]	
Idiopathic	23
Malignancy	22
Iatrogenic	18
Acute myocardial infarction	8
Purulent (including tuberculous)	8
Renal failure	3
Miscellaneous	18
Aortic dissection	
Myxedema	
Trauma	
Connective tissue disorders	
Radiation therapy	

[a]Frequency of common etiologies of tamponade is based on 119 cases in Barcelona, Spain. Other relatively common causes of effusion include congestive heart failure, hypoalbuminemia, coagulopathy, and postcardiotomy and Dressler syndromes. Etiologies of tamponade will be dependent on geography and patient demographics and also will be strongly influenced by the presence of oncology, trauma, or dialysis units. For a comprehensive list of tamponade etiologies based on prior data, see Box 6.1.

Data from Sagrista-Sauleda J, Merce J, Permanyer-Miralda G, et al. Clinical clues to the causes of large pericardial effusions. *Am J Med.* 2000;109:95–101.

• BOX 25.1 Tamponade Settings in Which Pulsus Paradoxus May Not Be Present

- Nonrestrictive (large) atrial septal defect
- Severe aortic insufficiency
- Loculated effusion
- LV hypertrophy and other causes of elevated LV diastolic pressure
- Shock caused by hypovolemia, or profound circulatory collapse with tamponade
- Severe left ventricular dysfunction
- Low-pressure tamponade
- Right ventricular hypertrophy or other cause of impaired RV filling.
- Positive-pressure ventilation
- Arrhythmias

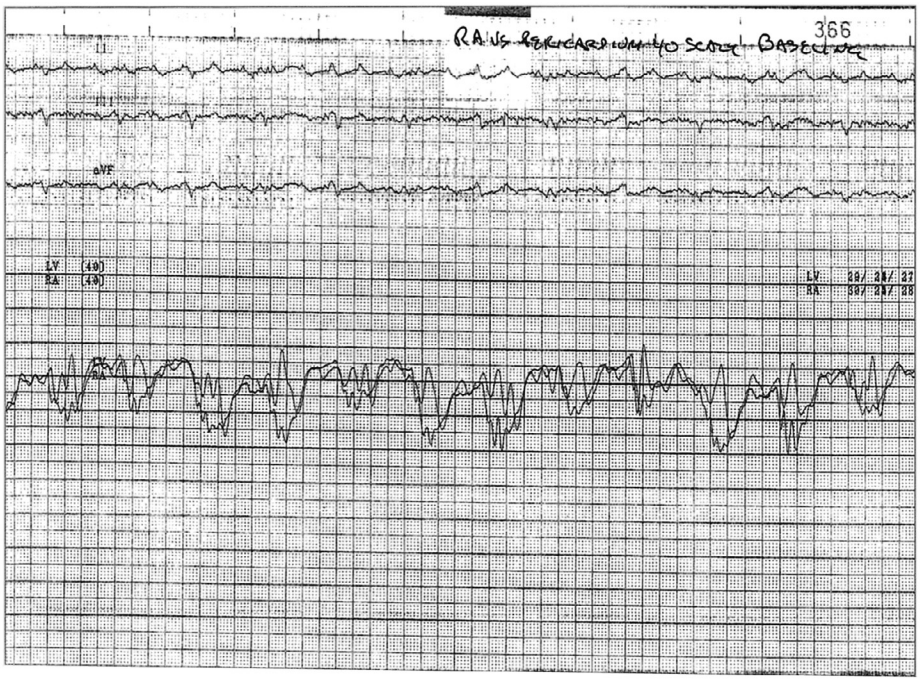
LV, *Left ventricular;* RV, *right ventricular.*

arterial pressure, and a small, quiet heart. As described earlier, pulsus paradoxus is the result of cardiac chamber interdependence and a decrease in left ventricular chamber volume with inspiration. It can be detected at the bedside by auscultation of Korotkoff sounds, identifying the highest and lowest pressures at which sounds are first heard during inspiration and expiration; alternatively, a simpler and more useful technique is to palpate the radial artery pulse with the cuff inflated to the maximum pressure at which the pulse appears and then to lower the cuff pressure in increments of 10 mm Hg to detect the pressure at which pulses are continuously noted throughout the respiratory cycle. In the patient whose systolic pressure is shown in Fig. 25.4, simple palpation of the radial pulse would detect the loss of pulse pressure in the beat indicated by the red arrow. It is important to recognize that although pulsus paradoxus is a classic feature of severe tamponade, as a diagnostic feature it is of limited sensitivity and specificity.

Various thresholds other than the relatively arbitrary 10-mm Hg threshold have been proposed to increase specificity, including a 10% decrease, rather than a 10-mm Hg fall.[28] A drop in *systolic* pressure greater than 50% of the *pulse* pressure has also been proposed.[5] Use of a 15- or 20-mm Hg fall in pressure by physical examination is a less sensitive but far more specific finding for tamponade but may result in a delayed diagnosis. Pulsus paradoxus may be present in other conditions that result in exaggerated decrease in systolic pressure with inspiration, such as massive pulmonary embolism, severe chronic obstructive pulmonary disease (which also can feature constrictive physiology because of limited expansion of the heart in the setting of hyperexpanded lungs),[28] and RV infarction.[29] Furthermore, other features of the systemic blood pressure and pulse are important to consider. With a progressive decrease in cardiac filling overall, a decline in systemic pressure (regardless of phase of the respiratory cycle) as well as a decrease in pulse pressure (the difference between systolic and diastolic pressures) occurs, reflecting decreasing stroke volume and decreasing cardiac output. Thus it may be impossible to palpate radial artery pulsations; with severe tamponade, the patient is likely to feel cool and clammy, a finding consistent with severe peripheral vasoconstriction.

Tachycardia is almost invariable, except for comorbid conditions associated with a decrease in heart rate, such as electrical conduction disturbances, severe hypothyroidism, or aggressive β-blockade. Tachycardia, a compensatory mechanism for decreased stroke volume, also is caused by high catecholamine levels and may result from pericardial irritation of the sinus node that stimulates a higher heart rate. On occasion, acute bradycardia may be seen in tamponade, and is sometimes the first finding after hemorrhage into the pericardial sac. Although a well-preserved systolic pressure and a wide pulse pressure are uncommon in tamponade, neither low pressure nor a narrow pulse pressure is completely specific. Further, early in the course of tamponade, acute surge in catecholamine levels may result in hypertension rather than shock. In addition, patients with tamponade in the setting of renal disease and chronic hypertension appear to present more often with elevated systolic pressures.[30]

The pulsus paradoxus may be absent in conditions in which ventricular interdependence is masked[31] (Box 25.1), such as a nonrestrictive atrial septal defect, in which inspiration also increases left atrial filling, or aortic insufficiency, in which left ventricular filling in diastole is increased by regurgitation from a high-pressure source: the aorta. Localized tamponade may have some general tamponade features (such as decreased stroke volume) but may not result in ventricular interdependence—hence, the clinical picture may be that of a sick patient with tamponade but without pulsus paradoxus. Markedly elevated left-sided heart diastolic pressures in severe left ventricular hypertrophy and other disease states may exceed the elevated right atrial and intrapericardial pressures in tamponade, decreasing the effect of inspiration on interdependence of right and left sides of the heart. An example in which both pulse pressure and pulsus paradoxus would be insensitive markers of tamponade is aortic dissection that combines aortic insufficiency with tamponade, in which a wide pulse pressure may be seen in some patients with partial compensation, and in which pulsus paradoxus, as discussed, may be masked. By contrast, conditions



• **Fig. 25.5** Hemodynamic tracings showing right atrial *(RA)* and intrapericardial pressures (incorrectly labeled LV) on 40–mm Hg scale. Note the equivalence of pressures as well as the high mean pressure, 27 mm Hg, consistent with tamponade and hemodynamic decompensation. The y descent is nearly absent.

resulting in impaired RV filling, such as RV hypertrophy in severe pulmonary hypertension, also may result in absence of a pulsus paradoxus[32]; furthermore, in settings such as cor pulmonale, the dramatic elevation in right-sided diastolic pressures will delay onset of the otherwise highly sensitive and early finding of right atrial and RV diastolic collapse until tamponade is severe.[33] A substantial number of case reports describe physiologic conditions in which the classic findings for tamponade are not seen or are attributable to other etiologic disorders.[34]

Venous Pressure

Because impairment of right-sided filling is usually the first manifestation of increasing pericardial pressure, high jugular venous pressure manifested by prominent venous pulsations may be the earliest finding on physical examination, occurring with increasing intrapericardial and right atrial pressures. Jugular venous distention may, however, be simultaneously absent because venoconstriction, a common finding with acute tamponade, makes detection of elevated venous pressures difficult. It also will be masked by low-volume tamponade, including volume-depleted states such as trauma, when, in addition to hemorrhage into the pericardium, significant blood loss has occurred. Other settings in which venous distention may not be observed include postdialysis patients with uremic pericardial effusions, and excessive diuresis, sometimes as part of treatment for symptoms of congestive heart failure when the cause of elevated filling pressures has not been appreciated.[35] In general, lack of venous engorgement in tamponade, particularly when the latter is acute, is not uncommon. Thus prominent jugular venous distention may suggest an alternative diagnosis, such as severe right-sided heart failure. Increased venous pressure with inspiration (Kussmaul's sign) is a feature of constriction, reflecting increased venous return to the thorax without increased right atrial filling, because the latter is constricted by the pericardium. This is in contrast to tamponade, in which negative intrathoracic pressure is transmitted through the pericardial effusion, and results in increased right-sided heart filling with decreased venous pressure. Because these findings are difficult to differentiate in most acutely ill patients, much of the subsequent description about right atrial pressure is based on catheter-based hemodynamic findings rather than the physical examination.

The y descent, in contrast with pericardial constriction in which it is prominent, typically is limited or absent (Fig. 25.5). Unlike in pericardial constriction, filling of the right ventricle (and hence emptying of the right atrium) is impaired throughout the cardiac cycle, because extrinsic compression by pericardial fluid results in elevated diastolic pressures in the right ventricle when rapid filling would otherwise occur. Because the pericardium allows additional atrial expansion during ventricular ejection (when ventricular volume decreases), the x descent (which occurs in early ventricular systole) is typically the more prominent negative pressure wave seen. The classic square root sign seen in the RV pressure tracing in constriction is absent in tamponade.

In contrast to acute tamponade, with chronic effusion the persistent elevation in pericardial pressure leads to parallel rise in central and peripheral venous pressure, as well as fluid retention with elevated intravascular volume. Venous congestion as well as peripheral edema and end-organ signs of chronic venous hypertension, such as passive congestion of the liver, become more common in this setting.

Cardiac and Chest Examination

The quiet heart in Beck's triad relates to several features that tend to muffle the intensity of heart sounds. First, the insulating effects of pericardial fluid on sound waves tend to decrease the sound

volume transmitted to the chest wall. Second, low stroke and filling volumes tend to decrease the forces that cause the sounds generated by heart valve closure, with low pulse pressure in both the aortic and the pulmonary arteries. Because the S_3 gallop is created by rapid ventricular filling, a phenomenon absent in tamponade, it would not be expected, nor would an S_4, because the hemodynamic characteristics of late diastolic atrial emptying that causes the fourth heart sound are not seen.[5] If pericarditis is involved, a pericardial friction rub may be heard. Except in severe tamponade, the pericardium around the apex of the heart may contain relatively little fluid, and left ventricular contraction typically is vigorous unless underlying left ventricular dysfunction also is present. Hence, a palpable point of maximal impulse may be felt.

A particular feature that differentiates tamponade from decompensated congestive heart failure is the typical presence of clear lungs in the case of the former. Although both right and left atrial pressures are markedly elevated, flow into the pulmonary circulation is limited, and the pressure-volume curve for the pulmonary vascular system is not affected.

Diagnostic Tests

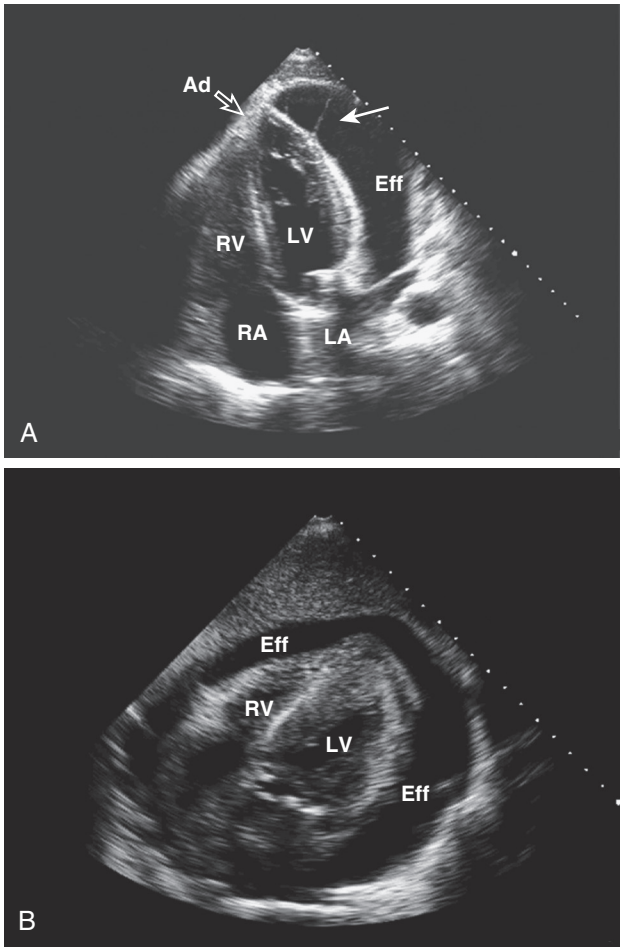
Echocardiography

Echocardiography is the most easily accessible and accurate means for the timely diagnosis of tamponade and remains the diagnostic modality of choice.[36] Besides evaluating presence and degree of chamber collapse, the echocardiogram is useful for assessing the amount and location of effusion in the pericardial space, for characterizing the fluid, and for judging the hemodynamic effect. Cardiac tamponade represents an echocardiographic continuum, from a small accumulation of fluid with at most subtle clinical findings, to large, usually circumferential[37] accumulations with resultant cardiogenic shock. Until effusions are at least moderate in size, fluid may be shifted by gravity to a location primarily posterior to the heart, because most patients are recumbent during echocardiography (Fig. 25.6).

Several echocardiographic features have been described in tamponade that result from an increase in intrapericardial pressure. These include exaggerated late diastolic right atrial collapse, early diastolic RV collapse, significant respiratory variation in Doppler inflow velocities across the tricuspid and mitral valves, plethora of the inferior vena cava (IVC), exaggerated expiratory flow reversal of the hepatic veins, and blunted diastolic flow of the inferior vena cava during expiration.[38] Since the right-sided cardiac chambers are more compliant, thin-walled, and at relatively low pressure, the increase in intrapericardial pressure will result in the collapse of these chambers first.

Immediately after atrial contraction, the right atrial volume is at its lowest, whereas RV volume is at its maximum; total pericardial volume in cardiac tamponade is relatively fixed. The increase in ventricular filling during diastole increases pericardial pressure, which prevents expansion of the right atrium during atrial relaxation (late ventricular diastole).[39] Persistence of right atrial collapse for more than one-third of the cardiac cycle is a useful marker for early tamponade physiology. This phenomenon is best appreciated from the apical or subcostal four-chamber views (see Fig. 8.42B).

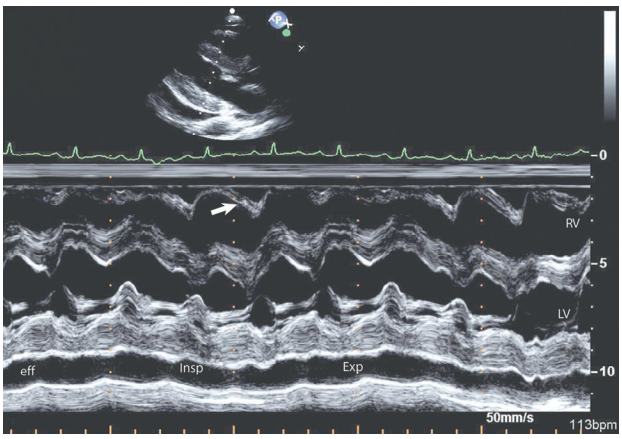
The right ventricle, conversely, is more vulnerable to collapse during early diastole, when its pressure is at its lowest as it expands after closure of the pulmonic valve. The RV outflow tract is the more compressible area of the right ventricle and hence tends to collapse first.[38] With increasing intrapericardial pressure, the collapse extends



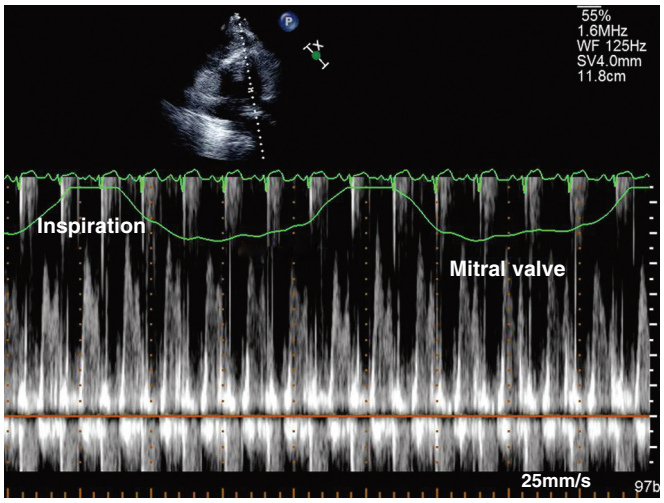
• **Fig. 25.6** Echocardiographic images of two types of pericardial effusions. A, A large posterior pericardial effusion, with relatively little fluid anterior to the heart or at the apex. The apex is adherent to the pericardial surface. The *arrow* points to a fibrous strand. This is a fairly typical appearance of a chronic postcardiotomy effusion. Needle access would be problematic. B, By contrast, this effusion is circumferential, with somewhat more fluid behind the left ventricle, a largely gravitational effect. Leaning the patient forward 20 to 30 degrees would facilitate pericardiocentesis, although the patient was not significantly hemodynamically compromised. *Ad,* Adhesion; *Eff,* effusion; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Courtesy Priscilla Peters, BA, RDCS, FASE.)

to the RV free wall, which is best appreciated on parasternal long- or short-axis views (see Fig. 8.43). This is a more specific finding for tamponade than right atrial collapse because the latter can occur in the setting of hypovolemia alone. However, RV diastolic collapse may not be seen in conditions that result in significantly elevated RV diastolic pressure (because transmural pressure is relatively high) or in RV hypertrophy. Collapse of the higher-pressure left-sided chambers, particularly the left ventricle, is uncommon, but when seen it is highly specific for tamponade. Collapse of the left atrium is not uncommon in the immediate postcardiac surgery period, frequently a result of loculated effusion causing regional tamponade.[40]

Although cardiac chamber collapse is a highly sensitive marker and is typically seen before clinical manifestations of tamponade, a number of other findings are more specific. As discussed previously, pulsus paradoxus results from exaggerated ventricular coupling. The ventricular interdependence (Fig. 25.7) can be appreciated on echocardiography by demonstration of marked respiratory variation



• **Fig. 25.7** Classic findings for ventricular interdependence in cardiac tamponade (see legend Fig. 8.44). (Courtesy Priscilla Peters, BA, RDCS, FASE.)



• **Fig. 25.8** Doppler inflow of mitral valve with tamponade, demonstrating enhancement with expiration and decrease with inspiration (see legend 8.49). (Courtesy Priscilla Peters, BA, RDCS, FASE.)

of Doppler flow across the atrioventricular or semilunar valves (see Figs. 8.49 and 8.50). During inspiration, the drop in intrathoracic pressure results in increased RV filling. As RV cavity size increases during diastole, expansion of the RV free wall is impaired by the increased intrapericardial pressure, and continued RV filling is accomplished only by diastolic expansion of the interventricular septum. The consequent bulging of the interventricular septum into the left ventricular cavity during diastole results in marked reduction in LV compliance and inspiratory filling.[21,41] These filling changes are reflected in a marked inspiratory increase in tricuspid valve Doppler inflow velocities with simultaneous inspiratory decrease in mitral valve inflow velocities. Reciprocal changes are noted during expiration (Fig. 25.8). A corollary to these respiratory changes is noted in the hepatic vein and vena cava flow patterns. Normal vena cava flow into the right atrium occurs during both ventricular systole and diastole. In tamponade, already impaired diastolic flow is further compromised in expiration by the exaggerated ventricular interdependence. This hemodynamic effect manifests on Doppler as blunted diastolic caval flow during expiration with increased expiratory flow reversal in the Doppler flow pattern of hepatic veins.[42] Although it is expected that in tamponade the IVC will be dilated and nonreactive,[43] plethora of the IVC can be seen in any condition causing elevation of right atrial pressure, including positive-pressure ventilation in an intubated patient.

Portable echocardiography, performed at the bedside, in the emergency department, or in critical care units, is highly reliable in cardiac tamponade.[44,45] However, adequate training in basic technique and fundamental anatomy is essential to avoid misdiagnosis. Epicardial fat can be confused with effusion,[46] and isolated or coexistent pleural effusions, mediastinal masses, and atelectasis can confound the diagnosis as well.[47] It is important to assess the heart from as many echocardiographic windows as possible for small but opportunistic loculated accumulations of fluid, for presence of clot, fibrinous "strandlike" material or masses, and for compression from processes outside the pericardium, such as a mediastinal hematoma and pleural effusion, all of which will have a significant impact on management.

X-Ray Studies

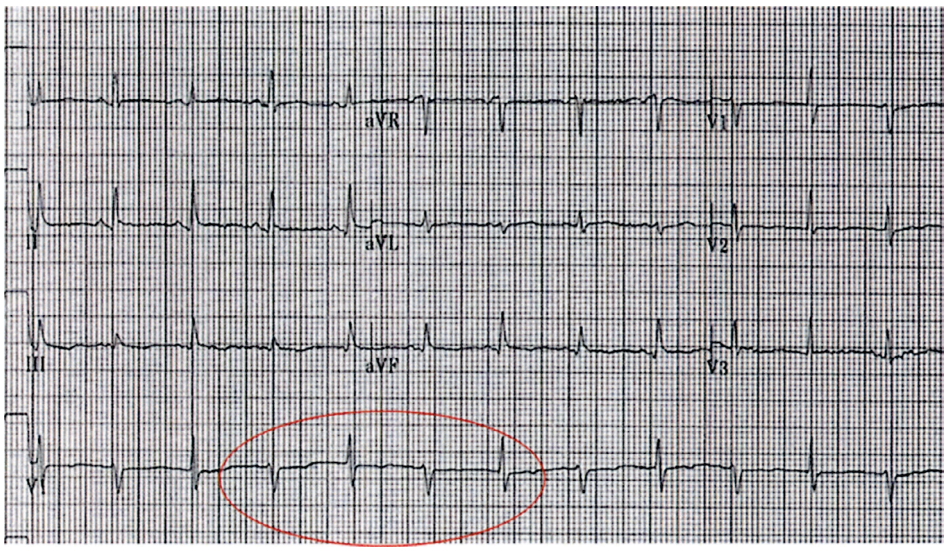
The classic "water bottle" configuration of the heart is due to a large pericardial effusion and therefore occurs only if the pressure-volume curve has altered sufficiently through chronic accumulation to allow significant increase in pericardial volume. It is a misconception that a normal-sized heart excludes tamponade; in acute tamponade the heart size can be expected to appear normal or minimally enlarged.[21] With marked enlargement of the cardiac silhouette, the finding is nonspecific and not readily distinguishable from cardiomegaly, although in tamponade pulmonary vascular congestion is usually not seen, although prominence of the vena cava may be noted. Other modalities such as computed tomographic (CT) scanning and magnetic resonance imaging show large effusions and can demonstrate chamber collapse. In addition, characterization of pericardial thickness and of the pericardial fluid to differentiate between blood and fluid of different densities can be useful. Although CT and magnetic resonance imaging show primarily anatomy rather than physiology, they can identify chamber collapse, characterize soft tissue, and demonstrate reflux into the azygous vein, a useful sign of tamponade.[48] CT scanning can provide information supplemental to that seen on echocardiography, including identification of extracardiac disease lesions,[49] and can provide additional sensitivity for detection of loculated effusions.[46] Coronary sinus compression on CT scanning is an early and specific indicator of tamponade.[50]

Electrocardiography

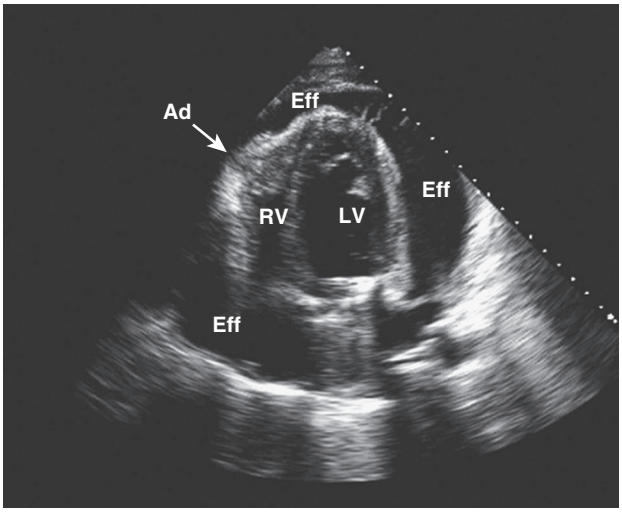
The classic electrocardiographic features include low voltage, a result of poor transmission of electrical activity across the fluid in the pericardial space, and electrical alternans, an insensitive but relatively specific finding for tamponade generated by swinging of the heart in the fluid-filled chamber (Fig. 25.9). Electrical alternans typically is seen only with large effusions in the later stages of tamponade, although the finding is related more to fluid volume and the ability of the heart to swing within the pericardial space. It may involve alternans of both QRS complexes and P waves. Thus tamponade with adhesions (Fig. 25.10), loculation, or masses that restrict heart motion may not manifest the alternans phenomenon.

Overall Assessment

In general, the severity of tamponade can be judged by the extent of hypotension, tachycardia, and pulsus paradoxus on physical



• **Fig. 25.9** Electrocardiogram demonstrating classic electrical alternans in a patient with pericardial tamponade. Note the change in amplitude of the R wave in lead V1 *(red oval)*. Similar findings are seen throughout the limb and precordial leads shown.



• **Fig. 25.10** Echocardiogram showing pericardial tamponade with right-sided collapse, adhesion of the right ventricle to the pericardium *(arrow),* and fibrous strands of early adhesions seen at the 1-o'clock position near the apex of the left ventricle. Even if the effusion accumulates further, electrical alternans would be less likely because of lack of mobility of the heart. *Ad,* Adhesion; *Eff,* effusion; *LV,* left ventricle; *RV*, right ventricle. (Courtesy Priscilla Peters, BA, RDCS, FASE.)

examination and confirmed by findings on echocardiography.[51] Mild tamponade features no hypotension or tachycardia, and no pulsus, with mild RV collapse by echocardiography. Patients with moderate tamponade have preservation of systemic pressure, but they have tachycardia, some degree of pulsus paradoxus, and clear RV collapse on echocardiography. Severe tamponade is associated with tachycardia, shock, profound pulsus paradoxus, and chamber collapse with a swinging heart on ultrasound.[29] Hemodynamic findings correlate with increasing pericardial pressure at each stage of tamponade,[52] initially less than right atrial or pulmonary wedge pressure, then equilibrating with right but less than left atrial pressure, and in severe tamponade equilibrating with both.

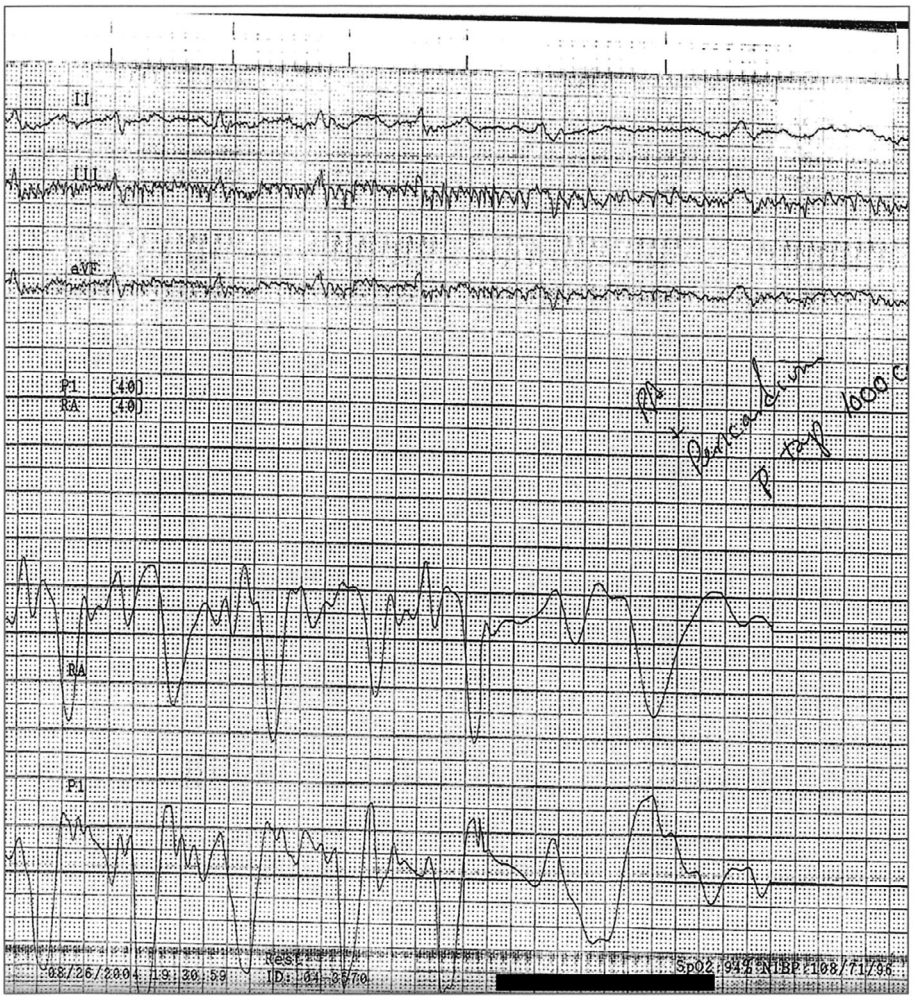
Special Syndromes in Tamponade

Although most cases of tamponade have at least some of the classic features, there are several important variants. Loculated effusions that compress the heart primarily in one region typically occur after surgery, although they may be due to neoplasms or a number of other etiologies as discussed later in the chapter. There are also a number of conditions in which pulsus paradoxus does not occur or is masked (see Box 25.1).

Effusive Constrictive Disease

This phenomenon is an important-to-recognize condition that occurs in less than 10% of patients with tamponade,[53] but in up to 40% of patients in some series. Hospitals with disproportionately high populations of oncology patients, either because of tumor metastases or postradiation pericardial involvement or tuberculosis, will have a higher percentage of tamponade patients with this diagnosis. The syndrome can occur after acute pericarditis of multiple etiologies and may even be transient.[54] The classic features of tamponade are seen on presentation, and a history of malignancy should increase the suspicion prepericardiocentesis.

Effusive constrictive disease is a setting in which careful hemodynamic monitoring is very helpful for accurate diagnosis. Monitoring of intrapericardial and right atrial or wedge pressure during pericardiocentesis demonstrates findings as seen in Fig. 25.11. In general, intrapericardial hypertension resolves with relief of tamponade, and classic respiratory variation is seen in most patients, whereas right atrial pressure remains elevated, though lower than before the pericardiocentesis. The y descent becomes prominent because of the elimination of high transmural pressures that restrict filling during early diastole in tamponade, unmasking classic constrictive physiology. Fig. 25.12 shows echocardiographic images in a typical patient with this syndrome.



• **Fig. 25.11** Hemodynamic tracings (40–mm Hg scale) obtained 1 hour after those shown in Fig. 25.5. After pericardiocentesis of 1 L of fluid, the pericardial pressure has achieved a mean equivalent to atmospheric pressure (0 mm Hg by convention), while right atrial pressure remains elevated near 22 mm Hg. This is physiology consistent with effusive-constrictive disease. On removal of the effusion, the hemodynamics, including the newly seen steep y descent, are classic for constriction. This patient had a malignant pericardial effusion. *P,* Intrapericardial pressure; *RA,* right atrium.

Low- and High-Pressure Tamponade

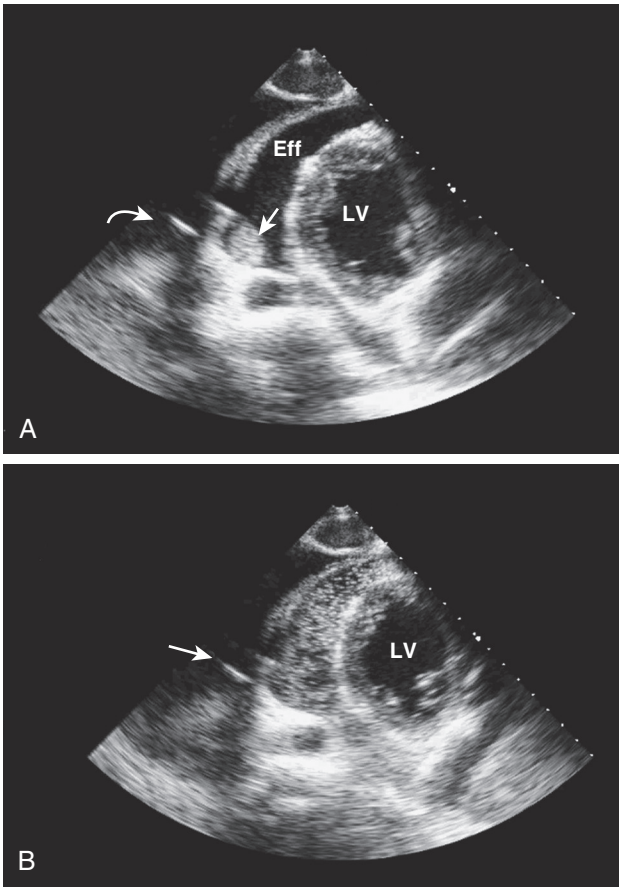
Low-pressure tamponade has been defined as featuring hypotension secondary to pericardial effusion but with low venous and intrapericardial pressures, most commonly in the setting of hypovolemia caused by dehydration or blood loss. A more formal definition, based on a single site experience, was described by Sagrista-Sauleda and colleagues[55] as an intrapericardial pressure less than 7 mm Hg, with a postpericardiocentesis right atrial pressure less than 4 mm Hg and equalization of intrapericardial and right atrial pressures before pericardiocentesis. Importantly, 20% of their patients with cardiac tamponade met these criteria (and 10% of their patients with large pericardial effusions), suggesting that low-pressure tamponade, previously the subject primarily of case reports and small series, may be more common than previously appreciated. Because of low pressures, there is a lack of features such as pulsus paradoxus or jugular venous distention, with only 24% demonstrating these classic findings, making the diagnosis significantly more difficult. Fluid challenge may result in more typical findings.

Patients with chronic hypertension in whom tamponade develops occasionally have high blood pressure despite tamponade physiology, presumably because of an exaggerated systemic pressure response to the catecholamine storm associated with tamponade.[56] In this setting, injudicious use of the usual medications to lower blood pressure can result in profound hemodynamic compromise.

Settings in Which Tamponade Is Seen

Emergency Department

The primary cause of tamponade in the emergency department relates to hemopericardium, although the complete range of medical etiologies can be seen in this setting. Trauma includes gunshot and stab wounds, as well as penetrating and crush wounds to the chest, including those related to automobile accidents.[57–59] Penetrating wounds are significantly more likely to result in tamponade than crush injuries.[60] Medical presentations with acute hemopericardium include aortic dissection with tamponade, post–myocardial



• **Fig. 25.12** Echocardiographic images from a patient with effusive-constrictive disease. A, Tamponade. The *curved arrow* points to the needle in the pericardial space; the *straight arrow* points to the tumor mass. The pericardium is thickened. B, Agitated saline solution has been injected through the needle *(arrow)* to confirm entry into the pericardial space. *Eff,* Effusion; *LV,* left ventricle. (Courtesy Priscilla Peters, BA, RDCS, FASE.)

infarction (MI) rupture, or leaking thoracic aneurysm, situations in which pericardiocentesis may lead to further hemodynamic decompensation,[61,62] as well as hemopericardium secondary to overanticoagulation. In general, acute hemopericardium may be associated with continued hemorrhage as well as clot in the pericardium; the latter makes complete drainage difficult. Clot alone can compress the heart and cause tamponade-like physiology. The clinical presentation of acute intrapericardial hemorrhage is typically shock, and jugular venous distention may or may not be present because of venoconstriction and hypovolemia as previously described. Use of echocardiography in the emergency department in patients with unexplained dyspnea is an important diagnostic tool.[63]

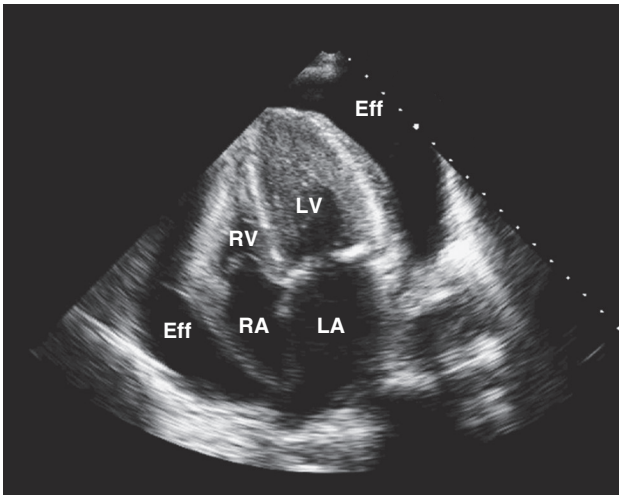
Cardiac Catheterization and Electrophysiology Laboratories

Perforation of the heart, including coronary arteries and cardiac chambers, during invasive cardiac procedures has become an increasingly important cause of pericardial tamponade.[64] Common scenarios include electrophysiology procedures, where relatively stiff catheters are placed in the relatively thin-walled structures of the right heart, including the right atrium, right ventricle, and the coronary venous system including the coronary sinus. Anticoagulation, when required for electrophysiology procedures, such as those involving left atrial ablation, raises the risk substantially. Perforation of coronary arteries occurs in particular with atheroablation devices such as those used for rotational atherectomy, directional atherectomy and lasers, with guidewires used in chronic total occlusions or injudiciously manipulated distal to the target lesion, and with oversized balloons and stents.[65] Even with normal sizing, settings such as myocardial bridges or ruptured balloons are associated with vessel perforation or rupture. A third setting is transseptal puncture, a resurgent technique because of burgeoning technologies requiring left atrial access[66] but associated with a significant risk of tamponade.[67–69] Besides left-sided ablations, mitral valvuloplasties, and percutaneous circulatory bypass (with its intake source in the left atrium), transseptal puncture is required for a rapidly expanding number of procedures, including left atrial appendage occlusion[70] and percutaneous mitral valve repair.[71] The risk of pericardial effusion and tamponade with these interventions contributes significantly to their overall morbidity and mortality.[64] However, and somewhat counterintuitively, electrophysiologists now frequently anticoagulate before transseptal puncture or perform the procedure in patients already using full oral anticoagulation.[72] This practice is driven by fear of thromboembolism rather than tamponade; the former is an important complication of left-sided ablations in particular, which can be long procedures, and is associated with clot-inducing char formation. Other endovascular procedures associated with tamponade include myocardial biopsy and central venous line placement, pacemaker lead extraction,[73] as well as erosion of devices implanted across the atrial septum or in the left atrial appendage[74–78] or acute or delayed perforation of the right ventricle from pacemaker or implantable cardioverter defibrillator lead.[79–81]

The potentially catastrophic setting of free perforation during coronary interventions is usually readily diagnosable during the procedure, with free flow in the pericardium seen during coronary injection, sometimes before the patient shows any signs of hemodynamic deterioration. This is readily treatable with balloon occlusion of the coronary artery at the perforation site, pericardiocentesis if necessary, and excluding the fenestration with a covered stent. However, lower-grade perforations that result in pooling of contrast or small adventitial craters can be more subtle. It is essential to discontinue anticoagulation in such patients and consider heparin reversal, and to ensure that personnel responsible for postprocedure management monitor the patient closely for hypotension and tachycardia. With transseptal punctures, hypotension at any time during the case, but especially after anticoagulation is administered, should raise the possibility of tamponade. A quick and relatively specific finding in the catheterization laboratory is straightening and lack of motion of the left heart border on anteroposterior fluoroscopy associated with hypotension (and sometimes reflex bradycardia); rapid intervention is essential in these patients. Hypotension after the procedure should raise the possibility that left atrial access involved a "stitch perforation" whereby the needle exited the right atrium and then entered the left atrium through the pericardial space; this mishap is possible with low punctures and frequently manifests only when catheters are removed from the fenestration at the end of the procedure. In patients who have had pacemaker placement, tamponade can develop acutely or after considerable delay as in the case of lead erosion.[82]

Critical Care Units and Medical Wards

Tamponade in the critical care unit typically is due to complications of MI, concomitant sepsis with purulent pericarditis, or hemorrhage into the pericardium because of anticoagulation (either



• **Fig. 25.13** Echocardiogram showing large circumferential pericardial effusion in myxedema. Severe tamponade is rare. *Eff,* Effusion; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Courtesy Priscilla Peters, BA, RDCS, FASE.)

iatrogenic or endogenous) or, most commonly, is secondary to neoplasms. In MI, tamponade can be acute, secondary to massive or limited rupture, or somewhat more insidious in onset as part of Dressler syndrome, with hemodynamic compromise sometimes exacerbated by anticoagulation. Tamponade also can be iatrogenic, in particular, secondary to placement of various lines through the venous or arterial circulation. Uncommon causes of tamponade, even with pericardial effusions of sometimes significant size, are viral pericarditis, congestive heart failure, uremia, myxedema (Fig. 25.13), and connective tissue disorders.

In patients with malignancy, several possible causes of tamponade are seen, including tumor involvement in the pericardium, postradiation pericarditis, graft-versus-host disease, and direct or indirect complications of therapy.[83] Patients with malignancies also are at increased risk for infectious pericarditis, coagulopathies or thrombocytopenia with secondary hemorrhage, and hypothyroid- and hypoalbuminemia-related effusions. Patients with AIDS and other immunosuppressed patients similarly are predisposed to infectious tamponade, as well as pericardial tumor involvement, including that from lymphoma. The mechanisms of pericardial effusion in cancer are varied but include direct spread to the pericardium from primary tumors such as lung, mediastinal, and esophageal cancer; hematogenous spread such as with lymphomas; and obstruction of the lymphatic drainage of the heart by tumors in the mediastinum.

Tamponade after cardiac surgery is an important phenomenon, usually occurring as a result of hemorrhagic effusion. Early postoperative tamponade is not uncommon and is important to recognize as a cause of hypotension because it has been reported to occur with a frequency of 5% to 10%, although this generally is thought to be in the 1% range in the modern era.[84] Moderate to large pericardial effusions that do not cause hemodynamic compromise have been much more common.[85] Delayed tamponade after heart surgery, with onset on average at 2 to 3 weeks postoperatively but as late as 6 months or more, occurs in less than 1% of patients but is disproportionately more common in patients undergoing valve surgery, probably related to postoperative anticoagulation in this cohort.[86,87] Delayed tamponade probably is a variant of the more common postcardiotomy syndrome.

Late tamponade typically is due to loculated effusion resulting from formation of adhesions (see Figs. 25.6 and 25.10) during recovery from surgery. Such adhesions can cause decreased cardiac output if they compress the left side of the heart, and in some cases pulmonary edema occurs if obstruction to inflow results. A variety of clinical problems related to increased right-sided heart pressure occur when tamponade involves the right side, including a clinical picture that resembles superior vena cava syndrome; several case reports have described right-to-left shunting across a patent foramen ovale as well.[88] Pericardiectomy to prevent postoperative tamponade has an uncertain risk-benefit ratio but does appear to decrease the incidence of hemodynamic compromise.[89]

Patients treated with dialysis present a special diagnostic and management problem. With underdialysis, volume overload can exacerbate chronic fluid accumulation in the pericardial space. Hypotension during or after dialysis may be secondary to inadequate intravascular volume and diminished venous pressure and needs to be avoided as well.

Management

Pericardial tamponade is life-threatening, requiring difficult diagnostic and, in particular, management decisions. When hemodynamics do not suggest significant compromise and effusion is small to moderate in volume, intervention frequently is not necessary and may involve increased risk to the patient, whereas late intervention may be fatal. Typically, the risk associated with pericardiocentesis is inversely related to the volume of accumulated fluid and also is related to the location of the effusion. Thus relatively small effusions, early in the course of tamponade, usually are located primarily posteriorly because of gravity-dependent accumulation. Waiting until the effusion is large and occupies significant volume anteriorly decreases the risk of percutaneous drainage but increases the possibility of decompensation and death before intervention. No validated risk stratification criteria for pericardiocentesis exist. A scoring system based on the etiology, the clinical presentation, and the imaging data has been proposed as a triage strategy for urgent management of cardiac tamponade by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.[90] Frequent monitoring of hemodynamics and application of sound clinical judgment remain essential for the timely and effective management of tamponade. Comorbid conditions such as endogenous or extrinsic anticoagulation may substantially confound the situation.[91] The clinical decision to drain the effusion percutaneously or to send the patient for thoracotomy will be a function of the clinician's assessment of risk of the former versus the potential advantages of surgery in obtaining pericardial tissue and providing a pericardial window as well. If the percutaneous approach is chosen, performing pericardiocentesis in the cardiac catheterization laboratory has significant advantages. However, the benefit of positioning the pericardial effusion anteriorly, for increased safety during needle entry into the pericardial space, requires that the patient's chest be elevated during the procedure, which typically can be accomplished only to a 20- or 30-degree angle on most catheterization tables because of the image intensifier unless the table has tilt capabilities. A moribund patient frequently needs pericardiocentesis performed at the bedside without fluoroscopic guidance, sometimes without adequate hemodynamic monitoring, and at times without echocardiographic monitoring—all of which are associated with increased risk of failed pericardiocentesis and adverse cardiac events. Patients with severe tamponade are often anxious and hypoxic; sedation is hazardous as is intubation, although the latter

is at times necessary. Because of associated positive intrathoracic pressure, intubation may cause abrupt hemodynamic deterioration because it decreases venous return to the heart.[6] Cardiopulmonary resuscitation using chest compression is unlikely to be effective; immediate pericardiocentesis or thoracotomy are ordinarily the only possibilities for survival. Further discussion of percutaneous interventions for tamponade can be found in Chapter 6.

Little in the way of medical treatment is clearly therapeutic for tamponade. Volume expansion in relatively acute tamponade will support right-sided filling in patients with low circulatory volumes, such as are seen in trauma.[92] Patients with chronic tamponade typically have considerable fluid retention, and additional hydration is unlikely to be of benefit. Pressors may be modestly helpful, but for patients with preserved cardiac function, catecholaminergic drugs provide only modest augmentation of cardiac output; patients with hemodynamically important tamponade are usually already maximally catecholamine stimulated. Vasodilator therapy is less clearly beneficial, and drugs that decrease preload, such as nitrates and nitroprusside, should be avoided if the patient is hypotensive. Reversal of anticoagulation is essential, both to stop bleeding into the pericardial space and to decrease the risk of trauma to the heart or major blood vessels during pericardiocentesis (e.g., coronary arteries, hepatic vessels). The introduction of direct thrombin inhibitors may affect this portion of the management algorithm because they are not reversible with vitamin K, and there are case reports of hemopericardium occurring after introduction of oral versions of these agents[93–96] as well as failed pericardiocentesis during PCI associated with bivalirudin administration.[97] However, a reversal agent for dabigatran was approved in 2015 and antidotes for factor Xa inhibitors are currently under investigation.[95] Antibiotic therapy in the setting of purulent pericarditis and tamponade is not expected to acutely relieve hemodynamic decompensation in most settings; postdrainage treatment is discussed in Chapter 6. A targeted approach for patients with malignant pericardial disease includes the use of sclerosing agents combined with antineoplastic drugs infused into the pericardial space, sometimes combined with radiation; a variety of such management strategies continue to be applicable for some cancer patients.[98] Leaving an indwelling drain is controversial because of the associated risk of infection, although there is some evidence that it can decrease the risk of recurrent tamponade.[99] An excellent review of the clinical approach to pericardial disease in general has been published by the European Society of Cardiology.[14]

Acknowledgment

The authors wish to acknowledge Priscilla Peters for kindly providing Figs. 25.6, 25.7, 25.8, 25.10, 25.12, and 25.13.

Key Points

- Pericardial tamponade represents a continuum, ranging from effusions associated with little or no hemodynamic compromise to hemodynamic collapse.
- The primary physiologic feature of tamponade is impairment of cardiac chamber filling owing to high intrapericardial pressure, with resultant decrease in cardiac output.
- Acute tamponade occurs after relatively limited accumulation of fluid in the setting of a nondistensible pericardium.
- Chronic tamponade may involve a pericardial effusion of 1 L or more; because hemodynamic decompensation occurs in the steep part of the pressure-volume curve, accumulation of a small amount of additional fluid can result in substantial hemodynamic deterioration.
- Pulsus paradoxus is seen in a variety of conditions besides cardiac tamponade and is absent despite tamponade in a number of settings. A large pericardial effusion and right ventricular collapse, a 10- to 20-mm Hg or larger decrease in systolic pressure with inspiration, and a significant decline in pulse pressure combined are specific for tamponade.
- Right atrial pressure, except in settings such as hypovolemia, usually is significantly elevated, but jugular venous distention may not be seen with acute tamponade.
- Despite markedly elevated right and left atrial pressures, pulmonary vascular congestion usually is not seen.
- Persistent high right atrial pressure after fluid drainage suggests effusive-constrictive disease, most commonly associated with malignancy but also seen with infection and acute pericarditis.
- Management of pericardial tamponade involves determining the optimal timing and method of intervention. Fluid and drug therapy constitute modest adjunctive care only.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. Tamponade physiology usually results from:
   - **a.** Abrupt accumulation of 50 to 100 mL of fluid in a patient with normal heart and pericardium
   - **b.** Gradual accumulation of 1 L or more of fluid in a patient with chronic pericardial effusion
   - **c.** Abrupt accumulation of an additional 50 to 100 mL of fluid in a patient with chronic pericardial effusion
   - **d.** All of the above

   Answer: d. Tamponade occurs when the patient reaches the upward sloping portion of the curve in Fig. 25.1. Patients with a normal, nondistensible pericardium require very little volume to achieve a critical drop in transmural pressure. In contrast patients with slow fluid accumulation—such as those with slow-growing malignancies, uremia, and other chronic conditions—frequently accumulate a liter or more before their pericardial pressure rises dramatically. However, abrupt accumulation in the latter settings, superimposed on substantial volume already in the pericardial space, will also cause tamponade.
2. A patient with effusive-constrictive disease undergoes pericardiocentesis and 500 mL of fluid is removed; no effusion is seen on postprocedure echocardiography. The initial hemodynamics showed an intrapericardial pressure of 20 mm Hg and a right atrial pressure of 20 mm Hg. Post tap the hemodynamics are likely to show:
   - **a.** Intrapericardial pressure >5 mm Hg; right atrial pressure 5–10 mm Hg
   - **b.** Intrapericardial pressure 0 mm Hg; right atrial pressure 5–10 mm Hg
   - **c.** Intrapericardial pressure >5 mm Hg; right atrial pressure 15 mm Hg
   - **d.** Intrapericardial pressure 0 mm Hg; right atrial pressure 15 mm Hg

   Answer: d. With complete resolution of the effusion, intrapericardial pressure typically decreases to atmospheric pressure, which by definition is 0 mm Hg. However, the patient with effusive-constrictive disease will continue to demonstrate features of pericardial constriction—namely, a high right atrial pressure and a steep y descent (see Fig, 25.5 and 25.11).
3. Beck's triad incorporates:
   - **a.** Small quiet heart, pulsus paradoxus, and jugular venous distention
   - **b.** Pulsus paradoxus, jugular venous distention, tachycardia
   - **c.** Small quiet heart, tachycardia, jugular venous distension
   - **d.** Small quiet heart, jugular venous distention, hypotension

   Answer: d. Claude Beck, the first professor of cardiovascular surgery in the United States, described his triad as jugular venous distension, a small quite heart of physical examination, and low arterial pressure. The other choices shown—pulsus paradoxus and tachycardia—are also seen commonly in tamponade, but are not part of the classic triad.
4. In differentiating tamponade from congestive heart failure, both of which are associated with elevated left atrial pressures, which of the following is true?
   - **a.** Both conditions feature an S_3 gallop.
   - **b.** Rales are uncommon with acute tamponade.
   - **c.** Both conditions feature an S_4 gallop.
   - **d.** A square root sign is common with acute tamponade.

   Answer: b. A distinguishing feature of tamponade is that the patient's lungs are usually clear. This is despite the fact that left atrial pressure is typically elevated (and equal to right atrial pressure). Limited right ventricular flow into the pulmonary circulation prevents pulmonary congestion in classic acute tamponade. Neither an S_3 nor an S_4 gallop are likely given impaired inflow into the ventricular chambers. A square root sign is associated with constriction, although even in the setting of constriction plus tamponade this sign is absent while there is substantial fluid in the pericardial space because it depends on rapid inflow during early diastole.
5. On echocardiography, a finding highly specific for tamponade is:
   - **a.** Right atrial collapse during early diastole
   - **b.** Left atrial collapse after open heart surgery
   - **c.** Left ventricular collapse during diastole
   - **d.** Lack of respiratory variation in Doppler inflow velocities across the tricuspid and mitral valves

   Answer: c. Chamber collapse in tamponade is caused by diminished transmural pressure, caused by rising intrapericardial pressure. Because pressures in the right-sided chambers are typically much lower than on the left, chamber collapse occurs much earlier on the right side, and may be caused by a variety of other factors as discussed in the text. Left atrial collapse after coronary artery bypass grafting is not uncommon and is associated with fluid surrounding the left atrium after open heart surgery. Left ventricular collapse is uncommon, even in tamponade, and when it does occur, it suggests very high intrapericardial pressure; it is highly specific. Respiratory variation, not "lack of," is a consequence of ventricular interdependence (see Figs. 25.7 and 25.8) and a classic finding in tamponade.
6. An electrocardiogram finding associated with tamponade and rarely seen with other conditions is:
   - **a.** Low voltage
   - **b.** ST elevation
   - **c.** Electrical alternans
   - **d.** Respiratory variation in QRS voltage

   Answer: c. Low voltage is a very common finding, but it is seen in a wide variety of clinical settings, including pulmonary disease, infiltrative myocardial disorders, muscle loss from prior infarction, hypothyroidism, and others. ST elevation may be associated with infarction or pericarditis, but it does not suggest tamponade per se. Respiratory variation in QRS voltage is a normal finding and is exacerbated in pulmonary disease and a variety of other settings. Electrical alternans, on the other hand, is typically seen when the heart swings back and forth in a large pericardial effusion and is a relatively specific, although not sensitive, finding for tamponade.
7. Pericardiocentesis can result in worsening hemodynamic status in patients with tamponade and:
   - **a.** Aortic dissection
   - **b.** Free wall rupture after myocardial infarction
   - **c.** Leaking thoracic aneurysm
   - **d.** All of the above

   Answer: d. The presence of an intact pericardium may prevent exsanguination in all of these clinical settings. Pericardiocentesis may result in catastrophic bleeding.
8. Which of the following is true?
   - **a.** Chest compression for shock in tamponade is usually effective.
   - **b.** In respiratory decompensation with tamponade, intubation should be avoided if possible.
   - **c.** When a patient with tamponade is anxious and tachypneic, sedation is helpful.
   - **d.** Patients with tamponade should undergo aggressive diuresis.

Answer: b. Chest compression is usually ineffective because it does not significantly address the underlying pathology and is unlikely to allow a higher stroke volume to be ejected. Anxiety and tachypnea are a common occurrence with tamponade related to catecholamine release and low cardiac output; sedation may undermine one of the last remaining protective mechanisms for maintaining cardiac output and aeration. Patients need to maintain intracardiac chamber pressure; diuresis in acute tamponade is counterproductive in many cases because venous return is decreased. Intubation increases thoracic pressure, also decreasing venous return in the setting of tamponade intubation may cause sudden hemodynamic collapse.

26

Hypovolemia and Traumatic Shock: Nonsurgical Management

DAVID J. DRIES

CHAPTER OUTLINE

Classic Neuroendocrine Response

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- Initial Management
- Fluid Resuscitation
- Vasoactive Drugs
- Resuscitation Strategy and Goals

Inflammation and Shock After Injury
- Immune Mediator Cascades
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Blood Component Therapy

Endpoints
- The Problem
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Clinical Strategies
- Early Limited Resuscitation
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Management of Traumatic Shock in the ICU
- Massive Transfusion
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- Risks of Early Red Blood Cell Transfusion

Special Problems
- Abdominal Compartment Syndrome
- Extremity Compartment Syndrome
- Pelvic Fractures

In 1934 Blalock suggested four categories of shock: hypovolemic, vasogenic, neurogenic, and cardiogenic.[1,2] In more recent clinical practice, additional categories of shock have been proposed.[3] Hypovolemic shock, the most common, results from a reduction in circulating blood volume. Volume loss may be loss of whole blood, plasma, or extracellular fluid or a combination of all three. Vasogenic shock occurs as a result of changes in the compliance of the vascular bed so that a normal blood volume fails to occupy the available space. Neurogenic shock (spinal shock) is a form of vasogenic shock in which spinal anesthesia or spinal cord injury leads to vasodilation. Septic shock is another form of vasogenic shock in which there is increased capacitance. A decrease in peripheral arterial resistance, an increase in venous capacitance, and a peripheral arteriovenous maldistribution occur. Cardiogenic shock results from failure of the heart as a pump. Obstructive shock results from mechanical obstruction to cardiac function, as seen with tamponade, tension pneumothorax, or massive pulmonary embolism.[4] Traumatic shock includes several components of the conditions mentioned previously.[5] Hypovolemia caused by blood loss is compounded by neurogenic, cardiogenic, or obstructive shock plus the vasogenic component of maladaptive mediator cascades initiated by tissue injury. Traumatic shock involves hemorrhage in combination with soft tissue trauma and fractures. As a result, the study of pure hemorrhagic shock may have limited relevance to the pathophysiologic condition of traumatic shock. Most studies have shown significant differences in the biologic condition of traumatic shock compared with that of pure hemorrhagic shock based on the activation of mediator cascades.

Conflicting observations in literature are due at least in part to the assumption that hemorrhagic shock and traumatic shock are identical insults.[2,4] Pulmonary complications after simple hemorrhage are uncommon in clinical practice, but pulmonary dysfunction is a common comorbid condition after major trauma with attendant soft tissue or long bone injury.[2,6] Activation of mediator systems is far more intense with traumatic shock than with pure hemorrhage.[7] Conflicting data regarding changes in cytokine levels after a traumatic insult are likely due to the fact that systemic cytokine levels do not reflect local production of these mediators. Measurement of tissue levels of mediator production may be necessary to determine accurately whether there is upregulation of various mediator systems after trauma and hemorrhage.

Soft tissue injury alone upregulates mediator systems.[2,8] A small animal study with closed femur fractures showed Kupffer cell activation 30 minutes after injury.[9] Another study assessed the effects of skeletal muscle injury in combination with hemorrhage in a porcine model of hemorrhagic shock. To reach a given physiologic endpoint (reduction in cardiac index and oxygen delivery), hemorrhage of 40% of the blood volume was required in a pure hemorrhagic shock model. If skeletal muscle injury was added, hemorrhage of only 29% of blood volume was necessary to reach the same endpoint.[10] The ability to maintain cardiac function after

hemorrhage was impaired in this study by superimposition of a soft tissue injury, emphasizing the difference between hemorrhagic shock and traumatic shock. A synergy in activation of neuroendocrine and inflammatory mediator systems is likely when traumatic injury and hemorrhagic shock are present. More recent work describing coagulation changes occurring with injury emphasizes the danger of combined injury and hypoperfusion of soft tissue with failure of appropriate coagulation response.[11]

Classic Neuroendocrine Response

The essential homeostatic response to fluid volume or blood loss is preservation of cerebral and cardiac perfusion with maintenance of normal blood pressure as sensed by carotid body and aortic arch receptors. Peripheral vasoconstriction and curtailment of urine output are seen. Cardiac contractility and peripheral vascular tone also are altered. Pain, hypoxemia, acidosis, infection, changes in temperature, and availability of substrates such as glucose affect this response. A decrease in blood volume alone without hypotension may activate the hypothalamic-pituitary axis. The magnitude of neuroendocrine response depends not only on the volume of fluid lost, but also the rate at which this occurs. This response may be modified by patient age, prescribed medications, preexisting illness, and the use of ethanol or other drugs. With spinal cord transection, operative intervention below the level of injury does not produce typical activation of the hypothalamic-pituitary axis. Similarly, consciousness is unnecessary for activation of this response because it may occur with the patient under anesthesia.[2,12–14]

The initial effect seen with hemorrhage is sympathetic vasoconstriction. Capacitance of the circulatory system is reduced, and aortic arch or carotid sinus baroreceptors respond to changes in blood pressure by modulation of sympathetic tone.[15] Atrial receptors respond to changes in vascular wall stretch and pressure. Afferent vagal fibers carry signals leading to loss of tonic inhibition of heart rate and immediate activation of thoracolumbar sympathetic outflow with norepinephrine release from postganglionic sympathetic fibers. As blood loss increases, so does the role played by arterial baroreceptors. Another part of this hormonal response is corticotropin-releasing factor secreted by the hypothalamus, vasopressin release, and growth hormone–releasing factor production.[12]

The clinician sees cool extremities in response to these changes associated with hypovolemia. Venous capacitance also decreases, resulting in accelerated venous return to the heart. Selective arterial vasoconstriction maintains blood flow to the heart and brain until compensation fails. Intense triggering of sympathetic signals is seen when arterial blood pressure decreases to less than 50 mm Hg and is maximally stimulated when systolic blood pressure is less than 15 mm Hg.[2] Although metabolic vasoregulation in the heart and brain helps to avoid local vasoconstriction, blood flow to other tissues decreases dramatically. Renal blood flow may be reduced to 5% to 10% of normal with acute hypovolemia. Flow to the splanchnic circulation, skin, and skeletal muscle also decreases. These vasoconstrictor responses are mediated by epinephrine and norepinephrine from the adrenal medulla and local sympathetic activity at the vasculature. With increases in acidosis and hydrogen ion concentration, coronary vasodilation occurs as opposed to constriction of arteries in skeletal muscle and the splanchnic circulation.[3,16]

Multiple endocrine responses are seen with hypovolemia. Plasma levels of glucagon, growth hormone, cortisol, and corticotropin (adrenocorticotropic hormone) increase.[2,3,5] The renin-angiotensin-aldosterone axis is stimulated with release of vasoconstrictive angiotensin II. Vasopressin release also occurs after hemorrhage, resulting in water absorption in the distal tubule of the kidney. Vasopressin induces splanchnic vasoconstriction. Endocrine studies suggest that with ongoing volume loss, vasopressin depletion may occur, and supplements of this hormone by clinicians may be warranted. Growth hormone and glucagon promote gluconeogenesis, lipolysis, and glycogenolysis. Catecholamines that inhibit insulin release with hyperglycemia and increased blood osmolarity are thought to shift fluid from cells and the interstitium into the intravascular space. More recent data associate hyperglycemia in the setting of injury with adverse outcome, however. The cellular mechanism for this response remains unclear. Loss of fluid or salt through the kidneys also is limited by these hormonal effects, which serve to conserve the circulating blood volume.[17–19]

Compensated acute hypovolemia occurs when the aforementioned mechanisms are sufficient to avoid widespread cellular injury and organ decompensation.[2] If volume loss continues or resuscitation is inadequate, a cycle of decline occurs with regional perfusion defects, leading to tissue and microcirculatory changes. Progression from compensated to decompensated and irreversible shock is often defined in retrospect. Frequently a patient with acute irreversible hemorrhage has been hypotensive for an extended period and cannot be resuscitated despite fluid administration and use of vasoactive drugs.[2,3] Presumed mechanisms include microcirculatory failure with loss of vasomotor response and integrity of the vascular bed. Patients with subacute but ultimately irreversible shock can be resuscitated initially, but progressive organ injury and end-organ dysfunction follow.

The Hypovolemic Patient

The diagnosis of shock is based on clinical, hemodynamic, and biochemical signs that can be broadly summarized into presentation of arterial hypotension (systolic blood pressure <90 mm Hg or MAP <70 mm Hg with associated tachycardia), tissue hypoperfusion, and metabolic changes typified by elevated serum lactate reflecting abnormal cellular oxygen metabolism.[20] In a recent study in which more than 1600 patients with nontraumatic shock were randomly assigned to receive either dopamine or norepinephrine, septic shock occurred in 62% of patients, cardiogenic shock in 16%, hypovolemic shock in 16%, and other types of distributive shock in 4% and obstructive shock in 2%.[21]

In the case of injury, the cause of shock is obvious from medical history and physical examination. Shock after traumatic injury continues blood loss and a direct insult to tissues. Other forms of shock may occur but are much less common. Physical examination, including skin color and temperature, jugular venous distention, and peripheral edema, is appropriate in any patient with shock. The diagnosis of shock can be refined at the bedside with point-of-care ultrasonography, including evaluation for pericardial effusion, measurement of left and right ventricular size and function, assessment for respiratory variation in vena cava dimension, and with some techniques by calculation of aortic velocity-time integral, which is a measure of stroke volume.[20,22,23]

Initial Management

Resuscitation of the hypovolemic patient should be initiated even while investigation of details of the cause is ongoing. Unless the patient's condition is rapidly reversed, an arterial catheter should be considered for monitoring of arterial blood pressure and blood sampling plus a central venous catheter for infusion of fluids and

vasoactive agents. Data obtained through the central venous catheter may also guide fluid therapy. Initial management of shock is problem-oriented and goals are similar regardless of the etiology. Treatments used to reach these goals may be varied.

Administration of oxygen should be started immediately to increase oxygen delivery. Pulse oximetry may be unreliable because of peripheral vasoconstriction, and precise determination of oxygen requirements requires blood gas monitoring. Mechanical ventilation incorporating endotracheal intubation should be seriously considered to provide reliable support of respiration and oxygen delivery. This therapy is considered in nearly all patients with dyspnea, hypoxemia, or persistent or worsening acidemia (pH <7.30). Invasive mechanical ventilation has additional benefits in reduction of oxygen demand of respiratory muscles and decreasing left ventricular afterload by increasing intrathoracic pressure. An abrupt decrease in arterial pressure after endotracheal intubation and initiation of invasive mechanical ventilation suggests hypovolemia and a decrease in venous return.[20]

Fluid Resuscitation

Fluid therapy to improve microvascular blood flow and increase cardiac output (CO) is an essential part of the treatment of any form of shock. The patient with hypovolemic, nontraumatic shock more commonly requires crystalloid solutions than the individual with hypovolemia in the setting of significant injury. Fluid administration must be closely monitored given the risk of edema and associated consequences.[11,20,24]

The ideal resuscitation fluid should produce predictable and sustained increase in intravascular volume and replace extracellular fluid. An ideal fluid is metabolized and completely excreted without accumulation in tissues and does not produce adverse metabolic or systemic effects. Resuscitation fluid must also be cost-effective. Unfortunately, there is no such fluid currently available.

Resuscitation fluids are broadly categorized into crystalloid and colloid solutions (Table 26.1). Crystalloids are solutions of ions freely permeable but containing concentrations of sodium and chloride that determine their tonicity. Colloids are suspensions of molecules within a carrier solution relatively incapable of crossing a healthy semipermeable capillary membrane owing to the molecular weight of the molecules.

Proponents of crystalloid solutions argue that colloids, particularly human albumin, are expensive and impractical particularly under field resuscitation conditions. Crystalloids are inexpensive and widely available and have an established role as first-line resuscitation fluids. Crystalloids have been associated with clinically significant interstitial edema.

Colloid solutions are more effective in expanding intravascular volume and are retained in the intravascular space and maintain colloid oncotic pressure more effectively than crystalloids. The volume-sparing effect of colloids, compared with crystalloids, is considered an advantage that is conventionally described in a 1:3 ratio of administered colloids to crystalloids to maintain a given intravascular volume.[24]

Crystalloids

Sodium chloride is the most commonly used crystalloid solution, particularly in the United States. Normal 0.9% saline solution contains sodium and chloride in equal concentrations, making it isotonic compared with extracellular fluid. The strong ion difference of 0.9% saline solution is zero, with the result that administration of large volumes of saline solution results in hyperchloremic metabolic acidosis. Adverse effects such as immune and renal dysfunction have been attributed to this phenomenon, although the clinical consequences are less well established.[24,25]

Concern about sodium and water overload associated with saline solution resuscitation has resulted in the concept of small-volume crystalloid resuscitation with the use of hypertonic saline (3%, 5%, and 7.5%) solutions. However, early use of hypertonic saline solution for resuscitation, particularly in patients with traumatic brain injury, has not improved short-term or long-term outcomes.[24,26]

Crystalloids with a chemical composition that approximates extracellular fluid have been termed *balanced* or *physiologic* solutions and are derivatives of the original crystalloid solutions. However, none of these proprietary solutions are truly balanced or physiologic. Balanced salt solutions are relatively hypotonic because they have a lower sodium concentration than extracellular fluid. Because of the instability of bicarbonate-containing solutions in plastic containers, alternative anions such as lactate, acetate, gluconate, and malate have been used. Excessive administration of balanced salt solutions may result in hyperlactatemia, metabolic alkalosis, and hypotonicity (with sodium lactate), and cardiotoxicity (with acetate). The addition of calcium in some solutions may generate microthrombi with citrate-containing red blood cell transfusions.[24]

Given the concern regarding an excess of sodium and chloride associated with normal saline solution, balanced salt solutions are becoming more popular as first-line resuscitation fluids in patients undergoing surgery, patients with trauma, and patients with diabetic ketoacidosis. Resuscitation with balanced salt solutions is a key element in the initial treatment of patients with burns, although there is increasing concern about the adverse effects of fluid overload and a strategy of permissive hypovolemia in such patients is being investigated.[24,27–29]

A recent observational study compared major complications in patients receiving only normal saline solution with a calcium-free balanced salt solution for replacement of fluid losses on the day of surgery. The use of a balanced salt solution was associated with a significant decrease in the rate of major complications, including a lower incidence of postoperative infection, renal replacement therapy, blood transfusion, and problems associated with acidosis. Another single-center observational intensive care unit (ICU) study using a colloid-restrictive fluid strategy (lactated and calcium-free balanced solutions) to replace chloride-rich intravenous (IV) fluids (normal saline solution, 4% albumin, or succinylated gelatin) was associated with a significant decrease in acute kidney injury (AKI) and the need for renal replacement therapy.[30,31]

Colloids

Human albumin (4%–5%) in saline solution is considered the reference colloid. It is produced by fractionation of blood and is heat-treated to prevent transmission of viruses. It is an expensive solution to produce and distribute and its availability is limited in low- and middle-income countries.

Albumin has been compared to saline solution in a major recent trial conducted by investigators in Australia and New Zealand, the Saline versus Albumin Fluid Evaluation (SAFE) study, conducted in approximately 7000 ICU patients. The study assessed the effect of resuscitation with 4% albumin compared to saline solution on the rate of death at 28 days. No significant difference between albumin and saline with respect to the rate of death or development of new organ failure was identified.[24,32]

A number of subanalyses of the SAFE study data have been conducted. Resuscitation with albumin was associated with a

TABLE 26.1 Types and Compositions of Resuscitation Fluids[a]

		COLLOIDS									CYSTALLOIDS		
			Hydroxyethyl Starch						4% Succinylated Modified Fluid Gelatin	3.5% Urea-Linked Gelatin			
Variable	Human Plasma	4% Albumin	10% (200/0.5)	6% (450/0.7)	6% (130/0.4)		6% (130/0.42)				0.9% Saline Solution	Compounded Sodium Lactate	Balanced Salt Solution
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Haemaccel	Normal saline solution	Hartmann Ringer lactate	Plasma-Lyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mOsm/L)	291	250	308	304	308	286	308	296	274	301	308	280.6	294
Sodium (mmol/L)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol/L)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol/L)	2.2–2.6			5.0				2.5		6.25			
Magnesium (mmol/L	0.8–1.0			0.9		1.5		1.0					
Chloride (mmol/L)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol/L)						34		24					27
Lactate (mmol/L)	1–2			28								29	
Malate (mmol/L)								5					
Gluconate (mmol/L)													23
Bicarbonate (mmol/L)	23–27												
Octanoate (mmol/L)		6.4											

[a]To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114.
From Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369:1243–1251.

significant risk in the rate of death at 2 years among patients with traumatic brain injury. This outcome has been attributed to increased intracranial pressure, particularly during the first week after injury. Resuscitation with albumin was associated with a decrease in the adjusted risk of death at 28 days in patients with severe sepsis, suggesting a potential but unsubstantiated benefit in patients with severe sepsis. There was no significant between group difference in the rate of death at 28 days among patients with low albumin levels.[32–34]

In the SAFE study, no significant difference in hemodynamic resuscitation endpoints, such as mean arterial pressure (MAP) or heart rate, was observed between the albumin and saline solution groups, although the use albumin was associated with a significant but clinically small increase in central venous pressure (CVP). The ratio of volume of albumin to the volume of saline solution administered to achieve comparable resuscitation endpoints was observed to be 1:1.4.[32]

Another important study conducted in sub-Saharan Africa, the Fluid Expansion As Supportive Therapy (FEAST) study, compared the use of boluses of albumin or saline solution with no boluses in resuscitation fluid for approximately 3000 febrile children with impaired perfusion. In this study, bolus resuscitation with albumin or saline produced similar rates of death at 48 hours, but there was a significant increase in the rate of death at 48 hours associated with both therapies compared with no bolus therapy. The principal cause of death in these patients was cardiovascular collapse rather than fluid overload or neurologic causes, suggesting an adverse interaction between bolus fluid resuscitation and compensatory neurohormonal responses. Although this trial was focused on a pediatric population with limited critical care facilities, the results call into question the role of bolus fluid resuscitation in populations of critically ill patients.[35,36]

In acute illness, it appears that hemodynamic effects and effects on patient-centered outcomes of albumin are largely equivalent to those of saline solution. Examination of these fluids in specific populations of patients continues.

Semisynthetic Colloids

The limited availability and relative expense of albumin have prompted development of semisynthetic colloid solutions.[24] Globally, semisynthetic colloids are known as hetastarch, succinylated gelatin, urea-linked gelatin polygeline preparations, and dextran solutions. The use of dextran solutions has largely fallen out of favor.

Hydroxyethyl starch solutions are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes. A high degree of substitution on glucose molecules protects against hydrolysis by nonspecific amylases in the blood—thus prolonging intravascular volume expansion—but this action increases the potential for hydroxyethyl starches to accumulate in the reticuloendothelial tissues such as the skin and kidney. The use of hydroxyethyl starch, particularly high-molecular-weight preparations, is associated with alterations in coagulation, specifically changes in viscoelastic measurements and fibrinolysis, although the clinical consequences of these effects in specific patient populations such as those undergoing surgery or trauma are unclear. A small number of studies have questioned the safety of concentrated hydroxyethyl starch solutions in patients with severe sepsis, noting increased risks of death, AKI, and the use of renal replacement therapy.[37,38]

Currently readily available hydroxyethyl starch solutions have reduced concentrations and are available with various types of crystalloid carrier solutions. Hydroxyethyl starch solutions are widely used in patients undergoing anesthesia for major surgery, particularly as a component of goal-directed perioperative fluid management strategies, as a first-line resuscitation fluid in military theaters, and particularly in patients in the ICU. Because of the potential for fluid accumulation in tissues, limits are recommended for maximal daily doses of hydroxyethyl starch solutions.

Two important recent trials demonstrate no significant difference in short-term hemodynamic resuscitation endpoints when hydroxyethyl starch solutions are compared to saline solution. The observed ratio of hydroxyethyl starch to crystalloids in these trials was approximately 1:1.3, consistent with the ratio of albumin to saline solution reported in the SAFE study previously described.[24,39,40]

Hydroxyethyl starch solutions are associated with increases in urine output in patients at low risk for AKI but with parallel increases in serum creatinine levels in patients at increased risk for AKI.[24] The use of hydroxyethyl starch solutions was associated with an increased use of blood products and an increased rate of adverse events, particularly pruritus.

There are a variety of other semisynthetic colloid solutions such as gelatins and polygeline preparations that have not been studied. However, another recent observational study has raised concern about the risk of AKI associated with the use of gelatin solutions. These solutions have not been studied in high-quality trials to date. In light of current evidence of lack of clinical benefit, potential nephrotoxicity, and increased cost, the use of semisynthetic colloids for fluid resuscitation in critically ill patients is difficult to justify.[24,41,42]

Vasoactive Drugs

If hypotension is severe or persistent despite fluid administration, vasoactive drugs may be considered (Table 26.2). It is acceptable to administer a vasoactive drug temporarily while fluid resuscitation is ongoing with the aim of discontinuing the vasoactive medication after hypovolemia has been corrected.

Adrenergic agonists are first-line vasopressors because of rapid onset of action, high potency, and short half-life. Norepinephrine is widely considered to be the vasopressor of choice. It has predominantly α-adrenergic properties but modest β-adrenergic effects to help maintain CO. Administration generally results in a clinically significant increase in MAP with little change in heart rate or CO. The usual dose is 0.1 to 2.0 μg/kg of body weight per minute.[20]

Dopamine has predominantly β-adrenergic effects at lower doses and α-adrenergic effects at higher doses. Its effects are relatively weak. Dopaminergic effects at very low doses (0.5–2 μg/kg per minute given intravenously) may selectively dilate the hepatosplanchnic and renal circulation, but controlled trials have not shown a protective effect of this agent on renal function. Dopaminergic stimulation may also have undesired endocrine effects on the hypothalamic-pituitary system resulting in immunosuppression, particularly through reduction in prolactin release. In recent trials, dopamine had no advantage over norepinephrine as a first-line vasopressor. Dopamine induced more arrhythmias and was associated with an increased 28-day rate of death among patients with cardiogenic shock. Dopamine is no longer recommended for treatment of patients with shock.[20,21,43]

Epinephrine has predominantly β-adrenergic effects at low doses and α-adrenergic effects becoming more significant at higher doses. Epinephrine administration may be associated with increased frequency of arrhythmias and a decrease in splanchnic blood flow. This agent can also increase blood lactate levels, presumably by increasing cellular metabolism. Prospective, randomized trials have

TABLE 26.2 Vasoactive Agents Commonly Used in Shock Resuscitation

Agent	Dose Rate (μg/kg/min)	Physiologic Action	Intended Effects	Adverse Effects
Dopamine				
Low	<5	DA_1 receptor	Selective vasodilation	↑ HR
Medium	5–15	β_1 receptor	↑ CI, ↑ MAP, ↑ CWP	Arrhythmia
High	>15	α_1 receptor	↑ MAP	
Dobutamine	5–20	α_1, β_1, β_2 receptors	↑ CI, ↓ PCWP	↑ HR, ↓ MAP, arrhythmia
Norepinephrine	0.01–0.05	α_1, α_2, β_1 receptors	↑ CI	↑ Afterload
	>0.05	α_1 receptor	↑ MAP	Vasoconstriction
Nitroprusside	0.25–10	NO donor	↓ Afterload, ↑ CI	↓ MAP, ↓ Pao_2 thiocyanate toxicity
Phenylephrine	0.2–0.9	α_1 receptor	↑ MAP	Vasoconstriction
Vasopressin	0.04 Units/min	Vasopressin receptor	↑ MAP	Vasoconstriction

DA_1, Dopaminergic postsynaptic receptors in renal, splanchnic, cerebral and coronary vessels; *CO*, cardiac output; *HR*, heart rate; *MAP*, mean arterial pressure; Pao_2, partial pressure of arterial oxygen; *PCWP*, pulmonary capillary wedge pressure; α_1, postsynaptic receptor on vascular smooth muscle; α_2, Presynaptic receptor; β_1, largely cardiac; β_2, largely smooth muscle receptor of the vasculature and bronchial tree.

From Moore FA, McKinley BA, Moore EE, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma.* 2006;61:82–89.

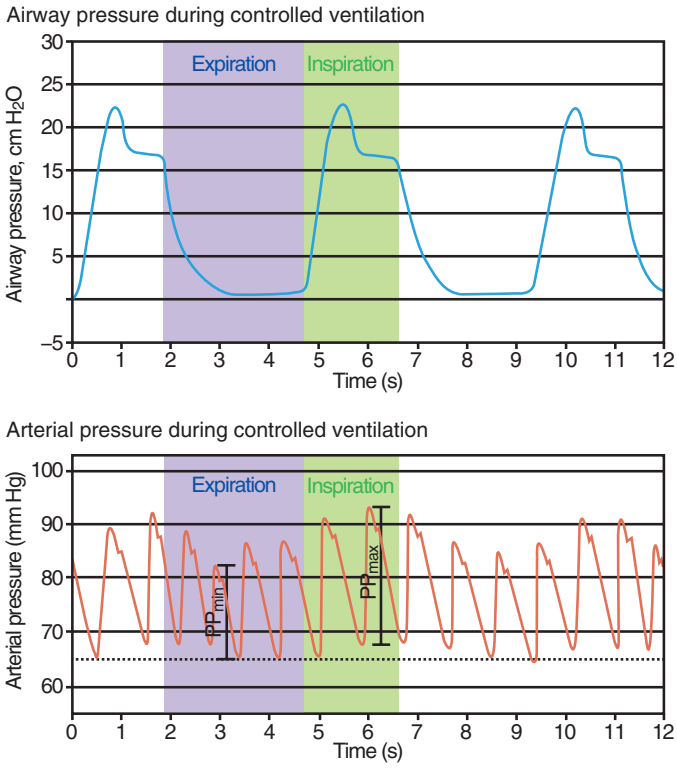
not shown beneficial effects of epinephrine over norepinephrine in septic shock. Epinephrine is a second-line agent for severe cases.[20,44]

Vasopressin deficiency may develop in patients with hyperkinetic forms of distributive shock or hypovolemia. Administration of low-dose vasopressin may result in substantial increases in arterial pressure. In studies of patients with sepsis, administration of low-dose vasopressin in addition to norepinephrine was safe. Comparable data in the hypovolemic patient are not available. Typically, if used, vasopressin should not be given at doses at higher than 0.04 U/min and should be administered in patients with high CO.[20,45]

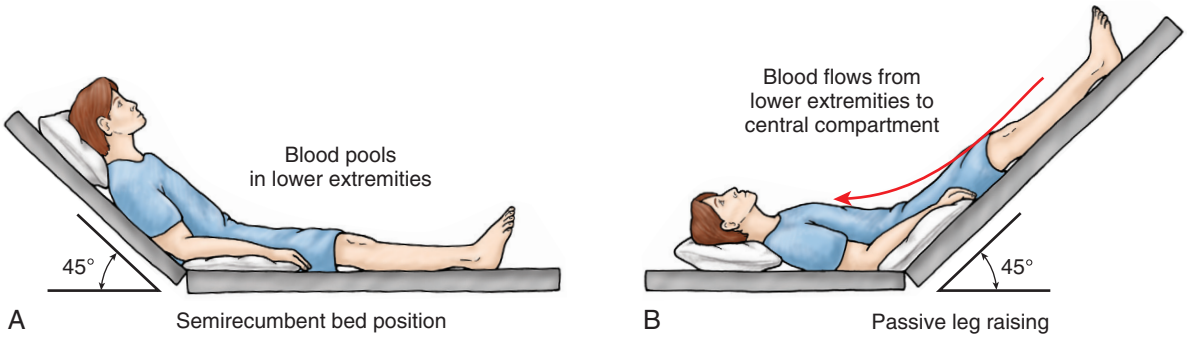
Dobutamine is the inotropic agent of choice for increasing CO regardless of whether norepinephrine is also being given. It is predominantly a β-adrenergic stimulus with less likelihood to induce tachycardia than agents such as isoproterenol. A very low dose may substantially increase CO. IV doses in excess of 20 μg/kg per minute provide little additional benefit. Dobutamine has limited effects on arterial pressure, although pressure may increase slightly in patients with myocardial dysfunction as the primary abnormality or may slightly decrease in patients with hypovolemia. Phosphodiesterase type III inhibitors such as milrinone combine inotropic and vasodilating properties by decreasing the metabolism of cyclic adenosine monophosphate. These agents may reinforce the effects of dobutamine. Unacceptable adverse effects are seen in patients with hypotension, and long half-lives of these agents compromise moment-to-moment dose adjustment.[20]

Resuscitation Strategy and Goals

Endpoints for fluid resuscitation are difficult to define. In general, CO should become preload-independent but this is difficult to evaluate clinically. Patients supported by mechanical ventilation may show signs of fluid responsiveness from beat-to-beat stroke volume measurements with the use of CO monitors or indirectly from observed variation in pulse pressure on the arterial pressure tracing during the ventilator cycle (Fig. 26.1). All



• **Fig. 26.1** Representation of airway pressure changes with positive pressure of ventilation and corresponding changes in arterial pressure waveform as expiration and inspiration are compared. Changes in systolic and diastolic pressure increase in the hypovolemic patient. (From Bentzer P, Griesdale DE, Boyd J, et al. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA.* 2016;316:1298–1309.)



• **Fig. 26.2** Illustration shows patient positions for straight leg-raising test as a means to evaluate responsiveness to a fluid challenge. Raising the patient's legs with enhanced venous return serves as the fluid challenge in this technique. (From Bentzer P, Griesdale DE, Boyd J, et al. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA.* 2016; 316:1298–1309.)

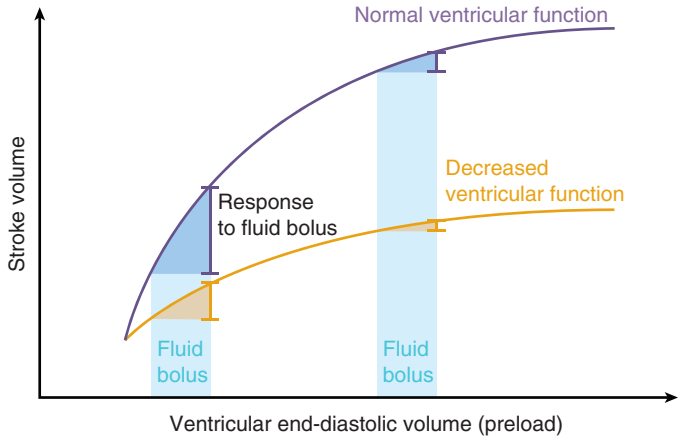
such bedside assessments have limitations and may be unreliable in patients with changing types and degree of organ system support.[20]

The fluid challenge technique has been advocated to determine a patient's actual response to fluids while limiting the risks of complications associated with fluid administration (Fig. 26.2). The fluid challenge requires definition of its elements. First, the type of fluid must be selected. Crystalloid solutions (discussed later) are the first choice because they are well tolerated and inexpensive. The use of albumin to correct severe hypoalbuminemia is reasonable in some patients. Second, the rate of fluid administration must be defined. Fluid should be infused rapidly to induce a rapid response but not so fast that an artificial stress response develops. Typically, 300 to 500 mL of fluid is administered during a period of 20 to 30 minutes. Third, the objective of the fluid challenge must be defined. In hypovolemic shock, the objective is usually an increase in systemic arterial pressure, although surrogates include a decrease in heart rate or an increase in urine output. Finally, safety limits must be defined. Pulmonary edema is the most serious complication of fluid administration. Some clinicians advocate limiting CVP changes to a few millimeters of mercury above baseline to prevent dangerous fluid overload.[20]

In the historical approach to resuscitation that emphasized protocolized care, critically ill and injured patients frequently received large amounts of crystalloids regardless of hemodynamic status. Recent trials suggest that aggressive fluid resuscitation produces severe tissue edema, compromising organ function and leading to increased mortality and morbidity. A recently completed important global survey suggests that the aggressive approach to fluid resuscitation studied in more than 40 countries is arbitrary, without basis and evidence, and is potentially harmful.[46,47]

Fluid Responsiveness

Patients are given a fluid challenge to increase stroke volume and CO. If an increase in stroke volume cannot happen, fluid administration serves no useful purpose and is possibly harmful. The patient is considered fluid-responsive if his or her stroke volume increases by at least 10% after a fluid challenge (usually 500 mL of a crystalloid solution). Fluid administration will increase stroke volume only if the fluid bolus increases stressed blood volume. This will cause the mean circulating filling pressure to increase greater than the increase in CVP, which increases the gradient for venous return, and if both ventricles are functioning, the gradient on the ascending limb of the Frank-Starling curve[46,48] (Fig. 26.3).



• **Fig. 26.3** Examples of Frank-Starling–type curves for the setting of normal ventricular function and decreased ventricular function. Note that stroke volume increases in either case but the maximum gain in stroke volume is less with compromised ventricular performance. (From Bentzer P, Griesdale DE, Boyd J, et al. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA.* 2016; 316:1298–1309.)

A growing number of trials in critically ill and injured patients and those undergoing surgery demonstrate that approximately 50% of hemodynamically unstable patients are fluid responsive. This fundamental point is not widely appreciated and challenges the widely accepted notion that fluid administration is the cornerstone of resuscitation. Patients who are fluid responsive should be resuscitated with limited fluid boluses. Thus determination of fluid responsiveness is essential in managing resuscitation of critically ill patients.[46,48–50]

Although clinical signs such as hypotension, tachycardia, narrow pulse pressure, poor skin perfusion, and slow capillary refill are helpful in identifying inadequate perfusion, these signs are unable to determine volume status or fluid responsiveness.[51] Change in CVP after a fluid challenge is no more accurate in predicting fluid responsiveness than flipping a coin and should be abandoned for this purpose.[46,48] It should also be recognized that the change in MAP after a fluid bolus is poorly predictive of fluid responsiveness.[48] Ultrasonography of the vena cava and its respiratory variation are frequently no more predictive than the CVP for assessing fluid responsiveness. Echocardiography has limited ability for assessing volume and fluid responsiveness. Transthoracic measurements of

left ventricular outflow tract velocities for estimation of stroke volume require considerable expertise as for other ultrasound-based studies and are not easily obtained or reproduced in the critical care setting. Ultrasound-based technologies are not ideal for detecting rapid changes in stroke volume after passive leg-raising maneuvers or fluid challenges.[46]

Fluid Challenge

Currently there are two techniques that are readily available, practical, easy to perform, and physiologically based that can be used to determine fluid responsiveness with a relevant degree of accuracy.[46,48] These techniques are passive leg raising and actual fluid administration as a fluid challenge (see Fig. 26.2). These techniques are best combined with minimally invasive or noninvasive CO monitors that can track changes in stroke volume in real time. The passive leg-raising maneuver is simple to perform and takes less than 5 minutes to compete. Beyond ease of use, this method has the advantage of reversing its effects once the legs are returned to the horizontal position. A meta-analysis that pooled the results of 21 trials confirmed excellent diagnostic value of the passive leg-raising maneuver to predict fluid responsiveness in critically ill patients. The gold standard to determine fluid responsiveness is change in stroke volume after a fluid challenge. As crystalloids redistribute rapidly, the fluid bolus should be given as quickly as possible and ideally in 30 minutes or less. A bolus between 300 and 500 mL is recommended. Larger fluid boluses (20–30 mL/kg), although still widely recommended, may be unphysiologic and have an increased risk of volume overload with tissue edema.[46–52]

Fluid boluses are most frequently administered to patients with hypotension. It is not widely recognized, however, that the hemodynamic response to a fluid challenge is usually small and short-lived. In a recent study of patients with circulatory shock, 65% of patients were fluid responders, defined as those with a cardiac index increase by 25% at the end of infusion (30 minutes). Further, cardiac index had returned to baseline 30 minutes after the end of infusion.[53] Another systematic review that examined the hemodynamic response to fluid boluses in patients with sepsis reported that although MAP increased by approximately 8 mm Hg immediately after a fluid bolus, this parameter had returned to baseline at 1 hour with no increase in urine output.[54] Other data from the ARDSNet demonstrated an increase of MAP of only 2 mm Hg after a fluid bolus with no increase in urine output. Fluid boluses are generally ineffective for management of hypotension, circulatory shock, and oliguria.

Critically ill and injured patients and patients undergoing surgery do not need to be pushed to the top of their Frank-Starling curve. Patients should receive a fluid bolus if they are preload responsive and are likely to benefit from the fluid bolus, which is to say that the potential benefits and risks should be evaluated before each fluid bolus. Patients should receive fluid boluses only if the hemodynamic benefits are likely to outweigh the risks of an accumulating positive fluid balance.[46,48] Patients should not receive repeated fluid boluses until they are no longer fluid responsive. As patients' results ascend on the Frank-Starling curve, the adverse effects of fluid bolus administration outweigh the benefits as atrial pressures increase with increasing hydrostatic edema. Because of the short-lived effect of a fluid bolus, it may be preferable to treat the fluid-responsive septic patient with norepinephrine as this agent will increase venous return, stroke volume, and MAP while limiting tissue edema.[46,55] Comparable data for the patient with hypovolemia shock are not available.

Finally, organ blood flow is driven by the difference between the arterial and venous pressures in the circulation. The MAP minus the CVP is the driving force for organ blood flow. When MAP is in an organ autoregulatory range, the CVP becomes a factor determining organ and microcirculatory perfusion.[46,56] The kidney is particularly affected by increased venous pressure, which leads to increased renal subcapsular pressure and lowered renal blood flow and glomerular filtration rate. Physiologic studies have demonstrated a linear relationship between increasing CVP and AKI with a high CVP being the only hemodynamic variable independently associated with AKI. In critically ill patients and those with heart failure, CVP greater than 8 mm Hg has been demonstrated to be predictive of AKI. A growing body of data supports the primary hemodynamic goal in critically ill and injured patients and those undergoing surgery is an MAP above 65 mm Hg and a CVP less than 8 mm Hg. Ironically, fluid loading of oliguric patients with a low CVP with a goal of increasing CVP to more than 8 mm Hg may also increase the risk of progression to AKI.[46,48,57–59] Fluid administration should be guided by assessment of fluid responsiveness combined with determination of benefits and harms of fluid administration. Large fluid boluses should be avoided.

Inflammation and Shock After Injury

In addition to blood loss, extensive research suggests that trauma may be considered an inflammatory disease.[60–63] It has been shown that a variety of mediators and indicators of inflammatory response are elevated in severely injured patients. For many of these factors, it could be shown that markers of inflammation were significantly elevated in patients eventually dying compared with survivors, and that prediction of outcome is possible with a significant degree of accuracy. Peak inflammatory activity as measured by plasma values has been noted within hours of injury. Although it cannot at present be decided which of these parameters may play a direct pathophysiologic role in development and promotion of inflammatory response and consecutive organ dysfunction, and which is an indicator of this reaction, inflammatory mediators may reflect pathophysiologically relevant disturbances set off by tissue injury and blood loss with consecutive ischemia and reperfusion incidents.[64]

Shock after trauma differs from pure hypovolemic shock in that effects of release of mediators by tissue injury are superimposed on hypovolemia. It also is clear that not all damage after shock is the result of tissue hypoxia and that cellular damage follows reperfusion and subsequent inflammation. Loci of this inflammatory response are the wound, with activation of macrophages and production of proinflammatory mediator, and the microcirculation, with activation of blood elements and the endothelium.[64,65]

Immune Mediator Cascades

Although a variety of initiating events may occur, the subsequent inflammatory response is qualitatively similar.[2] Local activation of the complement cascade produces anaphylatoxins, which are strong attractants and stimulants of neutrophils. Local endothelium expresses endothelial leukocyte adhesion molecules, which attract the neutrophil population. Activated neutrophils also express adhesion molecules, leading to aggregation, margination in the vascular endothelium, and migration through vessel walls at the area of injury. This inflammatory response produces a respiratory burst with formation of oxygen radicals and synthesis of proteolytic

enzymes. Local release of bradykinin, histamine, and prostaglandin induces local vasodilation and increased capillary permeability from macromolecules, resulting in a protein-rich exudate. Local phagocytes release messenger molecules, such as granulocyte-macrophage colony-stimulating factor and macrophage colony-stimulating factor, which activate the bone marrow to produce more inflammatory cells. Neutrophils injure otherwise healthy tissues.[2,66,67]

In a slower response, the monocyte population is attracted to the site of injury, where it differentiates to macrophages and contributes to the inflammatory process by consuming and killing bacteria or disposing of necrotic tissue or both. Macrophages are activated further by triggers such as hypoxia or C5a, macrophage-activating factor, and interleukin (IL)-1–like activity from neutrophils. On stimulation, macrophages release a variety of classes of secretory products, which may be proinflammatory (proteolytic enzymes, oxygen radicals, IL-1, IL-6, tumor necrosis factor) or antiinflammatory (IL-10, prostaglandin E_2). Macrophage mediators, such as prostaglandin E_2, tumor necrosis factor, IL-1, IL-2, and IL-6, provide systemic signals adapting metabolic and defense mechanisms. Macrophages take several days after activation to develop full inflammatory capacity. They also may release nitric oxide and cytotoxic radicals. In the setting of injury, this local inflammatory process spills over to cause an exaggerated systemic response with inflammatory damage to otherwise healthy cells and organs distant to the site of injury. Secondary infection may occur in the compromised host, leading to generalized inflammation and multiorgan dysfunction (Box 26.1).[2,68,69]

Catecholamines are neurotransmitters that affect immune response humorally through circulating adrenal-derived epinephrine and locally through neuronal release of norepinephrine. The functional effects of catecholamines on cells of the immune system have been confirmed in human volunteers. In addition, relevance of this control mechanism and the implications for dysregulation have been shown by rapid systemic release of IL-10 and the high incidence of infection in patients with sympathetic storm from accidental or iatrogenic brain trauma.[70] Although detrimental effects of sustained and exaggerated sympathetic nervous system activation on cardiovascular and metabolic homeostasis have long been recognized, attention is now directed to the likelihood of immune dysregulation as well.

The neuroimmune axis is a bidirectional network composed of descending pathways linking the central nervous system (CNS) to peripheral immune tissues and a parallel afferent arm linking the immune system with the CNS. The integrity of this loop allows for communication between the CNS and peripheral immune system integrating neuronal and immune signals in the periphery and in the CNS. Cells from the immune system express functional receptors and signal transduction pathway components for several neuroendocrine mediators, allowing functional cellular responses to agonist stimulation. Similarly, cells in the CNS are capable of synthesizing, secreting, and responding to inflammatory and immune molecules. There is considerable evidence that the peripheral immune system can signal the brain to elicit a sickness response during infection, inflammation, and injury. Peripheral immune molecules such as cytokines influence CNS action through mechanisms, including entry into the brain through a saturable transport mechanism or through areas that lack the blood-brain barrier. Afferent neurons of the vagus nerve also are activated (Fig. 26.4).[71–73]

Severe trauma is characterized by the classic activation of the sympathetic nervous system and the recently recognized contribution of the inflammatory and neuroimmune response to injury.[70] The sympathetic nervous system has significant anatomic and functional interaction with cells of the immune system and plays an important role in control of the magnitude of early inflammatory response to injury by ensuring expression of adequate cytokine balance. Sympathetic neural pathways exert direct effects on cells of the immune system, affecting cytokine expression, lymphocyte function, and cytotoxic activity. In return, the inflammatory mediators released communicate with the CNS through stimulation of sensory and vagal afferents or by crossing the blood-brain barrier through active transport mechanisms and pathways allowing access to hypothalamic-pituitary structures. Immune-derived mediators, such as cytokines and chemokines, can modulate neurotransmission affecting activation of descending autonomic and neuroendocrine pathways.[70]

• BOX 26.1 Inflammatory Mediators Associated With Development of Multiple Organ Dysfunction Syndrome in Injured Patients[a]

First 24 h

- Thromboxane B_2
- C3a
- Terminal cytolytic complement complex
- C-reactive protein
- Elastase
- Tumor necrosis factor α
- Interleukin 6
- Lipofuscin
- Lactate
- Antithrombin III

Days 2–5

- Elastase
- Interleukin 6
- Lipofuscin
- Soluble intercellular adhesion molecule 1

Day >8

- Elastase
- Interleukin 1
- Interleukin 6
- Neopterin
- Lipofuscin
- Tumor necrosis factor α if sepsis

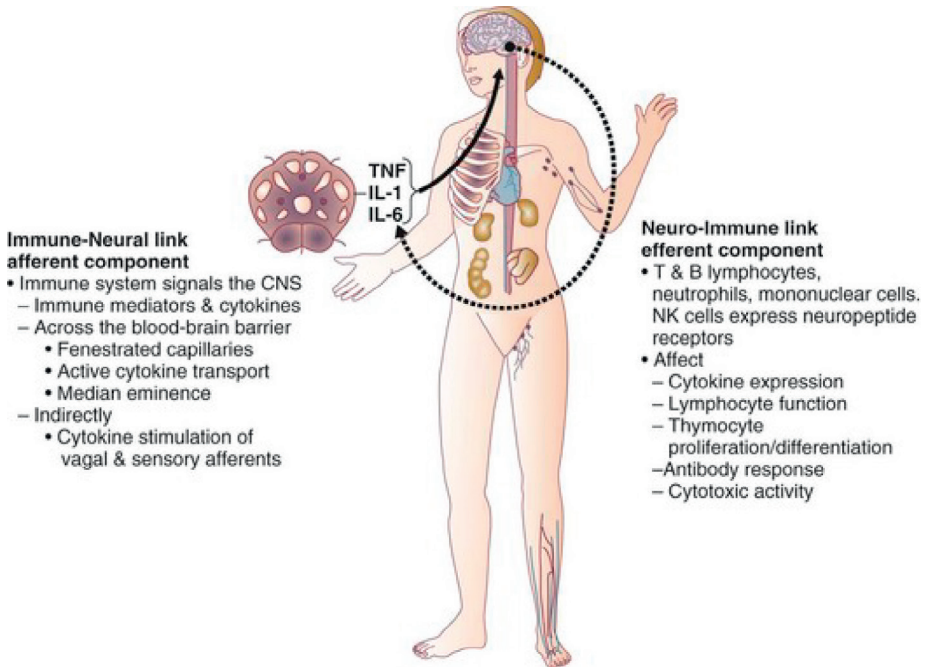
[a]*A variety of inflammatory mediators are associated with soft tissue injury, bony injury, and blood loss associated with various forms of trauma. The time course of mediator appearance in limited studies completed to date is suggested in this box. In experimental models and limited clinical data, the presence of soft tissue or bony injury in addition to hemorrhage accelerates and magnifies the production of these mediators over clinical and experimental models in which hemorrhage alone is seen.*

From Goris RJ. Pathophysiology of shock in trauma. Eur J Surg. *2000;166:100–111.*

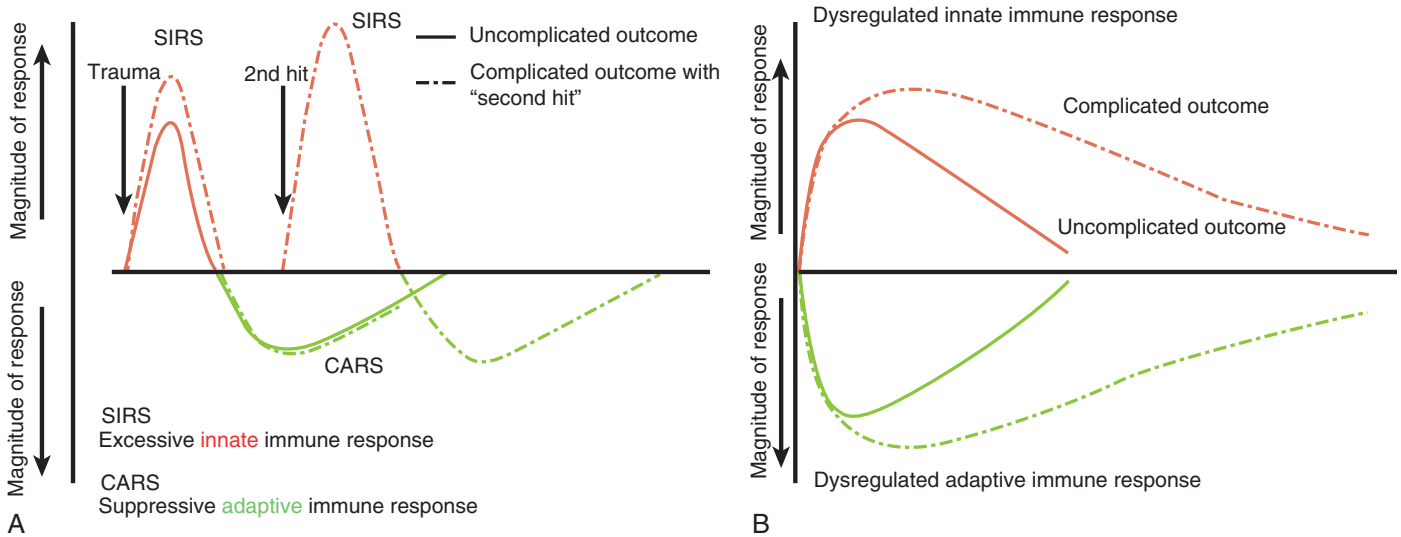
Genomics of Injury

A series of elegant clinical studies evaluated gene response to injury in a multicenter trial in patients receiving comparable resuscitation.[74] When leukocytes of normal volunteers were compared to those sustaining blunt injury, a "*genomic storm*" was identified. This work is taken from the Inflammation and the Host Response to Injury investigations[75] (Fig. 26.5).

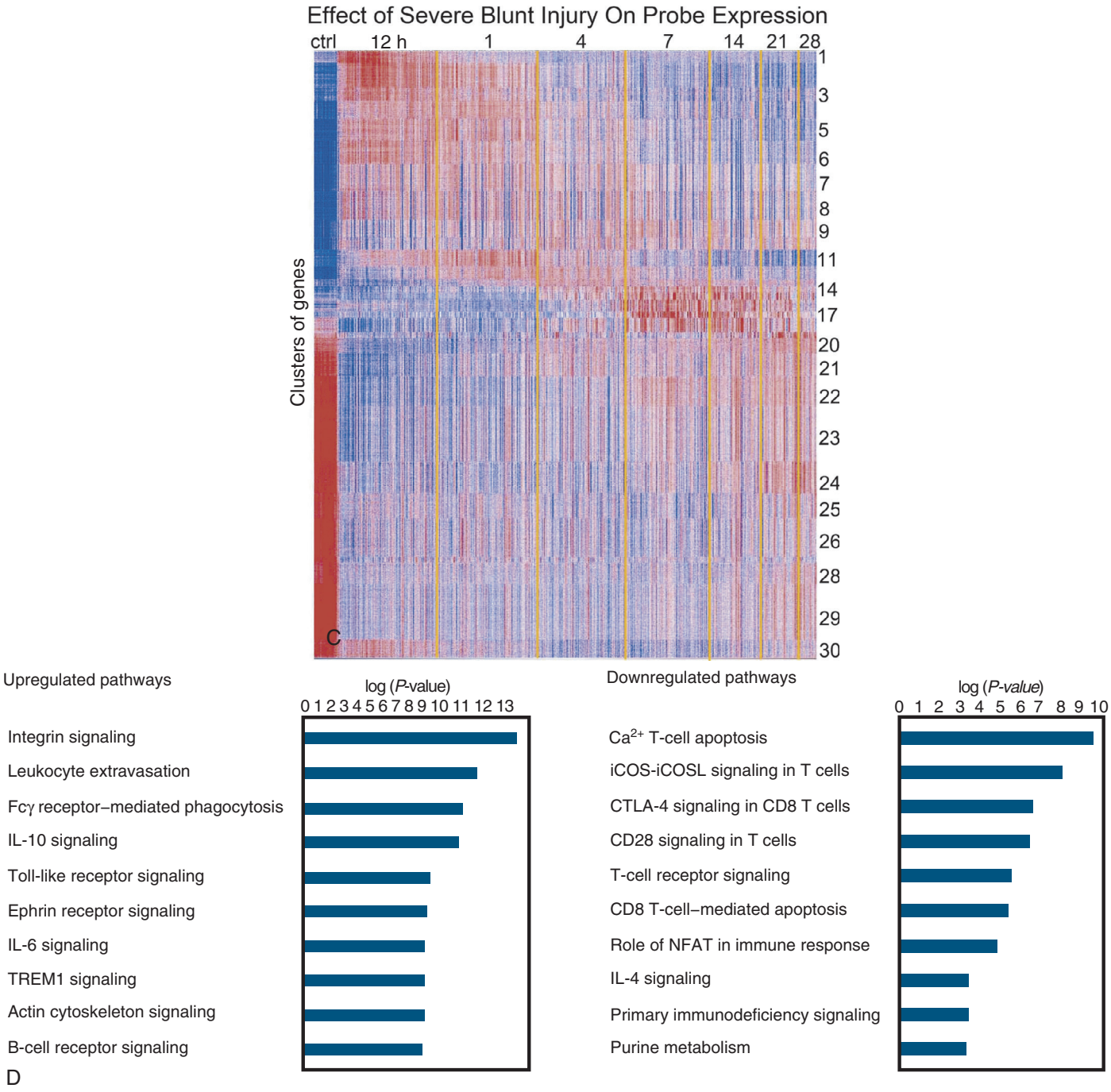
Genes examined by these workers clustered into 30 groups by similarity to temporal patterns. One group of genes featured



• **Fig. 26.4** Endocrine, neurologic, and immunologic responses to injury are linked through afferent and efferent arcs as described in the text and shown in this figure. Patients sustaining blunt injury or soft tissue loss in addition to hemorrhage show clinical evidence of increased cytokine and inflammatory mediator production with acceleration of the process described here. The best clinical data in support of this pair of arcs are from patients with traumatic brain injury. *CNS,* Central nervous system; *IL-1,* interleukin 1; *IL-6,* interleukin 6; *NK,* natural killer; *TNF,* tumor necrosis factor. (From Molina PE. Neurobiology of the stress response: contribution of the sympathetic nervous system to the neuroimmune axis in traumatic injury. *Shock.* 2005;24:3–10.)



• **Fig. 26.5** A, The genomic storm after injury. Line drawings in A and B begin with the previous conceptual model to the left with complications of severe injury as a result of excessive proinflammatory response *(SIRS)* followed by compensatory antiinflammatory response syndrome *(CARS)* and suppression of adaptive immunity. A second hit phenomenon results from sequential insults that lead to more severe and recurrent SIRS with organ dysfunction. B, A more recent paradigm proposed by the Inflammation and the Host Response to Injury investigators on the top right panel involves simultaneous and rapid induction of innate (proinflammatory and antiinflammatory genes) and suppression of adaptive immunity genes. Complicated recoveries are delayed, resulting in a prolonged dysregulated immune and inflammatory response.



• **Fig. 26.5, cont'd** C and D represent some of the summary genetic data from the trial. C shows multicolored heat maps reflecting genes that are upregulated and downregulated after severe blunt injury. Upregulated genes are shown in *red,* whereas suppressed or downregulated genes are shown in *blue*. In D, the two final sets of horizontal bars label key upregulated and downregulated pathways. *Ca^{2+},* Calcium ion; *CTLA4,* cytotoxic T-lymphocyte–associated protein 4; *iCOS,* inducible T-cell costimulator; *iCOSL,* inducible T-cell costimulatory ligand; *IL,* interleukin; *NFAT,* nuclear factor of activated T cells; *TREM1,* triggering receptor expressed on myeloid cells 1. (From Xiao WZ, Mindrinos MN, Seok JH, et al. The inflammation and host response to Injury Large-Scale Collaborative Research Program. A genomic storm in critically injured humans. *J Exp Med.* 2011;208(13):2581–2590.)

upregulation of proinflammatory cytokines such as IL-1β and tumor necrosis factor α. This pattern of gene expression resolved within the early days after injury. Other gene upregulation patterns took a longer period of time. Gene expression for IL-10 is an example of a gene with prolonged expression after injury. Some genes remained highly expressed up to 28 days after injury, whereas genes favoring proinflammatory cytokines tended to be upregulated for short periods of time. Other genes were downregulated, a response that could be seen for many days after injury. Immunoglobulin response is such an example.[75]

Fig. 26.5 shows the most significantly regulated pathways of the most upregulated pathways in circulating white blood cells. Eight of the 10 featured pathways are components of the innate immune system, which is consistent with a massive innate immune response seen after injury. Of the downregulated pathways, 9 of the 10 are included in the adaptive immune system.[75] Many of these downregulated pathways involve antigen processing. Patients with complicated clinical trajectories followed by this group of investigators demonstrated persistence of cellular necrosis, apoptosis, and autophagy in directly damaged tissues and remote tissues after trauma. Other examples of upregulated genes are those coding Toll-like receptors. These upregulated genes reflect receptors that are an important component of the innate immune system, which is immediately available but relatively nonspecific in nature. Changes in these receptors are seen with the classic inflammatory response frequently observed after injury.

Of the genes significantly modified by injury, only 63 of the thousands studied were different between injured and normal cohorts at all time points. Two-thirds of these genes were directly related to protective immunity. Adaptive immunity pathways showed suppression of genes involved in antigen presentation such as HLA-DR (human leukocyte antigen–antigen D related) and with interferon and interferon-inducible genes.[76]

This genomic work suggests a paradigm to describe patient response to severe injury. From the standpoint of gene transcription, there is an immediate genomic response triggering upregulation of the innate immune response and a downregulation of the adaptive immune response. These transcriptional changes are more dramatic and long-lasting in patients with complicated injury. This genomic storm translates into the early inflammatory response and subsequent immune suppression seen in the critical care unit. In particular, immune suppression is not compensatory and transcriptional responses for this portion of immune response are continuous and do not wax and wane.[74–76] Thus interventions to affect immune response to injury must be planned for early hours and days after the traumatic insult.

Acute Coagulopathy After Trauma

Historical Perspective

Hemorrhagic shock accounts for a significant number of deaths among patients arriving at hospitals with acute injury. Patients with uncontrolled hemorrhage continue to die despite adoption of new surgical techniques with improved transport and emergency care. Coagulopathy, occurring even before resuscitation, contributes significantly to the morbidity associated with bleeding.[77–80] Recognition of the morbidity associated with bleeding and coagulation abnormality dates to the Vietnam conflict. At that time, standard tests including prothrombin time (PT) and partial thromboplastin time (PTT) correlated poorly with effectiveness of acute resuscitation efforts. Similar work in the late 1970s was performed in civilian patients receiving massive transfusion. Again, PT, PTT, and bleeding time were helpful only if markedly prolonged.[81,82]

Studies in the 1970s and 1980s provided additional detail regarding the limitation of simple laboratory parameters and factor levels.[81–83] In a study of multiple patients requiring massive transfusion, platelet counts fell in proportion to the size of transfusion, although factors V and VIII correlated poorly with the volume of blood transfused. When coagulopathy appeared, patients seemed to respond to platelet administration. In subsequent studies, patients receiving a large number of blood products were followed for microvascular bleeding. Moderate deficiencies in clotting factors were common, but they were not associated with microvascular bleeding. Microvascular bleeding was associated with severe coagulation abnormalities such as clotting factor levels less than 20% of control values. In statistical analysis, clotting factor activities less than 20% of control levels were predicted by significant prolongation of PT and PTT. These earlier investigators also suggested that empiric blood replacement formulas available at the time were not likely to prevent microvascular bleeding because consumption of platelets or clotting factors did not consistently appear and simple dilution caused by resuscitation fluids frequently did not correspond to microvascular bleeding.[82,83]

The attention of the American trauma community was drawn to coagulopathy after trauma with the description of the "bloody vicious cycle" by the Denver health team more than 20 years ago.[79] These investigators noted the contribution of hypothermia, acidosis, and hemodilution associated with inadequate resuscitation and excessive use of crystalloids. Subsequent work extended these observations describing early coagulopathy that could be independent of clotting factor deficiency.[84] In a more recent trial, early coagulopathy was noted in the setting of severe injury that was present in the field before emergency department arrival and initiation of fluid resuscitation. Coagulopathic patients were at increased risk for organ failure and death.

In a study questioning historical transfusion practice emphasizing administration of packed red blood cells (PRBCs) in the setting of massive trauma, Hirshberg and coworkers, using clinical data, developed a computer model designed to capture interactions among bleeding, hemodynamics, hemodilution, and blood component replacement during severe hemorrhage. Resuscitation options were offered in this model and their effectiveness evaluated.[85] After setting thresholds for acceptable loss of clotting factors, platelets, and fibrinogen, the authors modeled behavior of coagulation during rapid exsanguination without clotting factor or platelet replacement. The PT reached a critical level first followed next by fibrinogen and platelets. If patients were resuscitated with small amounts of crystalloid, leaving overall blood volume reduced, the effective life of components in the coagulation cascade was increased. More aggressive fresh frozen plasma (FFP) replacement in the patient with significant bleeding was supported by this model. The optimal ratio for administration of FFP to PRBCs in this analysis was 2:3. Delayed administration of FFP led to critical clotting factor deficiency regardless of subsequent administration of FFP. Fibrinogen depletion was easier to correct. After administration of 5 units of PRBCs, the hemostatic threshold for fibrinogen was not exceeded if a FFP-to-PRBC ratio of 4:5 was used. Analysis of platelet dilution demonstrated that even if platelet replacement was delayed until 10 units of PRBCs were infused, critical platelet dilution was prevented with a subsequent platelet-to-PRBC ratio of 8:10.[85]

The essential message of this work is that massive transfusion protocols, emphasizing PRBCs, in existence when this study was performed provide inadequate clotting factor replacement during major hemorrhage and neither prevent nor correct dilutional coagulopathy.

Recent Studies

Brohi and coworkers from the United Kingdom helped to reinvigorate discussion of coagulopathy after injury by adding new coagulation laboratory techniques to previous clinical observations.[86] After reviewing more than 1000 cases, patients with acute coagulopathy after injury had higher mortality rates throughout the spectrum of Injury Severity Scores (ISS). Contrary to historical teaching that coagulopathy was a function of hemodilution with

massive crystalloid resuscitation, these authors noted that the incidence of coagulopathy increased with severity of injury but not necessarily in relationship to the volume of IV fluid administered to patients. Brohi and others helped to reemphasize the observation that acute coagulopathy could occur before significant fluid administration, which was attributable to the injury itself and proportional to the volume of injured tissue. Development of coagulopathy was an independent predictor of poor outcome. Mediators associated with tissue trauma, including humoral and cellular immune system activation with coagulation, fibrinolysis, complement, and kallikrein cascades, have been associated with changes in hemostatic mechanisms similar to those identified in the setting of sepsis.[86–88]

Factors contributing to coagulopathy in the setting of injury have been further reviewed.[89] Hypothermia relates to development of coagulopathy by reduction in platelet aggregation and decreased function of coagulation factors in nondiluted blood. Patients with temperature reduction below 34°C had elevated PT and PTT. Coagulation, like most biologic enzyme systems, works best at normal temperature. Similarly, acidosis occurring in the setting of trauma as a result of bleeding and hypotension also contributes to clotting failure. Animal work shows that a pH less than 7.20 is associated with hemostatic impairment. Platelet dysfunction and coagulation enzyme system changes are noted when blood from healthy volunteers is subjected to an acidic environment.[90,91]

We are now seeing that with or without hypothermia and acidosis, posttraumatic coagulopathy may develop in a significant number of patients. Although dilution-driven coagulopathy must be considered, loss of clotting factors has been associated with exaggerated inflammation in association with injury.

Hess and coworkers, as part of an international medical collaboration, developed a literature review to increase awareness of coagulopathy independent of crystalloid administration following trauma.[88] The key initiating factor is volume of tissue injury. Patients with severe tissue injury but no physiologic derangement, however, rarely present with coagulopathy and have a lower mortality rate.[92,93] Tissue damage initiates coagulation as endothelial injury at the site of trauma leads to exposure of subendothelial collagen and activation of the coagulation cascade.

Hyperfibrinolysis is seen as a direct consequence of the combination of tissue injury and shock. Endothelial injury accelerates fibrinolysis because of direct release of tissue plasminogen activator.[88,94] Tissue plasminogen activator expression by endothelium is increased in the presence of thrombin. Fibrinolysis is accelerated because of the combined effects of endothelial tissue plasminogen activator release with ischemia and inhibition of plasminogen activator inhibitor in shock. Although hyperfibrinolysis may focus clot propagation on sites of actual vascular injury, with widespread insults, this localization may be lost.

A number of important cofactors must be present to stimulate coagulopathy in the setting of injury.[88] Shock is a dose-dependent cause of tissue hypoperfusion. Elevated base deficit has been associated with coagulopathy in as many as 25% of patients in one large study. Progression of shock appears to result in hyperfibrinolysis. One mediator implicated in coagulopathy after injury is activated protein C. Immediate postinjury coagulopathy is likely a combination of effects caused by large volume tissue trauma and hypoperfusion (Fig. 26.6).[88]

As discussed later, equivalent ratios of FFP, PRBCs, and platelets are now considered for management of significant hemorrhage with coagulopathy after injury. Hypothermia and acidemia must be controlled to reduce their impact on enzyme systems.[95] Similar to the case with sepsis, crosstalk has been noted between coagulation and inflammation systems with injury. Activation of coagulation proteases may induce inappropriate inflammation with activation of cascades such as complement and platelet degranulation.[96,97] Trauma patients are initially coagulopathic with increased bleeding. This condition may progress to a hypercoagulable state, putting them at risk for thrombotic events. This late thrombotic state bears similarities to coagulopathy of severe sepsis and depletion of protein C. Injured patients and those with sepsis share a propensity toward multiple organ failure and prothrombotic states.[98,99]

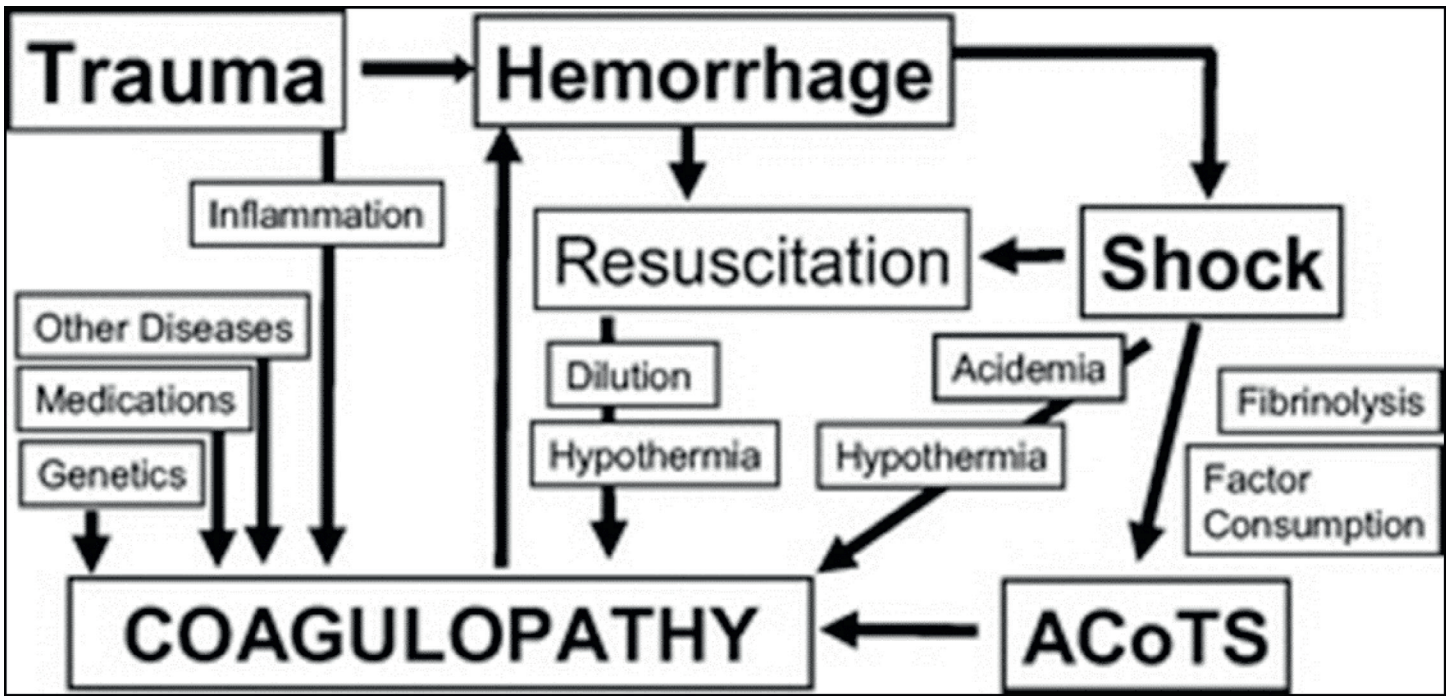
Fluid Therapy

Warmed isotonic electrolyte solutions are recommended for initial resuscitation of traumatic shock by the Committee on Trauma of the American College of Surgeons. This type of fluid provides transient intravascular expansion and stabilizes the intravascular volume by replacing accompanying fluid losses into the interstitial and intracellular spaces. Lactated Ringer solution is the initial fluid of choice. Normal saline solution is the second choice. Normal saline solution has the potential to cause hyperchloremic acidosis. This complication is more likely if renal function is compromised (Table 26.3).[100]

An initial warm fluid bolus is given rapidly—usually 1 to 2 L for an adult and 20 mL/kg for a child.[100] Patient response is observed during this initial fluid resuscitation and subsequent therapeutic decisions are based on this response. The required amount of fluid and blood is difficult to predict on initial evaluation of the patient. A rough guideline promulgated by the American College of Surgeons for the total amount of crystalloid volume acutely required is 3 mL of crystalloid fluid to replace each 1 mL of blood loss, allowing for restitution of plasma volume lost into interstitial and intracellular spaces. It is most important, however, to assess patient response to fluid resuscitation and evidence of adequate end-organ perfusion as measured by urine output and level of consciousness rather than providing fluid based on a specific formula. If the amount of fluid required to restore or maintain adequate end-organ function exceeds the previously mentioned estimates, careful reassessment of the situation and exploration for unrecognized injuries, bleeding, or other causes of shock are necessary (Table 26.4).

In clinical practice, large-volume resuscitation with lactated Ringer solution has become common in trauma care. However, recent military and laboratory work features a growing concern about tissue edema from large-volume resuscitation. The Inflammation and the Host Response to Injury investigators identify increased mortality, ICU and hospital length of stay, and a variety of infections in patients receiving more aggressive early crystalloid resuscitation. In recent years, a persisting picture of acute lung injury due to increase filtration across pulmonary microcapillaries with pulmonary inflammation has emerged. This event is seen as the acute respiratory distress syndrome (ARDS). Other observations include increased interstitial fluid in gut and cardiac tissues, abdominal compartment syndrome, extremity compartment syndrome in uninjured extremities, and pericardial effusion.[101]

Hemorrhage is a multifactorial disease; circulatory and inflammatory effects of hemorrhagic shock occur simultaneously. Unfortunately, laboratory studies have repeatedly shown that the choice of resuscitation fluid may worsen hemorrhage-induced cellular dysfunction, immune modulation, and inflammation. Fluids affect neutrophil activity by changing life span, activation, and gene expression. Resuscitation fluids also enhance the inflammatory cascade through upregulation of cellular receptors and



• **Fig. 26.6** A diagram showing some of the mechanisms leading to coagulopathy in the injured. Trauma can lead to hemorrhage, which can lead to resuscitation, which in turn leads to dilution and hypothermia causing coagulopathy and further hemorrhage. This is classic "dilution coagulopathy." Hemorrhage can also cause shock, which causes acidosis and hypothermia that in turn lead to coagulopathy, the "fatal triad." Trauma and shock can also cause the acute coagulopathy of trauma shock *(ACoTS)* associated with factor consumption and fibrinolysis. Coagulopathy is further associated with trauma-induced inflammation and modified by genetics, medications, and acquired diseases. (From Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma.* 2008;65:748–754.)

TABLE 26.3 Estimated Blood Loss and Other Critical Measures for Patients in Each Class of Shock[a]

Parameter	Class I	Class II (Mild)	Class III (Moderate)	Class IV (Severe)
Approximate blood loss	<15%	15%–30%	31%–40%	>40%
Heart rate	↔	↔/↑	↑	↑/↑↑
Blood pressure	↔	↔	↔/↓	↓
Pulse pressure	↔	↓	↑	↓
Respiratory rate	↔	↔	↔/↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit[a]	0 to –2 mEq/L	–2 to –6 mEq/L	–6 to –10 mEq/L	–10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive transfusion protocol

[a]These categories are based on the Advanced Trauma Life Support course presented by the Committee on Trauma of the American College Surgeons.
Data from Mutschler A, Nienaber U, et al. A critical reappraisal of the ATLS classification of hypovolaemic shock: does it really reflect clinical reality? *Resuscitation.* 2013;84:309–313; and American College of Surgeons. Signs and symptoms of hemorrhage by class. In: *Advanced Trauma Life Support Student Manual.* 10th ed. Chicago: American College of Surgeons; 2018:Table 3.1.
↑, Increase; ↑↑, greater increase; ↓, decrease; ↔, no change.

proinflammatory mediators. The choice of fluid also affects cellular gene expression, apoptotic cell death, and extracellular matrix integrity.[102–105]

Hypertonic Saline Solution in Trauma

Increased transmembrane sodium gradient caused by hypertonic saline solution generates intravascular volume expansion similar to hyperoncotic colloids and superior to conventional isotonic crystalloids such as lactated Ringer solution and normal saline solution. Animal models suggest that hypertonic saline solutions dilate precapillary arterioles and shunt oxygen to vital organs.[106,107] Hypertonic saline solutions also have fewer proinflammatory properties than other clinical crystalloids and colloids. Hypertonic saline solution does not induce expression of inflammatory cytokine

TABLE 26.4 General Guidelines for Establishing the Amount of Fluid and Blood Likely Required During Resuscitation[a]

	Rapid Response	Transient Response	Minimal or No Response
Vital signs	Return to normal	Transient improvement, recurrence of decreased blood pressure and increased heart rate	Remain abnormal
Estimated blood loss	Minimal (<15%)	Moderate and ongoing (15%–40%)	Severe (>40%)
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and crossmatch	Type-specific	Emergency blood release
Need for operative intervention	Possibly	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

[a]If the amount of fluid required to restore or maintain adequate oxygen perfusion and tissue oxygenation exceeds these estimates, reassess the situation and search for unrecognized injuries and/or other causes of shock. The usual initial dose of resuscitation fluid in the adult is 1 L of warmed isotonic fluid. Absolute volumes of resuscitation fluid are based on patient response to fluid administration, keeping in mind that this initial fluid amount includes any fluid given in the prehospital setting.
From American College of Surgeons. Responses to initial fluid resuscitation. In: *Advanced Trauma Life Support Student Manual*. 10th ed. Chicago: American College of Surgeons; 2018.

receptor genes in multiple studies and blunts hemorrhage-induced increase in plasma levels of proinflammatory cytokines, IL-10, and granulocyte-macrophage colony-stimulating factor. Hypertonic saline solution also does not increase apoptotic cell death in liver, lung, or bowel.[102]

What about the impact of hypertonic saline solution and associated hypernatremia in the setting of injury?[108] Studies in experimental animals and humans suggest that hypertonic saline solution may be highly effective in treating head injury, either alone or associated with hemorrhagic hypotension. Tissue swelling in a closed cranium threatens to cause pressure-induced brain damage or death, and concomitant hemorrhagic hypotension reduces cerebral oxygen delivery, resulting in a secondary ischemic insult. Historical data suggest a twofold higher incidence of adverse outcomes in patients with brain injury combined with hypotension. Patients are frequently treated with hypertonic saline solution for rapid intracranial pressure control. However, hypertonic saline solution has not seen general use in trauma resuscitation.[109,110]

Colloids in Trauma

Hyperoncotic colloid solutions have also been studied in resuscitation roles for traumatic hemorrhage. The natural colloid albumin does not induce neutrophil oxidative burst and may confer a protective immunologic effect by decreasing neutrophil expression of adhesion molecules.[111] At present, albumin has little application in resuscitation at the scene of injury but has been investigated in critical care practice.

An artificial colloid, 6% hetastarch, has been found to have a number of deleterious resuscitation effects in animal models, including increased neutrophil oxidative burst and pulmonary apoptosis. Beneficial effects include decreased neutrophil migration. At present, natural and artificial colloids have failed to show clinical benefits compared to crystalloid solutions.[112,113] Laboratory concerns and lack of a positive clinical outcome argue against the use of colloids in early resuscitation of hemorrhagic shock.

Recent reviews suggest important differences in safety among colloids. Examination of data comparing colloids with crystalloids must take into account the materials used. When albumin was used as a reference, the incidence ratio for anaphylactoid reactions was 4.51 after administration of hydroxyethyl starch, 2.32 after dextran, and 12.4 after gelatin. Artificial colloid administration was consistently associated with coagulopathy and clinical bleeding, most frequently in cardiac surgery patients receiving starches. Albumin had the lowest rate of total adverse events and serious adverse events.[114] Life-threatening anaphylactoid reactions were infrequent for all colloids. Hydroxyethyl starch, compared with albumin, more than quadrupled the incidence of anaphylactic reactions, whereas dextran more than doubled them. The incidence of these reactions in recipients of gelatin was greater by an order of magnitude than after albumin infusion. Because artificial colloids are derived from nonhuman source materials, they may be recognized as foreign and are more likely to provoke this immune-mediated response. The foreign nature of artificial colloids also may hinder metabolic clearance and promote tissue deposition. On the basis of extensive evidence, albumin is the safest colloid for consideration in resuscitation of traumatic shock.[114] Although factors such as desirability of anticoagulant activity may favor other artificial colloids, this is not true in the setting of injury.[115–117]

Multicenter data comparing albumin and saline solution for fluid resuscitation were obtained in Australia and published in 2004 (SAFE trial).[32] Nearly 7000 patients were randomly assigned to administration of 4% albumin or normal saline solution for intravascular fluid resuscitation procedures. Mortality rate and the incidence of single- and multiple-organ dysfunction were comparable in the two groups. Subset analysis suggests, however, poorer outcomes in the setting of injury. In the subgroup of 140 patients included with principal diagnoses of trauma, a treatment effect seemed to favor administration of saline solution. In this trial, the increased relative risk of death among patients with trauma compared with patients without trauma resulted from an excess number of deaths among patients who had trauma with brain injury. The difference in mortality rates between the albumin and saline solution groups among patients with trauma involving brain injury must be viewed cautiously because the number of involved subjects is small. In the SAFE study, patients with traumatic brain injury constituted only 7% of the study population, and the excess number of deaths in the albumin group was 21. Other parameters that could be helpful in evaluation of the impact of albumin in the setting of brain injury, such as functional neurologic status, were not provided. In contrast to the experience in trauma, the Australian trial suggests some evidence

of treatment benefit favoring administration of albumin in patients with severe sepsis. Given contemporary resuscitation technology, factors influencing the choice of resuscitation for critically ill patients include specific clinician concerns, treatment tolerance, safety, and cost.

Crystalloids Versus Colloids

Plasma and blood were the fluid replacements of choice in traumatic shock until the early 1960s, when a variety of investigators showed the need to replace the extracellular fluid deficit with crystalloid solutions. These observations were followed by a variety of clinical studies comparing colloid, typically albumin, solutions with crystalloids, typically lactated Ringer solution. Consistent with early studies, colloids, when given on an equal volume basis, more effectively increase CO and oxygen transport. Another finding of this early work was the need to administer crystalloids in far greater quantities than colloids to achieve consistent hemodynamic objectives.[118,119]

Later studies from the Vietnam era compared resuscitation of patients who were given whole blood and crystalloids with patients given whole blood plus 5% albumin. Fluid infusion volumes were far higher in the patients given crystalloid solutions. There was no evidence of pulmonary edema, and patients treated with crystalloids seemed to fare better than patients treated with resuscitation containing albumin. Albumin seemed to have less effect on restoration of renal function with suggestion of detrimental effects in pulmonary response, myocardial contractility, and coagulation. Large animal models suggested that pulmonary compromise could relate to increased capillary permeability with albumin. Increased losses of albumin to the heart, kidneys, liver, and brain also were reported.[118,120] More extensive studies in injured patients supported reservations regarding the use of albumin. Evaluation of patients randomly selected to receive 150 g of albumin per day intraoperatively and postoperatively noted poorer outcomes than in patients receiving lactated Ringer solution. Both groups received whole blood and FFP. Patients treated with albumin required greater ventilator support and had poorer oxygenation.[118,121,122] In another carefully conducted trial of patients with multiple trauma, no differences in cardiopulmonary function between patients resuscitated with lactated Ringer solution and patients given 5% albumin and lactated Ringer solution were identified.[123] Normal cardiac index was used as a therapeutic endpoint. To maintain adequate CO, patients who received crystalloids required far more resuscitation volume than patients treated with albumin. A clear cost advantage of crystalloids was identified.[118]

Guyton and Lindsey[124] examined the effect of colloid oncotic pressure on pulmonary edema. They observed that reducing the serum protein level lowered the threshold of left atrial pressure at which pulmonary edema could occur. Zarins and colleagues[125] subsequently showed that a low colloid oncotic pressure alone did not cause an elevation in extravascular lung water. Because of the remarkable efficiency of pulmonary lymphatics, arterial blood gases, shunt fraction, and lung compliance were unchanged despite a 14% increase in body weight caused by infusion of lactated Ringer solution to maintain high pulmonary artery occlusion pressures. No pulmonary edema was created despite the presence of ascites and marked peripheral edema. Demling and coworkers[126] confirmed these findings with a chronic lung lymph fistula in sheep. Holcroft and coworkers[127] produced pulmonary edema in baboons during resuscitation from hemorrhage by continuously administering large volumes of lactated Ringer solution sufficient to elevate pulmonary artery occlusion pressures 15 mm Hg above baseline levels. With cessation of infusion, filling pressure rapidly returned to normal.

Blood Component Therapy

Despite work from multiple groups suggesting that simple replacement of PRBCs was not a sufficient answer for the most severely injured patient, particularly in the setting of coagulopathy, the concept of combination blood component replacement remained outside the mainstream of trauma care for more than 20 years.[79,83,128] It took armed conflicts and experience in a multinational group of trauma centers to bring awareness of the need for multiple blood component therapy in massive bleeding to the level of general trauma practice.

The 1970s and 1980s saw several groups propose resuscitation of significant hemorrhage with combinations of blood components. Kashuk and Moore proposed multicomponent blood therapy in patients with significant vascular injury.[79] In a study of patients with major abdominal vascular injury, Kashuk and coworkers noted frequent deviation from a standard ratio of 4:1 or 5:1 for units of PRBCs to units of FFP. The ratio was 8:1 in nonsurvivors and 9:1 when overt coagulopathy was noted. In this series 51% of patients were coagulopathic after vascular control was obtained. Using multivariate analysis, Ciavarella and coworkers from the Puget Sound Blood Center and Harborview Medical Center proposed aggressive supplementation of platelets in the setting of massive transfusion. These investigators noted that platelet counts below 50×10^9/L correlated highly with microvascular bleeding in trauma and surgery patients. Fibrinogen repletion was also emphasized. Guides to resuscitation included fibrinogen level, PT, and PTT. Supplemental FFP or cryoprecipitate was recommended for low fibrinogen levels.[83] Weaver and colleagues, summarizing extensive preclinical and clinical studies, suggested administration of FFP after 6 units of PRBCs had been infused. Additional FFP was recommended for every five additional PRBC transfusions. Monitoring included platelet count, PT, and PTT after each 5 units of PRBCs are administered. Platelet transfusion is generally unnecessary unless the platelet count falls below 50,000 platelets per µL of blood.[128]

Another view of damage control hematology comes from Vanderbilt University Medical Center in Nashville, Tennessee. This group implemented a trauma exsanguination protocol involving acute administration of 10 units of PRBCs with 4 units of FFP and 2 units of platelets. In an 18-month period, 90 patients received this resuscitation and were compared with a historical set of control subjects. The group of patients receiving the trauma exsanguination protocol as described by these investigators had lower mortality rates, higher blood product use in initial operative procedures, and more frequent use of products in the initial 24 hours, although overall blood product consumption during hospitalization was decreased.[129]

The strongest multicenter civilian data report examining the impact of plasma and platelet administration along with red blood cells on outcome in massive transfusion comes from Holcomb and coworkers.[130] These investigators describe more than 450 patients from 16 adult and pediatric centers. Overall survival in this group is 59%. Patients were gravely ill as reflected by an admission base deficit of −11, pH 7.2, Glasgow Coma Scale (GCS) score of 9, and a mean ISS of 32. Examination of multicenter data reflects an improvement in outcome as the ratio of FFP to PRBCs administered approaches 1. FFP, however, is not the sole solution to improved coagulation response in acute injury. These workers also examined the relationship of aggressive plasma and platelet administration in

these patients. Optimal outcome in this massive transfusion group was obtained with aggressive platelet as well as plasma administration. Worst outcomes were seen when aggressive administration of plasma and platelets did not take place. When either FFP or platelets were given in higher proportion in relationship to PRBCs, intermediate results were obtained. Not surprisingly, the cause of death that was favorably affected was truncal hemorrhage.

A summary statement comes from Holcomb and a combination of military and civilian investigators.[87,88] These workers identify a patient group at high risk for coagulopathy and resuscitation failure owing to hypothermia, acidosis, hypoperfusion, inflammation, and volume of tissue injury. In the paradigm proposed by these authors, resuscitation begins with prehospital limitation of blood pressure at approximately 90 mm Hg preventing renewed bleeding from recently clotted vessels. Intravascular volume resuscitation is accomplished using thawed plasma in a 1:1 or 1:2 ratio with PRBCs. Acidosis is managed by use of tromethamine and volume loading with blood components as hemostasis is obtained. A massive transfusion protocol for these investigators included delivery of packs of 6 units of plasma, 6 units of PRBC, 6 units of platelets, and 10 units of cryoprecipitate in stored individual coolers. These coolers are supplied until discontinuation by the trauma team. Even in causalities requiring resuscitation with 10 to 40 units of blood products, Holcomb and coworkers found that as little as 5 to 8 L of crystalloid is used during the first 24 hours, representing a decrease of at least 50% compared with standard practice. The lack of intraoperative coagulopathic bleeding allowed surgeons to focus on surgical hemorrhage. The goal is arrival of the patient to the ICU in a warm, euvolemic, and nonacidotic state. International normalized ratio approaches normal and edema is minimized. Subjectively, patients treated in this manner are more readily ventilated and easier to extubate than patients with a similar blood loss treated with standard crystalloid resuscitation and smaller amounts of blood products. Holcomb and others suggest that massive transfusion will be required in 6% to 7% of military patients and 1% to 2% of civilian trauma patients.

A summary statement regarding transfusion in the trauma patient has been made by the Inflammation and the Host Response to Injury investigators[131] (Fig. 26.7). In hemodynamically stable patients, administration of PRBCs should be performed with a hemoglobin level below 7 g/dL. If the hemoglobin level is above 7 g/dL and there is evidence of hypovolemia, appropriate crystalloid fluid should be given to achieve normovolemia. If administration of IV fluids to achieve normovolemia decreases the hemoglobin concentration to less than 7 g/dL, then additional red blood cells may be administered.

If the patient is normovolemic and the hemoglobin level is above 7 g/dL, then the clinical state of a patient should be assessed to determine whether there is any clinical or laboratory evidence of impaired oxygen delivery. Based on evidence of impaired oxygen delivery, such as low mixed venous oxygen saturation, persistent base deficit, or the presence of lactic acidosis, additional administration of PRBCs may be appropriate with monitoring of oxygen delivery.[131]

Endpoints

The Problem

Severely injured trauma patients are at high risk of developing multiple-organ failure or dying. Initial treatment priorities include appropriate fluid administration and rapid hemostasis.[132,133] Inadequate tissue oxygenation leads to anaerobic metabolism and tissue acidosis. Depth and duration of shock are associated with cumulative oxygen and metabolic debt. Resuscitation is incomplete until the metabolic debt is paid, and tissue acidosis is eliminated with restoration of aerobic metabolism. Many patients seem to be adequately resuscitated based on normalization of vital signs but have occult hypoperfusion and ongoing tissue acidosis (compensated shock). These individuals are at risk for later organ dysfunction and death.[100]

As stated in the Advanced Trauma Life Support protocol, the standard of care remains restoration of normal blood pressure, heart rate, and urine output.[100] When these parameters remain abnormal (uncompensated shock), the need for additional resuscitation is obvious. After normalization of these parameters, however, many trauma patients still have evidence of inadequate tissue oxygenation. Recognition of this state and its reversal are crucial to reduce the risk of organ dysfunction or death. The optimal marker of adequate resuscitation in injury remains unclear.[134]

Not all patients can be managed in the same way. More recent literature describing management of neurologic trauma suggests poor outcome with any degree of hypotension during prehospital care, resuscitation, or subsequent in-hospital course. Episodes of hypotension and hypoxia were associated with poor neurologic outcome in a review of more than 700 patients from the Traumatic Coma Data Bank with a GCS score less than 9. In this large study, patients without hypotension or hypoxia had a 27% risk of death and a 51% chance of favorable recovery. In the presence of hypotension, with or without hypoxia, the risk of death increased to 65% to 75%. Contrary to the needs of patients with penetrating trauma in whom early aggressive resuscitation may lead to increased bleeding, hypotension should be avoided in patients with head injuries. Resuscitation parameters specific to many types of injury have not been reported.[135–137]

Oxygen Delivery Parameters

Shoemaker and various coworkers provided early stimulus to optimization of hemodynamic management in high-risk surgical patients by examining hemodynamic profiles of survivors of surgical shock states versus patients who died.[138] Survivors had significantly higher oxygen delivery and cardiac index values than nonsurvivors. Values correlating with survival included cardiac index greater than 4.5 L/min per m^2, oxygen delivery greater than 600 mL/min per m^2, and oxygen consumption equal to or greater than 170 mL/min per m^2. These initial observations led to a series of reports from this group suggesting reduction in resource consumption and improvement in morbidity and mortality rates with resuscitation to supranormal oxygen delivery parameters. Initial augmentation of oxygen delivery came with volume loading followed by dobutamine and blood transfusions as needed to a hemoglobin level of 14 g/dL.[139–141]

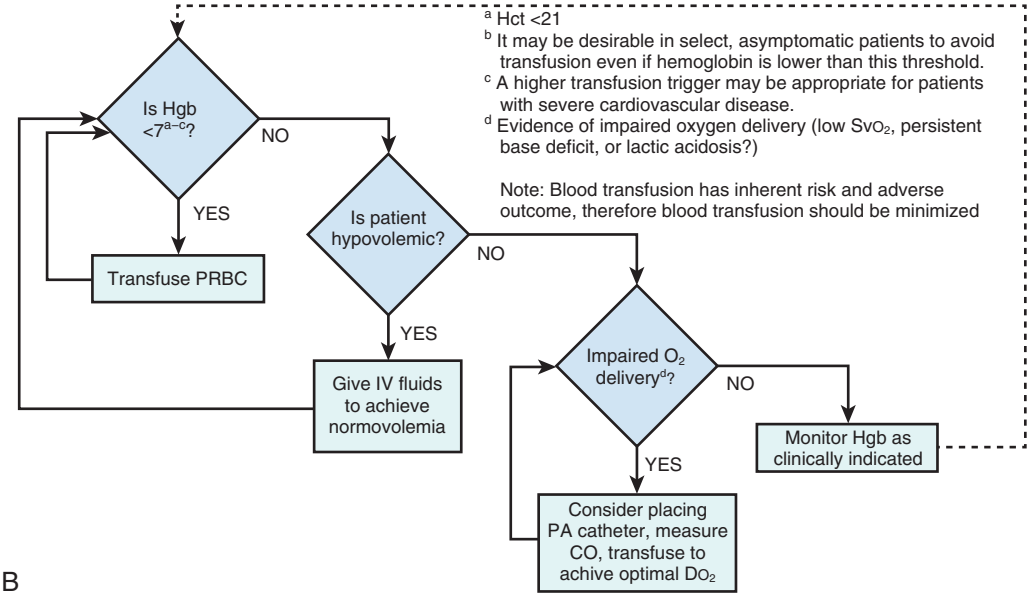
Attempts by other investigators to replicate these findings met limited success. Moore and coworkers used a resuscitation protocol aimed at maximizing oxygen delivery and found no benefit with resuscitation to achieve supranormal oxygen delivery.[134,142] A variety of studies suggested that patients who did not reach resuscitation goals were at increased risk for multiple organ failure. Other workers noted that patients who did not obtain supranormal oxygen delivery values were at high risk of developing organ failure regardless of treatment strategy.[143,144] Obtaining hemodynamic and oxygen transport parameters seems to be more predictive of survival than

Transfusion Guideline for Trauma Patient*
Inflammation and the Host Response to Injury

1. Identify critically ill patient will hemoglobin <7 g/dL (or Hct <21%).
2. If hemoglobin <7 g/dL transfusion of PRBCs is appropriate.
   a. For patients with severe cardiovascular disease, a higher transfusion trigger may be appropriate.
3. If hemoglobin >7 g/dL assess the patient for hypovolemia.
   a. If the patient is hypovolemic, administer IV fluids to achieve normovolemia.
   b. If the patient is not hypovolemic, determine whether there is evidence of impaired oxygen delivery (low Svo_2, persistent/worsening base deficit, presence/worsening of lactic acidosis).
4. If impaired O_2 delivery present, consider pulmonary artery catheter placement, measure cardiac output, and optimize O_2 delivery.
5. If impaired O_2 delivery not present, monitor hemoglobin as clinically indicated.

A ** This protocol assumes that acute hemorrhage has been controlled, the initial resuscitation has been completed, and the patient is stable in the ICU without ongoing hemorrhage.*

Transfusion Guidelines for Trauma Patient (excludes immediate resuscitation)



B

• **Fig. 26.7** Transfusion strategy for trauma patients based on the consensus documents of the Inflammation and the Host Response to Injury studies. See text for details. *CO,* cardiac output; *Do_2,* oxygen delivery; *Hct,* hematocrit; *Hgb,* hemoglobin; *ICU,* intensive care unit; *IV,* intravenous; *O_2,* oxygen; *PA,* pulmonary artery; *PRBCs,* packed red blood cells; *Svo_2,* venous oxygen saturation. (From West MA, Shapiro MB, Nathens AB, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. IV. Guidelines for transfusion in the trauma patient. *J Trauma.* 2006; 61:436–439.)

useful as a goal for resuscitation, particularly if fluid administration is adequate.

In addition to conflicting outcomes in oxygen transport trials, technical concerns have been raised. These studies cannot be totally blinded. Patients in control groups often obtain physiologic endpoints similar to those in treatment groups. Other aspects of care were sometimes inconsistent, and entrance criteria varied among investigators. There also is potential mathematical coupling of oxygen delivery and consumption because both are calculated values that share many of the same measured variables.[135] Some clinicians argue that the pathologic relationship between oxygen delivery and consumption trials cannot be accepted with confidence, unless oxygen consumption is measured directly. Finally, the use of traditional oxygen delivery and consumption as resuscitative endpoints requires a pulmonary artery catheter and special expertise for operation and insertion. Routine use of pulmonary artery catheterization or central venous catheters has not been a part of acute trauma resuscitation or emergency medical management.[100,134,135]

Lactate

As an indicator of shock, blood lactate has proved accurate at assessing severity, predicting mortality risk, and assessing response to resuscitation in the hands of various workers.[134,135] At the cellular level, the explanation is based on oxygen transport principles. With shock and inadequate oxygen delivery, mitochondrial respiration is impaired. The primary cellular fuel, pyruvate, is shunted from its normal aerobic path (conversion by pyruvate dehydrogenase to acetyl coenzyme A and subsequent entry into the tricarboxylic acid cycle) to the anaerobic pathway (conversion to lactate by lactate dehydrogenase). Anaerobic metabolism makes inefficient use of cellular substrate, and high-energy phosphate stores are rapidly depleted. During cellular ischemia, lactate is released into the bloodstream and ultimately converted to glucose in the liver and kidney via the Cori cycle. Because it directly reflects anaerobic metabolism, lactate is thought to serve as a mirror of global hyperperfusion because increasing lactate levels indicate increasing oxygen debt.[135,145]

Initial and peak lactate levels and duration of increased lactate concentration correlate with development of multiorgan dysfunction after trauma.[135] In a study of trauma patient resuscitation, patients who had normalized lactate levels at 24 hours survived, whereas patients who had normalized lactate levels between 24 and 48 hours had a 25% mortality rate; patients who did not have normalized levels by 48 hours had an 86% mortality rate.[146] More recent data come from a systematic review of lactate levels in the emergency department. Elevated emergency department lactate levels were associated with mortality and other outcomes, including injury severity, ICU admission, length of hospitalization, organ failure, blood product requirement, catecholamine support, and emergency operation.[147]

Base Deficit

Inadequate oxygen delivery to tissues leads to anaerobic metabolism. The degree of anaerobiosis is proportional to the depth and severity of hemorrhagic shock, which should be reflected in lactate and base deficit. Arterial pH is not as useful because compensatory mechanisms attempt to normalize this parameter. Serum bicarbonate levels offer better correlation with base deficit (removal or addition of base in the blood).[134,148,149]

Similar to lactate, base deficit has been carefully studied.[134] A greater base deficit has been associated with blood pressure reduction, increased blood loss, and transfusion requirements. A series of studies by Davis and coworkers link base deficit to resuscitation requirements and end-organ dysfunction, such as ARDS, renal failure, and coagulopathy. Cytokine and adhesion molecule changes also have been found to parallel changes in base deficit.[150–156]

Base deficit may vary with patient populations. Concern remains in older patients that base deficit is nonspecific and may reflect metabolic acidosis owing to a variety of causes, including renal dysfunction and diabetes.[134,135] Similar to temporal changes in lactate, base deficit variation over time may add to the value of this parameter.[148] Patients with elevated base deficit also showed impaired oxygen use reflected in lower oxygen consumption. The timing of base deficit measurement also is important. One study suggested that the worst base deficit in the initial 24 hours was predictive of mortality rate along with blood pressure and estimated blood loss.[154] Some workers debate whether alcohol intoxication may worsen base deficit for similar levels of injury severity and hemodynamics after trauma. In a large database survey, use of alcohol did not change the significant predictive value of admission lactate and base deficit.[157,158] Resuscitation with normal saline solution (hyperchloremic metabolic acidosis) or lactated Ringer solution (accumulation of D-lactate) may increase base deficit independent of injury severity. Acidosis associated with hyperchloremia is associated with a lower mortality rate than that from other causes, particularly anaerobic metabolism.[134,159] Base deficit levels and time to normalization of base deficit are similar to data for lactate in that correlation has been established with the need for resuscitation and risk of organ dysfunction and death after injury. Specific thresholds for outcome have not been determined.

Near-Infrared Spectroscopy

Measurement of skeletal muscle oxyhemoglobin levels by near-infrared spectroscopy offers a noninvasive measurement for evaluating adequacy of resuscitation from normalization of tissue oxygenation.[134,135,160] This technology allows simultaneous measurement of tissue partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), and pH. In human volunteers, cerebral cortex and calf oxygen saturation as measured by near-infrared spectroscopy decreased in proportion to blood loss. Studies in injury suggest correlation of tissue oxygen saturation with systemic oxygen delivery, base deficit, and lactate.[161]

This technology provides information regarding mitochondrial function. Normally, tissue oxyhemoglobin levels reflecting local oxygenation are tightly coupled to cytochrome function, reflecting mitochondrial oxygen consumption. In small studies, when patients showed a change in mitochondrial function, even in the absence of abnormality in systemic oxygen transport, multiple organ failure was more likely.[162] Nonetheless, at this time, work in this area is limited, and a role for this technology in routine management of traumatic shock has not been defined.

Adrenal Insufficiency

Adrenal insufficiency is reviewed in Box 26.2.

Clinical Strategies

Clinical observations of shock in injury have been made for hundreds of years, but the optimal treatment continues to be

• BOX 26.2 Adrenal Insufficiency

Check adrenal function in patients who fail to respond to resuscitation.[a–c] Adrenal insufficiency, a rare occurrence in the general population (<0.01%), is seen in 28% of seriously ill patients and 60% of severely injured trauma patients in contemporary series.[d] Severe illness and stress activate the hypothalamic-pituitary-adrenal axis and stimulate the release of corticotropin (adrenocorticotropic hormone) from the pituitary, which stimulates release of cortisol from the adrenal cortex. This action is an essential component of general adaptation to illness and contributes to maintenance of cellular and organ homeostasis.[a,c]

Although a growing body of literature reviews adrenal insufficiency in critical illness with an emphasis on sepsis, we have seen a significant incidence of adrenal insufficiency, reflected by low serum cortisol levels, in severe injury with or without direct trauma to the brain.[e,f]

We suspect adrenal insufficiency in patients who are young and otherwise healthy and require vasoactive drugs in addition to large amounts of resuscitation fluid. Our approach to making the diagnosis of acute adrenal insufficiency is a spot cortisol level. Although a variety of treatment protocols for hormonal replacement exist, we provide 50 mg of hydrocortisone every 6 hours or 100 mg of hydrocortisone every 8 hours for 5 days. Consistent with the treatment threshold reported by Marik and Zaloga,[b,f] we treat if a random cortisol concentration is less than 25 μg/dL. Severely injured patients have been reported to have random cortisol levels greater than 30 μg/dL.[d] Although outcome data are unavailable to suggest the value of adrenal replacement in critically stressed young trauma patients, we have seen the effectiveness of this intervention repeatedly in our own practice.

[a] *Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients.* N Engl J Med. *2003;348:727–734.*

[b] *Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem.* Chest. *2002;122:1784–1796.*

[c] *Burchard K. A review of the adrenal cortex and severe inflammation: quest of the "eucorticoid" state.* J Trauma. *2001;51:800–814.*

[d] *Offner PJ, Moore EE. Ciesia D. The adrenal response after severe trauma.* Am J Surg. *2002;184:649–654.*

[e] *Rivers EP, Gaspari M, Saad GA, et al. Adrenal insufficiency in high-risk surgical ICU patients.* Chest. *2001;119:889–896.*

[f] *Marik PE, Zaloga GP. Adrenal insufficiency during septic shock.* Crit Care Med. *2003;31:141–145.*

debated.[133] Early observations are attributed to Paré, Le Dran, Latta, and Gross.[163,164] Crile and Henderson were among the first to attribute the hemodynamic instability of shock to decreased intravascular volume and to propose therapy based on restoration of intravascular volume with administration of IV fluid.[164] During the First World War, physiologists Cannon and Bayliss observed patients in clinical shock.[6] These observers noted that patients with crush injuries despite absence of obvious blood loss also developed signs and symptoms of shock.[165,166] Cannon later suggested the concept of deliberate hypotension in the treatment of wounds to the torso during war with the intent of minimizing internal bleeding until the time at which operative intervention could control the hemorrhage.[167,168] In later studies, other authors reported laboratory models of ongoing arterial hemorrhage and concluded that regardless of the means used to increase blood pressure, either fluid resuscitation or vasopressor, bleeding would increase with subsequent death.[169,170]

Current guidelines for the treatment of hypotension secondary to hemorrhage after trauma recommend rapid infusion of crystalloid solutions to restore blood pressure.[100,168] This premise is based in part on clinical studies and laboratory data showing that hemorrhagic shock in animals produced with controlled blood loss was reversible when blood loss was replaced with two to three times that volume of a crystalloid solution.[171–173] Although controlled hemorrhage is a well-defined laboratory model, resuscitation of a patient with multiple injuries and active or uncontrolled bleeding may represent very different pathophysiology.[133]

In 1950 Wiggers[174] developed a standard hemorrhagic shock model in dogs. He and others showed that severe hypotension over several hours produced a condition in which infusion of withdrawn blood restored arterial pressure only temporarily.[133] After intervals ranging from 30 minutes to 3 hours, arterial pressure declined again. Additional infusions of blood were followed by progressively poorer recovery and more rapid development of circulatory failure, ultimately resulting in the demise of the animal. This decompensation point in shock, defining a time at which reinfusion of shed blood could not resuscitate the animal, led to the concept of irreversible shock.[175] The approach to resuscitation of cellular, organ, and organism changes after hemorrhagic shock using the Wiggers model has been applied to all types of injury based in part on the elegant experiments of Shires and colleagues[171] and a series of other investigators.[102]

Early Limited Resuscitation

Animal Studies

Several large animal studies explored the use of varying degrees of fluid resuscitation in animals receiving injuries leading to uncontrolled hemorrhagic shock. Bickell and coworkers[176] created infrarenal aortotomy using a stainless steel wire in 16 anesthetized Yorkshire swine weighing 23 to 40 kg that had been instrumented with pulmonary artery and carotid artery catheters. When the wire was pulled, a 5-mm aortotomy with subsequent intraperitoneal hemorrhage followed. Animals were alternately assigned to an untreated control group or a treatment group receiving 80 mL/kg of lactated Ringer solution as an IV bolus. The volume of blood loss and the mortality rate were significantly increased in animals treated with lactated Ringer solution relative to the untreated control group. All control animals survived, whereas animals treated with lactated Ringer solution died in less than 2 hours. The volume of hemorrhage identified in treated animals exceeded 2 L, whereas control animals lost on average less than 800 mL of blood.

Several observations may be made in relation to this widely cited report. First, the mortality rate in the control group was low, leading one to question the severity of injury in the animal model. Second, fluid resuscitation administered, although consistent with replacement of two to three times the volume loss in blood with crystalloid, far exceeds standard resuscitation for a human patient of comparable weight. In addition, the rapidity of fluid administration may have served to diminish further any potential positive impact of fluid administration in this model of injury. The effect seen was reproduced, however, with other types of fluid administration in a comparable injury model. Other large animal studies of hypotensive resuscitation used graded resuscitation protocols.[177,178]

Stern and coworkers[177] examined a swine model combining femoral artery hemorrhage via a catheter to an MAP of 30 mm Hg with subsequent intraabdominal aortic laceration producing a 4-mm tear and uncontrolled intraperitoneal hemorrhage. Three groups of animals were resuscitated to mean arterial pressures of 40, 60, and 80 mm Hg. No untreated control group was used. Resuscitation was begun when the pulse pressure of each animal reached 5 mm Hg. Animals were resuscitated with saline solution at 6 mL/kg per minute to a maximum of 90 mL/kg, after which resuscitation fluid was changed to shed blood at 2 mL/kg per minute to a maximal volume of 24 mL/kg. Animals were observed for 60 minutes or until death. As noted previously, the mortality rate was significantly higher in animals receiving the most aggressive resuscitation compared with less aggressively treated groups. Animals resuscitated most aggressively had higher volumes of intraperitoneal hemorrhage than the two other experimental groups. In addition, oxygen delivery, which was monitored in these animals, was significantly greater in the group resuscitated to an MAP of 60 mm Hg than in the two other experimental groups. Similar observations were made in a second report from this same group in a study by Kowalenko and colleagues.[178]

Clinical and preclinical studies focused on early limitation of crystalloid resuscitation and hemorrhagic shock focus on penetrating torso trauma but do not address initial care of patients with head injury, a leading cause of traumatic death in the United States. Historically, when shock accompanies head injury, the incidence of adverse outcome doubles. Because of the vulnerability of the injured brain to even brief periods of reduced perfusion, guidelines for the management of head injury state that delayed resuscitation cannot be considered applicable in head trauma.[137] Nonetheless, in a large animal model using a standard cerebral injury along with uncontrolled hemorrhage secondary to aortotomy, there was no evidence of increased secondary cerebral ischemia with delayed resuscitation. Conventional resuscitation with lactated Ringer solution resulted in signs of increased secondary brain injury.[179]

Clinical Studies

Martin and coworkers[180] provided preliminary data in patients on the effect of aggressive versus delayed prehospital resuscitation of uncontrolled hemorrhagic shock after penetrating injury. These workers evaluated the effect of delaying fluid resuscitation until surgical intervention could control the source of hemorrhage on outcome of hypotensive trauma victims. Injury severity was similar in standard resuscitation and delayed resuscitation groups. The rate of survival to hospital discharge was 69% in the delayed resuscitation group and 56% in the standard resuscitation group. The difference between these groups did not reach statistical significance owing to small sample size.

Much attention has been directed to resuscitation of patients after injury after a report from Bickell and associates[181] that appeared in the *New England Journal of Medicine.* The authors reported a prospective clinical trial of adults with penetrating truncal trauma who were hypotensive in the field as indicated by a systolic blood pressure less than 90 mm Hg. Patients were randomly assigned to placement of intravascular catheters with standard prehospital and trauma center fluid resuscitation using lactated Ringer solution or an experimental group in which vascular catheters were placed but IV fluids were not administered until patients reached the operating room. Patients were excluded from this trial if they were noted to have a field revised trauma score of zero consistent with cardiopulmonary arrest or had sustained fatal gunshot wounds to the head with neurologic injury that precluded long-term survival. In addition, patients with penetrating truncal injury who did not require operation were excluded. After 1069 patients were screened during the 37 months of this study, 598 patients were enrolled—309 in an immediate resuscitation group receiving standard fluids according to Advanced Trauma Life Support protocols and 289 in a delayed resuscitation group, which did not receive IV fluids until reaching the operating room.[100]

The immediate and delayed resuscitation groups were well matched with respect to age, gender, and anatomic injury as measured by the ISS, Revised Trauma Score (physiologic response to injury), and systolic blood pressure.[182,183] Field response times for prehospital providers in this trial were short, averaging 30 minutes or less. The trauma center interval (i.e., the interval in the hospital before operation) was surprisingly long: 44 minutes in the immediate resuscitation group and 52 minutes on average in the group receiving delayed resuscitation. Prehospital fluid administration averaged less than 900 mL in the immediate resuscitation group versus less than 100 mL in the delayed resuscitation cohort. Fluid administration in the trauma center before operation averaged greater than 1600 mL of fluid in the immediate resuscitation group, whereas the delayed resuscitation patients averaged 283 mL of fluid received. Operative blood loss between the study groups was not different. Among the 289 patients who received delayed fluid resuscitation, 203 (70%) survived and were discharged from the hospital. Of the 309 patients who received immediate fluid resuscitation, 193 (62%) survived ($P = 0.04$). Patients in the delayed resuscitation group displayed a trend toward reduced postoperative complications, including ARDS, sepsis syndrome, acute renal failure, coagulopathy, wound infection, and pneumonia, compared with patients in the immediate resuscitation group ($P = 0.08$).

The value of what we now call "hypotensive resuscitation" has been confirmed in subsequent studies of injured patients and victims of vascular insults such as aneurysm rupture. Placement of increased vascular access at the scene and rapid fluid administration has been associated with increased mortality.[184]

Although these early clinical studies represent a remarkable accomplishment in design, organization, and data analysis, many questions remain unanswered. None of the studies reported was blinded, and a randomization scheme was not used. In the trial by Bickell and colleagues, in which the difference in mortality rate rested in a difference in survival of a small number of patients in the experimental groups, 22 patients in the delayed resuscitation group were given IV fluids in violation of study design.[181] Although these individuals were appropriately included in an intent-to-treat analysis, the impact of selected fluid administration on study outcome is unclear. The authors also have been criticized for excluding patients *after* randomization because of injuries considered too minor (no operative therapy) or too severe (Revised Trauma Score of 0). Exclusion of these patients may invalidate the statistical approach used and increase the difficulty of the clinician seeking guidance from this work. Finally, time spent in the trauma center by these hypotensive patients with injuries requiring operation was surprisingly long. Although the resuscitation groups described differed statistically in vital signs and hematologic parameters, it is unclear whether the differences observed had clinical significance.

We await additional data on the military approach to resuscitation, which requires innovation and effectiveness in austere environments.[185] Contemporary recommendations include limitation of fluid administration unless systolic blood pressure is less than 80 to 85 mm Hg or is rapidly falling. Another clinical indicator for fluid resuscitation is decreasing mentation without evidence of head injury. Key assessment parameters are mental status and the presence of a radial pulse. In many settings, no fluids are administered in the presence of a strong radial pulse and normal mentation. Indicators for intervention are pulse deterioration or decreasing level of consciousness. When fluids are given, a number of small-volume colloids with high tonicity or colloids in combination with saline solution are being investigated. Even early hospital resuscitation is designed to emphasize the use of blood products and minimize crystalloids and nonblood colloids in the setting of major injury.

Clinical Pathway—Early Resuscitation

In all of the preclinical and clinical work described, the mechanism of injury and survival remains unclear. Among considerations is the impact of fluid resuscitation on early clot formation in the setting of uncontrolled hemorrhage.[133,177] Other workers suggest that rapidity in resuscitation of pulse pressure may relate to mechanical disruption of initial thrombus. Fluid resuscitation may contribute to dilution of clotting factors in the setting of exaggerated bleeding in uncontrolled hemorrhage.[168] The data to support these observations are limited. Coagulopathy proportional to volume of injured tissue and severity of shock may be seen even before resuscitation fluids are provided.[11]

Despite provocative preclinical and clinical data, there is insufficient evidence to propose practice guidelines or make recommendations. "Uncontrolled" hemorrhage itself remains undefined. This problem is best seen as injury with blood loss occurring in the absence of surgical or mechanical hemostasis or the "control" provided by regulated blood removal through a vascular cannula. It is unclear whether a vascular injury after a torso gunshot wound and a shattered spleen after an automobile crash are different in this regard. The message from all of the studies is that elevation of the blood pressure to normal or supranormal levels results in resumption of bleeding from the uncontrolled site, and rebleeding leads to recurrent shock and death of the experimental animal. Other work shows that animals subjected to shock could be successfully resuscitated at lower than "normal" mean arterial pressures if the bleeding site was controlled as part of the resuscitation program. Shock victims resuscitated with electrolyte solutions are subject to progressive hemodilution, and this may lead to death. The lessons that clinicians should learn from this body of data are as follows[11,100,133]:

1. Operation to control bleeding is part of resuscitation.
2. Blood pressure levels are convenient but possibly misleading endpoints for shock resuscitation in that resuscitation to normal or supranormal pressures may be harmful if the effort delays

operation to control bleeding or the pressure elevation causes rebleeding. Better endpoints (e.g., tissue oxygenation or other metabolic parameters) are needed.

3. Blood loss is increased in the setting of significant soft tissue insults combined with shock. Early administration of blood products should include use of a balanced administration strategy with PRBCs, FFP, and platelets given in equal proportions.
4. Resuscitation of traumatic shock, similar to fluid management of a burned patient, requires repeated observation, judgment, and skill and cannot be accomplished by recipe or formula.

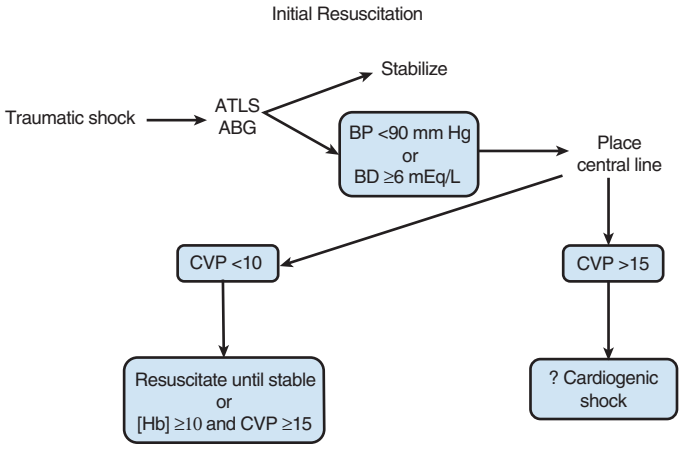
A protocol from the investigators on the Inflammation and the Host Response to Injury Project is shown in Fig. 26.8. Variables driving decision-making include systolic blood pressure, heart rate, base deficit, CVP, hemoglobin level, and clinical judgment.[186]

Patients with major trauma arriving with a systolic blood pressure below 90 mm Hg and/or a heart rate above 130 beats/min are initially managed using Advance Trauma Life Support fluid administration. Routine monitoring includes frequent vital signs, continuous electrocardiogram, and pulse oximetry with assessment of core body temperature. Arterial blood gas analysis is obtained in all patients presenting in traumatic shock. Patients with major torso trauma with evidence of shock (early systolic blood pressure <90 mm Hg and/or base deficit ≥6 mEq/L) and who require ongoing resuscitation should have a central venous catheter placed while they are in the emergency department. CVP measurements should be used to differentiate the type of shock and assist with monitoring of shock resuscitation. Early CVP above 15 mm Hg before extensive volume loading suggests cardiac insufficiency. Differential diagnosis of cardiovascular insufficiency after blunt trauma includes tension pneumothorax, myocardial contusion or infarction, pericardial tamponade, and infrequently, air embolus.[186]

CVP less than 10 mm Hg despite volume loading indicates persistent hypovolemia consistent with ongoing bleeding. The endpoint of initial resuscitation is controversial as described earlier. These investigators recommend hypotensive resuscitation to systolic blood pressure above 90 mm Hg and heart rate below 130 beats/min with moderate volume loading until hemorrhage control is accomplished. They recommend this approach as standard care for patients with penetrating trauma and believe it is most likely safe as well for patients with blunt torso trauma who do not have significant coexistent brain injuries.

Blood should be administered when lactated Ringer infusion exceeds 30 mL/kg. Earlier empiric blood transfusion is indicated in patients, especially the elderly, who arrive in severe shock or have injuries associated with significant bleeding, such as vertical shear pelvic fractures or bilateral femur fractures. Institution protocols for massive transfusion should be established and used in these patients. Coagulopathy is among the complications of massive blood and fluid administration. Stored blood is deficient in factors V and VIII and platelets. Timely administration of FFP and platelets reduces the risk of coagulopathy after massive transfusion. Presumptive factor replacement is usually not indicated in the early phase of resuscitation, but it may be appropriate in patients with massive hemorrhage caused by significant intracavitary bleeding or an unstable pelvic fracture.[186]

Before admission to the critical care unit, resuscitation is directed at maintaining blood pressure and reducing heart rate through simple volume loading with crystalloid and blood products as necessary. Simple clinical endpoints are used as described earlier. This approach should be adequate for the vast majority of injured patients.

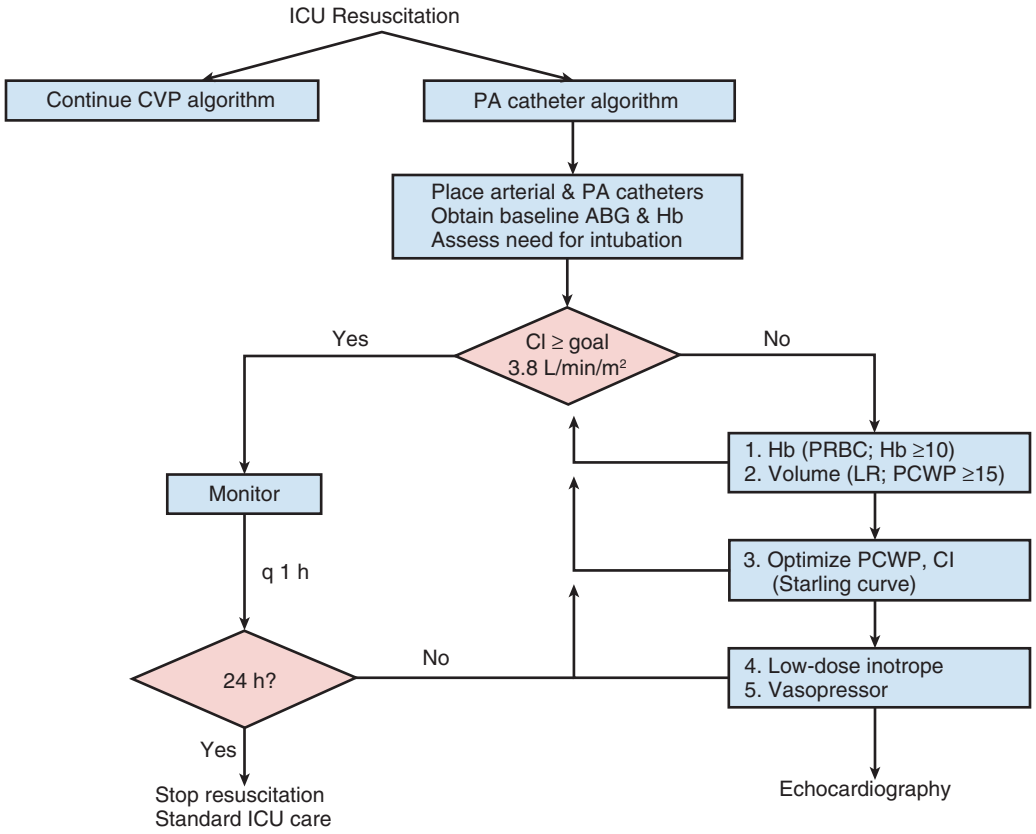


• **Fig. 26.8** Initial approach to resuscitation based on work from the Inflammation and the Host Response to Injury project. ATLS is resuscitation per the Advanced Trauma Life Support Program described earlier. Simple clinical goals are provided which are modified based on observed patient response. *ABG,* Arterial blood gas; *ATLS,* Advanced Trauma Life Support; *BD,* base deficit; *BP,* blood pressure; *CVP,* central venous pressure; *Hb,* hemoglobin. (From Moore FA, McKinley BA, Moore EE, et al. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma.* 2006;61:82–89.)

Management of Traumatic Shock in the ICU

In a series of studies characterizing resuscitation of injured patients in the ICU, Moore and coworkers used the pulmonary artery catheter to describe response to fluid administration.[187–189] Criteria identifying patients considered for placement of a pulmonary artery catheter and need for ICU resuscitation include major injury (two or more abdominal organs, two or more long bone fractures, complex pelvic fractures, flail chest, or major vascular injury), blood loss (anticipated need for >6 units of PRBCs during the first 12 hours after hospitalization), and metabolic stress (arterial base deficit >6 mEq/L during the first 12 hours after hospital admission). A trauma patient older than 65 years with any two of the previous criteria also warrants consideration of pulmonary artery catheter insertion and ICU resuscitation. Patients with these criteria who also incurred severe brain injury, defined as GCS score less than or equal to 8 in the trauma ICU and abnormality on brain computed tomography scan, were not resuscitated by protocol during development of this approach unless assessed by the attending neurosurgeon to be at low risk of secondary brain injury with these procedures.[187–189] In my practice, I find that the brain, similar to other organs, benefits from aggressive resuscitation.

Hemorrhage control is of paramount importance in initial management of patients with major torso trauma who arrive in shock. It is assumed that this issue has been addressed in the vast majority of patients by the time of ICU admission. Priorities in early ICU care are optimization of resuscitation; correction of hypothermia, coagulopathy, and acidosis; and monitoring for ongoing bleeding requiring operative or interventional radiology procedures.[186] As indicated in Fig. 26.9, an important early decision is to determine whether placement of a pulmonary artery catheter and an arterial catheter is necessary. The vast majority of patients do not require a pulmonary artery catheter. I do note, however,



• **Fig. 26.9** ICU resuscitation model based on the consensus documents of the Inflammation and the Host Response to Injury project. As noted in the text, it is unusual for patients to require a pulmonary artery *(PA)* catheter. Reasoned choices for vasoactive drugs are given earlier in this chapter. *ABG,* Arterial blood gas; *CI,* cardiac index; *CVP,* central venous pressure; *Hb,* hemoglobin; *ICU,* intensive care unit; *LR,* lactated Ringer; *PCWP,* pulmonary capillary wedge pressure; *PRBC,* packed red blood cells. (From Moore FA, McKinley BA, Moore EE, et al: Inflammation and the Host Response to Injury, a large-scale collaborative project: Patient-oriented research core-standard operating procedures for clinical care. III. Guidelines for shock resuscitation. J Trauma 2006; 61:82–89.)

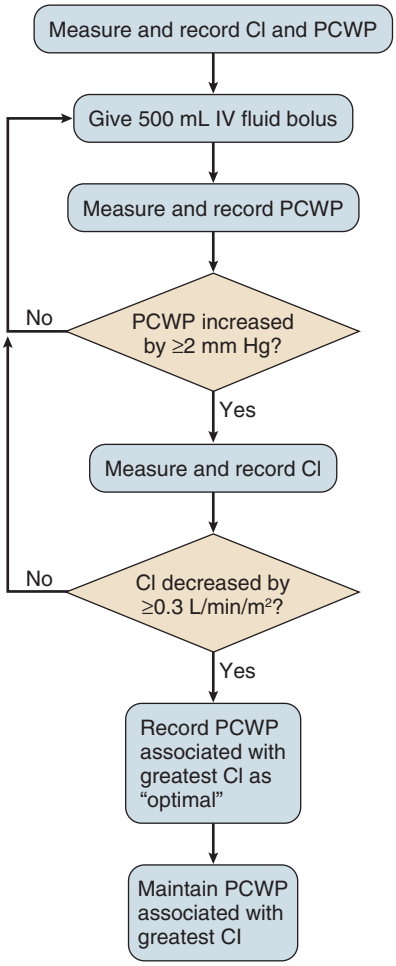
that CVP is a very indirect monitor of hemodynamic function and changes in CVP do not necessarily indicate propriety of fluid administration.

A pulmonary artery catheter could be considered for patients unresponsive to ongoing volume administration including blood transfusion by demonstrating low MAP or persistent high base deficit and/or demonstrating secondary organ dysfunction, such as worsening oxygenation or decreasing urine output[186] (see Fig. 26.9). The possibility of an impending abdominal compartment syndrome must also be considered if crystalloid fluid volume exceeds 10 L or PRBC transfusion exceeds 10 units. Periodic urinary bladder pressure measurements should be obtained to monitor for the onset of abdominal compartment syndrome. Urinary bladder pressure of 25 mm Hg or higher indicates significant abdominal hypertension and the need to consider decompressive laparotomy. I note that bladder pressures must be obtained in sedated, relaxed patients. Neuromuscular blockade may be required.

It is assumed that most patients treated by this protocol will be intubated. If they are not intubated and require ongoing volume loading, intubation should be considered because worsening pulmonary function is likely. If intubated and ventilator settings include positive end-expiratory pressure of 12 cm/H_2O or higher, the effects of high mean airway pressure on cardiac function may become important. This may also reflect the need to consider a pulmonary artery catheter or other CO monitor.

A general cardiac index goal is 3.8 L/min per m^2. Hemodynamic variables are assessed hourly and possibly more frequently as needed. Laboratory variables, including hemoglobin, blood gas data, and coagulation parameters, should be determined every 4 hours and possibly more frequently until the patient is fully resuscitated and stable. Most young patients easily exceed the cardiac index goal of 3.8 L/min per minute with crystalloid volume loading and blood transfusion. There is no need to increase cardiac filling pressures to high levels in responsive patients, but the hemoglobin level should be maintained at 10 g/dL or higher during acute resuscitation where bleeding may still be ongoing. Once acid-based status is normalized and the need for ongoing volume loading has resolved, a lower hemoglobin level is acceptable.[186]

Pulmonary capillary wedge pressure (PCWP) may not accurately reflect left ventricular end-diastolic volume, and increase in PCWP to 15 mm Hg or higher may enhance cardiac performance. The optimal relationship between PCWP and cardiac index may be determined by incrementally increasing left ventricular preload followed by measurement of CO response. In this process, a Starling curve is developed (Fig. 26.10).



• **Fig. 26.10** This simple algorithm describes a Starling curve protocol for optimization of filling pressures as a part of resuscitation of severely injured patients in the critical care unit where a pulmonary artery catheter is employed. *CI,* cardiac index; *IV,* intravenous; *PCWP,* pulmonary capillary wedge pressure. (From Marr AB, Moore FA, Sailors RM, et al. Preload optimization using "Starling curve" generation during shock resuscitation: can it be done? *Shock.* 2004;21:300–305.)

After obtaining optimal PCWP, if CO is below 3.8 L/min per m^2, infusion of a vasodilating inotropic agent should be considered. If a vasodilator is deemed appropriate, dobutamine is recommended with dosing beginning at 5 μg/kg per minute and increased in increments of 2.5 μg/kg per minute to a maximum of 20 μg/kg per minute to increase cardiac index. If the patient does not tolerate the vasodilatation associated with this agent, dopamine may be considered. Occasionally, an inotropic agent with vasocontrictive effects may be needed to maintain MAP at 60 mm Hg or higher, enhance myocardial contractility, and maintain coronary perfusion pressure. Norepinephrine is recommended as the preferred agent in this setting. Norepinephrine infusion should be started at 0.05 μg/kg per minute and increased in increments of 0.05 μg/kg per minute as needed to obtain a cardiac index above 3.8 L/min per m^2 and maintain MAP above 60 mm Hg. The maximum recommended norepinephrine dose rate is 0.2 μg/kg per minute. Adrenal insufficiency in patients requiring norepinephrine to maintain MAP must be considered. Low-dose vasopressin may complement the administration of norepinephrine and allow reduction in doses of this agent.[186]

The protocol-driven approach described has provided a variety of observations.[190] First, even elderly patients respond to ICU resuscitation after injury.[188] In general, the maximal oxygen delivery response is less than that of younger patients, and elderly patients have a greater requirement for inotropic support.[191] Second, a Starling curve generation approach is feasible and reliably improves hemodynamic resuscitation from major trauma. Supranormal resuscitation is neither necessary nor desirable in the management of patients with trauma associated with shock.[192] Third, aggressive resuscitation, particularly in the setting of ongoing bleeding, increases the risk of elevated intraabdominal pressure and abdominal compartment syndrome.[193] Preload-driven resuscitation may cause bowel edema with subsequent venous obstruction, declining CO, decreased urinary output, and compromise of systemic oxygenation. Finally, although many endpoints for interventions for goal-directed resuscitation in critical injury exist, systemic oxygen transport is the current state of the art in the most severely injured patients and is the basis for future development of clinical processes for resuscitation of shock caused by major trauma.[190]

The utility of the pulmonary artery catheter in the management of patients with severe injury is suggested by a study using data obtained in the National Trauma Data Bank.[194] From more than 450,000 records, 53,000 patients were reviewed. These patients were admitted between January 1994 and December 2001. Patients survived more than 48 hours and underwent at least one diagnostic or therapeutic procedure. The patients were 16 to 90 years old and distinguished by ISS and initial base deficit. Approximately 2000 patients who had insertion of a pulmonary artery catheter during hospitalization were compared with 51,000 patients who did not. Logistic regression analysis was used to develop a model that examined mortality rate after injury. Factors included in the model were use of a pulmonary artery catheter, age, emergency department base deficit, ISS, comorbid conditions, mechanism of injury, and specific injury patterns as identified by the Abbreviated Injury Scale. Overall, patients managed with a pulmonary artery catheter were older and had a higher ISS, greater emergency department base deficit, and higher mortality rates (29.7% with pulmonary artery catheter vs. 9.8% without pulmonary artery catheter). Patients with spine, abdominal, chest, or head injury and patients with at least one Abbreviated Injury Scale score of 3 or higher were more likely to be managed with a pulmonary artery catheter.

Pulmonary artery catheter use was associated with an increased mortality rate in all subgroups of ISS, emergency department base deficit, and age. As age, base deficit, and ISS increased, however, the risk of death associated with pulmonary artery catheter use decreased, and an apparent benefit of pulmonary artery catheter use emerged. In contrast, less severely injured trauma patients (ISS 16–24) and severely injured patients without high admission base deficit (greater than −5) had an increased mortality rate associated with pulmonary artery catheter placement regardless of age.

Although these observations are from a large database, retrospective study design and subgroup analysis are not optimal for definitive hypothesis testing. Finally, neither timing of placement for pulmonary artery catheters nor cause of death and specific relationship to placement of the pulmonary artery catheter could be conclusively examined by analysis of the National Trauma Data Bank. Nonetheless, these data suggest that carefully selected patients may derive benefit from pulmonary artery catheter–guided resuscitation to avert complications related to persistent perfusion deficits. Further focused examination of patients with risk factors for poor outcome is warranted.[194]

Massive Transfusion

Independent of mechanism of injury, hemorrhagic shock consistently is the second leading cause of early death among injured patients, with only CNS injury consistently more lethal.[195] Primary CNS injury is devastating and has a high rate of prehospital mortality; prevention is the best strategy.[196] Hemorrhagic shock accounts for 30% to 40% of trauma deaths and is more amenable to interventions to reduce mortality and morbidity rates.[195] In addition, approximately 25% of CNS injuries are complicated by hemorrhagic shock.[197,198] Hemorrhage contributes to death during the prehospital period in 33% to 56% of cases, and exsanguination is the most common cause of death among individuals found dead on arrival of emergency medical services personnel.[47] Hemorrhage accounts for the largest proportion of mortality within the first hour of trauma center care and more than 80% of operating room deaths after major trauma.[195,199] Although the need for massive transfusion (defined as administration of ≥10 units of PRBCs in <24 hours) is probably necessary in 5% or less of patients in busy trauma centers, this intervention can be lifesaving, and available data suggest that early aggressive administration of blood products reduces morbidity and mortality rate and decreases overall product use.[200]

Numerous general observations can be made.[200–202] Most patients receiving massive transfusion are treated initially with crystalloid fluids followed by non–cross-matched type O red blood cells. Plasma therapy is typically delayed while waiting for blood typing and plasma to thaw. Platelets frequently are not given until patients have received multiple units of PRBCs. Coagulopathy is common and difficult to correct. Plasma and platelets are inadequately used and greater emphasis is needed on plasma and platelet administration.

A typical massive transfusion protocol begins in the emergency department when the senior trauma practitioner orders transfusion of O-negative PRBCs and invokes an organization-specific massive transfusion protocol.[202,203] This is followed by administration of 4 to 6 additional typed or O-negative units of PRBCs and a similar number of units of FFP and platelets. Therapy continues with containers sent from the blood bank, each containing red blood cells, plasma, and platelets. Goals are normalization of the PT and elevation of the platelet count to 50 to 100×10^9/L. The fibrinogen level is checked after 6 to 12 units of PRBCs, and cryoprecipitate is given if the fibrinogen level is less than 1 g/L. Once a common component of massive transfusion strategies, recombinant activated factor VII has been deemphasized in both military and civilian practice.[204,205]

Major trauma centers have developed transfusion protocols to address rapid blood loss and trauma-associated coagulopathy. This strategy has demonstrated improved survival in severely injured trauma patients. Although many centers have implemented massive transfusion protocols, a standardized initiation policy has not been defined. Frequently, activation of massive transfusion protocols is provider dependent and variability exists among high-volume centers.

Several scoring systems have been developed to rapidly predict the patient requiring massive transfusion.[206–208] Of these scores, the ABC (assessment of blood consumption) score, which incorporates penetrating mechanism of injury, positive results on ultrasound examination of the abdomen in the emergency department, arrival systolic blood pressure of 90 mm Hg or less, and arrival heart rate of 120 beats/min or more, has been reported and validated in large patient sets. Although multiple more sophisticated criteria have been proposed, an ABC score of two or more criteria correctly classified the patient requiring massive transfusion in up to 85% of cases. Other investigators point out that hypotension and evidence of coagulopathy are the strongest predictors of massive transfusion. Additional data from military and civilian practice continues to clarify appropriate transfusion triggers.

Tranexamic Acid

Tranexamic acid is a derivative of the amino acid lysine that inhibits fibrinolysis by blocking binding sites on plasminogen. This agent has been used in a variety of surgical trials and has been demonstrated to reduce blood transfusion requirement. The massive CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) study, incorporating more than 20,000 patients, evaluated tranexamic acid as a means to address fibrinolysis occurring as a component of coagulopathy after trauma.[209,210] CRASH-2 was conducted in more than 250 hospitals and 40 countries. More than 20,000 patients with significant bleeding or at risk for significant bleeding were assigned within 8 hours of injury to receive either tranexamic acid or matching placebo. All-cause mortality rate was significantly reduced with tranexamic acid. Specific risk of death due to bleeding was also significantly reduced. This remarkable outcome was accomplished without a significant increase in thrombotic events. Subsequent analysis of the CRASH-2 data, however, reveals that greatest efficacy came when treatment was initiated within 3 hours after injury. In fact, treatment after 3 hours seemed to increase the risk of death owing to bleeding. A recent review of military experience with tranexamic acid, the MATTERs (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation) trial, also demonstrates improved outcomes with early administration of this inexpensive drug shortly after injury. This military experience with tranexamic acid suggests improvement in outcome in patients receiving as little as 1 unit of PRBCs. Incremental risk with administration of tranexamic acid was not demonstrated.[211]

The role for tranexamic acid in trauma systems where massive transfusion protocols incorporate FFP containing indigenous antifibrinolytic elements in plasma remains unclear. In developed trauma systems, the best place for tranexamic acid may actually be in the prehospital environment as this material can readily be maintained in helicopter and road transport programs. Prehospital administration of blood products, especially plasma, is not routine in civilian settings; thus tranexamic acid offers an early opportunity to manage coagulopathy.[212] Opportunities for use of this promising material in the critical care setting are being defined.

Risks of Early Red Blood Cell Transfusion

Blood transfusion in trauma has been identified as an independent predictor of multiple-organ failure, systemic inflammatory response syndrome, increased postinjury infection, and increased mortality rate in multiple studies.[213] Cumulative risks have been related to the number of units of PRBCs transfused, increased storage time of transfused blood, and possibly the presence of leukocytes in donor blood. Many authors have concluded that blood transfusion in an injured patient should be minimized when possible.[214]

Large single-institution data sets examined the impact of blood transfusion in postinjury multiple-organ failure.[215,216] Variables identified as early independent predictors of multiple organ failure included age older than 55 years, ISS of 25 or higher, and more than 6 units of PRBCs in the first 12 hours after admission. Base deficit greater than 8 mEq/L in the first 12 hours and lactate greater than 2.5 mol/L also were independent predictors of multiple-organ failure. Subsequent prospective work confirmed the

importance of blood transfusion as an independent risk factor for postinjury multiple-organ failure after controlling for other indices of shock, including base deficit and lactate. Additional studies of blood product use after injury associate blood transfusion with increased mortality rate. Potential confounding shock variables, including base deficit, serum lactate, age, gender, race, GCS score, and ISS, were controlled in this analysis.

Factors contributing to complications associated with red blood cell transfusion include storage time, increased endothelial adherence of stored red blood cells, nitric oxide binding by free hemoglobin in stored blood, donor leukocytes, host inflammatory response, and reduced red blood cell deformability.[212,217] Nonetheless, transfusion of an injured patient with balanced blood component therapy is the only option for treatment of severe hemorrhagic shock. Although other hemoglobin-based oxygen carriers hold promise and ultimately may provide better outcomes for injured patients, these materials have not come into routine use. In an effort to reduce adverse events, attempts to minimize the use of blood transfusion in injury are appropriate outside major hemorrhage.

Special Problems

Abdominal Compartment Syndrome

A compartment syndrome is a condition in which increased pressure within a confined anatomic space adversely affects the function and viability of tissues contained within. Confined anatomic spaces associated with compartment syndromes are fascial spaces of the extremities, the globe as in glaucoma, and the cranial cavity as in epidural or subdural hematoma. Abdominal compartment syndrome is a condition in which sustained pressure within the abdominal wall, pelvis, diaphragm, and retroperitoneum adversely affects the function of the gastrointestinal tract and related extraperitoneal organs. Abdominal compartment syndrome is receiving increasing recognition as a complication of massive resuscitation after trauma, burns, or other surgical procedures (Box 26.3). Operative decompression is frequently required. Pressures around 5 to 7 mm Hg in the peritoneal cavity are normal. Short-duration pressure increases frequently occur with coughing, Valsalva maneuvers, defecation, and weightlifting. Intraabdominal pressure can be nonpathologically increased in obese individuals. Elevated intraabdominal pressure is a common finding among critically ill medical and surgical patients.[218–220]

A consensus conference on abdominal compartment syndrome has created improved definitions of this problem (Table 26.5). For standardization, intraabdominal pressure should be expressed in mm Hg and measured at end-expiration with the patient supine after ensuring that abdominal muscle contractions are absent. The transducer is zeroed at the midaxillary line. The current reference standard for intraabdominal pressure measurement is pressure measured via an indwelling urinary drainage catheter within the bladder. The recommended technique for measuring intraabdominal pressure is to clamp the urinary catheter and instill a maximal volume of 25 mL of sterile, room-temperature saline solution into the bladder with the patient in the supine position. After zeroing a transducer and a stabilization period of at least 30 to 60 seconds, the mean intraabdominal pressure can be read on a bedside monitor or as the height of the fluid column in urinary drainage tubing.

Intraabdominal hypertension is defined by a sustained or repeated intraabdominal pressure greater than 12 mm Hg or an abdominal perfusion pressure less than 60 mm Hg, where abdominal perfusion pressure is MAP minus intraabdominal pressure. Abdominal compartment syndrome is present when organ dysfunction occurs as a result of intraabdominal hypertension. Abdominal compartment syndrome is further defined by sustained or repeated intraabdominal pressure greater than 20 mm Hg or abdominal perfusion pressure less than 60 mm Hg in association with new-onset single- or multiple-organ system failure. In contrast to intraabdominal hypertension, abdominal compartment syndrome is not graded but rather is considered an "all-or-none" phenomenon.[220,221]

Intraabdominal hypertension has a variety of physiologic effects. In experimental preparations, animals die as a result of congestive heart failure as abdominal pressure passes a critical threshold. Increased intraabdominal pressure decreases CO and left and right ventricular stroke work, while increasing CVP, PCWP, and systemic and pulmonary vascular resistance. Abdominal decompression reverses these changes. As both hemidiaphragms are displaced upward with increased intraabdominal pressure, decreased thoracic volume and compliance are seen. Decreased volume within the pleural cavity causes atelectasis and decreases alveolar clearance. Pulmonary infections also may result. Ventilated patients with abdominal hypertension require increased airway pressure to deliver a fixed tidal volume. As the diaphragm protrudes into the pleural cavity, intrathoracic pressure increases with reduction in CO and increased pulmonary vascular resistance. Ventilation and perfusion abnormalities result, and blood gas measurements show hypoxemia, hypercarbia, and acidosis.[222]

Elevation in intraabdominal pressure also causes renal dysfunction. Inadequate renal perfusion pressure and renal filtration gradient

• BOX 26.3 Risk Factors for Intraabdominal Hypertension and Abdominal Compartment Syndrome

Acidosis (pH < 7.2)
Hypothermia (core temperature <33°C)
Polytransfusion (>10 units packed red blood cells/24 h)
Coagulopathy (platelets <55,000/mm^3 *OR* activated partial thromboplastin time 2× normal *OR* higher or prothrombin time <50% *OR* international standardized ratio >1.5)
Sepsis (American-European Consensus Conference definitions)
Bacteremia
Intraabdominal infection or abscess
Peritonitis
Liver dysfunction or cirrhosis with ascites
Mechanical ventilation
Use of positive end-expiratory pressure (PEEP) or the presence of auto-PEEP
Pneumonia
Abdominal surgery, especially with tight fascial closures
Massive fluid resuscitation (>5 L colloid or crystalloid/24 h)
Gastroparesis, gastric distention, or ileus
Volvulus
Hemoperitoneum or pneumoperitoneum
Major burns
Major trauma
High body mass index (>30)
Intraabdominal or retroperitoneal tumors
Prone positioning
Massive incisional hernia repair
Acute pancreatitis
Distended abdomen
Damage control laparotomy
Laparoscopy with excessive inflation pressures
Peritoneal dialysis

From Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. Intensive Care Med. *2006;32:1722–1732.*

TABLE 26.5 Consensus Definitions List

Definition 1	IAP is the steady-state pressure concealed within the abdominal cavity.
Definition 2	APP = MAP − IAP.
Definition 3	FG = GFP − PTP = MAP − 2 × IAP.
Definition 4	IAP should be expressed in mm Hg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line.
Definition 5	The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25–50 mL sterile saline solution.
Definition 6	Normal IAP is approximately 5–7 mm Hg in critically ill adults.
Definition 7	IAH is defined by a sustained or repeated pathologic elevation in IAP ≥12 mm Hg.
Definition 8	IAH is graded as follows: grade I (IAH 12–15 mm Hg); grade II (IAP 16–20 mm Hg); grade III (IAP 21–25 mm Hg); grade IV (IAP >25 mm Hg).
Definition 9	ACS is defined as a sustained IAP >20 mm Hg (with or without an APP <60 mm Hg) that is associated with new organ dysfunction/failure.
Definition 10	Primary ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiologic intervention.
Definition 11	Secondary ACS refers to conditions that do not originate from the abdominopelvic region.
Definition 12	Recurrent ACS refers to the condition in which ACS redevelops after previous surgical or medical treatment of primary or secondary ACS.

ACS, Abdominal compartment syndrome; *APP*, abdominal perfusion pressure; *FG*, filtration gradient; *GFP*, glomerular filtration pressure; *IAH*, intraabdominal hypertension; *IAP*, intraabdominal pressure; *MAP*, mean arterial pressure; *PTP*, proximal tubular pressure.
From Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med.* 2006;32:1722–1732.

have been proposed as critical factors in the development of renal insufficiency associated with elevated intraabdominal pressure. The filtration gradient is the mechanical force across the glomerulus and equals the difference between glomerular filtration pressure and proximal tubular pressure. In the presence of intraabdominal hypertension, proximal tubular pressure may be assumed to equal intraabdominal pressure. Glomerular filtration pressure may be estimated as MAP minus intraabdominal pressure. Changes in intraabdominal pressure may have a greater impact on renal function and urine production than changes in MAP. Oliguria is thought to be one of the first signs of intraabdominal hypertension. Control of intraabdominal pressure leads to reversal of renal impairment. Oliguria may be seen with intraabdominal pressure of 15 to 20 mm Hg. Deterioration in CO plays a role in diminished renal perfusion, but even with maintenance of CO, impairment of renal function persists in intraabdominal hypertension.[218,223–225]

Other organs affected by increased intraabdominal pressure include the liver, where hepatic blood flow has been shown to decrease with abdominal hypertension.[226,227] It may be assumed that hepatic synthesis of acute-phase proteins, immunoglobulins, and other factors of host defense may be impaired by reduced hepatic blood flow. Other gastrointestinal functions may be compromised by increased intraabdominal pressure. Splanchnic hypoperfusion may begin with an intraabdominal pressure of 15 mm Hg. Reduced perfusion may create changes in mucosal pH, translocation, bowel motility, and production of gastrointestinal hormones. Finally, intracranial hypertension is seen with chronically increased intraabdominal pressure. Intracranial hypertension has been shown to decrease when intraabdominal pressure is reduced in morbidly obese patients and in intracranial injury.

Operative decompression is the method of choice for treatment of patients with intraabdominal hypertension and associated evidence of organ dysfunction. After decompression, improvements in hemodynamics, pulmonary function, tissue perfusion, and renal function have been shown in a variety of clinical settings. To prevent hemodynamic decompensation during decompression, intravascular volume should be restored, oxygen delivery should be normalized, and hypothermia and coagulation defects should be corrected. The abdomen should be opened in patients with adequate venous access and controlled ventilation. Adjunctive measures to combat reperfusion washout from by-products of anaerobic metabolism include acute use of vasoconstrictor agents to avoid sudden changes in blood pressure. After decompression of the abdomen, the fascial gap is left open using one of a variety of temporary abdominal closure methods.

In a recent report, Cheatham and Safcsak review their experience with percutaneous, ultrasound-guided drainage of ascitic fluid contributing to abdominal hypertension and abdominal compartment syndrome.[228,229] These investigators suggest that in patients with significant fluid accumulation creating abdominal hypertension, percutaneous drainage can avoid the need for decompressive laparotomy with its associated morbidity and occasional complications. Additional reports from other centers are required. To date, apart from the large experience described previously, percutaneous control of fluid accumulation to manage abdominal hypertension and compartment syndrome is limited to case reports.

Extremity Compartment Syndrome

The numerous causes of extremity compartment syndrome include complications of open and closed fractures, arterial injury, temporary vascular occlusion, snakebite, drug abuse, burns, physical exertion, and gunshot wounds. The most common cause of compartment syndrome is muscle injury leading to edema, which is correlated to the amount of tissue damage. Pressure is increased within the closed fascial space first by intracellular swelling followed by hematoma formation if a fracture is present. Because extremities, particularly at the calf, are composed of relatively unyielding fascial compartments, circulatory compromise occurs as tissue pressure increases with resulting ischemia and tissue damage. Leakage of intracellular fluid follows, and a further increase in intracompartmental pressure is seen.[230]

When extremity injuries produce complete ischemia, skeletal muscle that is deprived of oxygen may survive for 4 hours without irreversible damage. Total ischemia of 8 hours' duration produces irreversible change. Peripheral nerves conduct for 1 hour after onset of total ischemia and can survive for 4 hours with only neurapraxic damage. After 8 hours, irreversible damage occurs. Ischemia caused by reduction or cessation of blood flow occurs

when the perfusion gradient to a muscle compartment falls below a critical level. Perfusion is related to the compartment pressure. When intracompartmental blood pressure is 25 mm Hg, tissue perfusion in injured tissues is substantially decreased.[230–232]

Fasciotomy should be performed when intracompartmental pressure approaches 30 mm Hg, or if an extremity has been completely ischemic for 6 hours, the patient's clinical condition is worsening, substantial tissue injury is present, or tissue pressure is increasing.[232] Prophylactic treatment is valuable because fasciotomy does not reverse changes caused by initial extremity injury but can prevent changes resulting from secondary ischemic insults.

Pain, pallor, paralysis, paresthesias, and pulselessness are the classic hallmarks of extremity compartment syndrome. If treatment is not initiated until all of these signs are present, poor results are obtained. Pain and aggravation of pain by passive stretching of the muscles in the involved compartment is the most sensitive clinical finding. Assessment of pain is useful when patients are conscious and can respond cognitively to examination. In unconscious patients at risk for compartment syndrome, tissue pressure measurements may be the only objective criteria for diagnosis. Measurement of compartment pressures is obtained in all extremity compartments at risk and proximal and distal to any fractures. The highest pressure noted should serve as the basis for determining the need for fasciotomy.

Pelvic Fractures

Substantial blunt force is required to disrupt the pelvic ring. The extent of injury is related to the direction and magnitude of force applied. Associated abdominal, thoracic, and head injuries are common. Force applied to the pelvis can cause rotational displacement with opening or compression of the pelvic ring. Other types of displacement seen with pelvic fractures are vertical with complete disruption of the ring and the posterior sacroiliac complex.[233]

Patients with pelvic ring injuries are easily divided into two groups on the basis of clinical presentation—patients who are hemodynamically stable and patients who are hemodynamically unstable.[233] There is a dramatic difference in mortality rates between patients with pelvic fracture who are hypotensive and patients who are hemodynamically stable. Hemodynamic stability and biomechanical pelvic instability are separate though related issues, which tends to confuse the clinical picture. The source of bleeding may be multifactorial and not directly related to the pelvic fracture itself. Blood loss secondary to a pelvic fracture that contributes to hemodynamic instability is a significant risk factor, however. Early fracture diagnosis and stabilization using external skeletal fixation are sometimes essential in the acute phase of patient management.[233] Treatment of the patient also is directed by response to initial fluid resuscitation. Retroperitoneal bleeding in a pelvic fracture usually arises from a low-pressure source—the cancellous bone at the fracture site or adjacent venous injury. Significant retroperitoneal arterial bleeding occurs in approximately 10% of patients. Clinical evidence has suggested that provisional fracture stabilization using external fixation devices or even wrapping the fractured pelvis in a bed sheet can control low-pressure venous bleeding. Continued, unexplained bleeding after provisional fracture stabilization suggests an arterial source. Angiography with embolization of the involved vessel is indicated. Therapeutic angiography balloon occlusion of the aorta and preperitoneal pelvic packing also may be required with abdominal exploration if a rapidly expanding retroperitoneal hematoma is encountered.[234,235]

Key Points

- Although flaws in current crystalloid resuscitation preparations exist, a clear benefit of routinely available colloids has not been shown.
- A variety of hemodynamic, metabolic, and oxygen transport endpoints for resuscitation have been identified. None of the available resuscitation endpoints is consistently effective to limit or guide therapy after injury at this time. Guides to drive resuscitation in injury will vary from those used for hypovolemia not caused by injury.
- Shock after trauma is not the same as simple hemorrhage. Blood loss is combined with an inflammatory component.
- Because of inflammation associated with hemorrhage, the rate and amount of resuscitation are increased after injury compared with hemorrhage outside the setting of trauma.
- The classic neuroendocrine response leading to conservation of salt and water in traumatic shock can be linked to neuroimmune feedback loops, which modulate inflammatory response.
- Resuscitation to supranormal oxygen transport parameters does not improve outcome after injury. A staged approach using a pulmonary artery catheter, which should be necessary in less than 5% of injured patients, may be helpful.
- Although massive transfusion reduces overall blood product requirements in patients with rapid blood loss, limited resuscitation and blood product conservation are seen as appropriate in many injured patients.

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Review Questions

1. A 19-year-old, 90-kg man sustains a grade IV splenic laceration caused by a motor vehicle collision. Because of hemodynamic instability, he is taken from the emergency department to the operating room, and there he undergoes damage control laparotomy. He is brought to the intensive care unit (ICU) for ongoing resuscitation. His vital signs on arrival include a blood pressure of 80/40 mm Hg and a heart rate of 125 beats/min, and he has urine output of 15 mL/h. After resuscitation with crystalloid and blood products, his blood pressure is 117/75 mm Hg, heart rate 99 beats/min, urine output 100 mL/h. The lactate level is 5.2 mmol/L and base deficit is −9. Which of the following statements is most correct?

- **a.** Given the normalization of his vital signs and urine output, this patient's resuscitation is complete, and further aggressive resuscitation should be withheld.
- **b.** His base deficit should be corrected by the administration of sodium bicarbonate.
- **c.** Despite normalization of vital signs and urine output, he continues to have evidence of tissue hypoperfusion and likely still warrants aggressive resuscitation.
- **d.** This patient should have a pulmonary artery catheter placed to better define his hemodynamics and titrate his resuscitation.

Answer: c. Despite some strong feelings on this topic, the fact is that the optimal endpoint for trauma resuscitation is not known. Although it is a good sign that urine output and vital signs are normalized, what is known is that if resuscitation stops there, a significant percentage of patients are left underresuscitated ("cryptic shock") and at risk for multiorgan failure and death. It is likely that the most prudent strategy involves combining the entire clinical picture with multiple markers of hypoperfusion to include vital signs, physical examination, urine output, lactate, base deficit, mixed venous oxygen saturation, and so on while weighing the risk/benefit ratio of ongoing fluid and product administration (e.g., potential for worsening oxygenation or abdominal compartment syndrome). Base deficit has been studied in the trauma population, with a correlation to outcome. However, these data are not robust and no specific threshold level or correction time frame can be reported with any confidence. Furthermore, base deficit is a crude marker of hypoperfusion that can be highly influenced by treatment provided, such as chloride administration. There is no role for a pulmonary artery catheter in this patient.

2. A 25-year-old man sustains a stab wound to the upper abdomen with omentum visible on examination. He arrives at the emergency department with a systolic blood pressure of 86 mm Hg and is answering questions appropriately. Which of the following should be done for this patient?

- **a.** Given his normal mental status, he should be taken for computed tomography (CT) scan of the chest and abdomen to better define his injury and for operative planning.
- **b.** Large-bore intravenous (IV) access should be obtained and crystalloid and packed red blood cell transfusion should be immediately undertaken until blood pressure is normalized.
- **c.** Emergent local wound exploration should be performed to assess the need for operation.
- **d.** Large-bore IV access should be obtained and the patient should be allowed to be hypotensive with no resuscitative efforts until reaching the operating room.

Answer: d. The concept of permissive hypotension and delayed resuscitation for penetrating trauma has gained increased traction since a landmark study published in the 1990s showed that this strategy reduced mortality rate. By increasing blood pressure with initial resuscitative efforts, there is a concern that the initial friable clot will be dislodged and lead to increased rebleeding. Therefore, unless this patient's blood pressure falls further or his mental status is lost, he should be taken immediately to the operating room, and then resuscitation should commence. There is no role for CT scan or local wound exploration in this patient, as it is obvious that his injury violates the peritoneum.

3. A 31-year-old man is brought to the ICU after emergent laparotomy for blunt trauma. In the operating room, he was found to have liver, bowel, and splenic injuries that required bowel resection and reanastomosis and splenectomy. He received 25 units of packed red blood cells, 15 units of fresh frozen plasma, 6 units of platelets, and 4 units of crystalloid. He requires ongoing resuscitation for reversal of tissue hypoperfusion while in your ICU. Two hours later, his abdomen is distended and his bladder pressure is elevated. What constellation of signs would be most congruent with abdominal compartment syndrome?

- **a.** Central venous pressure (CVP) 25 cm H_2O, elevated peak and plateau airway pressures, oliguria, bladder pressure 25 mm Hg
- **b.** CVP 25 cm H_2O, elevated peak and plateau airway pressures, oliguria, bladder pressure 6 mm Hg
- **c.** CVP 5 cm H_2O, elevated peak pressure, normal plateau airway pressure, normal urine output, bladder pressure 15 mm Hg
- **d.** Bladder pressure 30 mm Hg with no other significant findings

Answer: a. This patient is an example of a classic setup for abdominal compartment syndrome: blunt trauma to the abdomen requiring massive resuscitation. Normal intraabdominal pressure is 5 to 7 mm Hg and should be measured at end-expiration, in the supine position, absent of abdominal muscle contraction, with a zeroed transducer at the level of the midaxillary line. Intraabdominal hypertension can exist without abdominal compartment syndrome in conditions such as morbid obesity and ascites. Abdominal compartment syndrome is the presence of intraabdominal hypertension (>20 mm Hg) associated with new or worsening organ dysfunction. Abdominal compartment syndrome can affect most all organ systems. This patient has some of the classic findings. CVP will be elevated. Owing to a reduction in compliance, both peak and plateau airway pressures will increase, and ventilation will become increasingly difficult. Of note, an elevated peak airway pressure and normal plateau pressure would be indicative of a resistance problem, such as endotracheal tube occlusion or bronchoconstriction. Owing to a reduction in perfusion pressure to the kidney, oliguria will occur. Option b is not correct as the bladder pressure is normal. Other causes for deterioration should be sought. Option b could be caused by something such as acute respiratory distress syndrome with concomitant acute cor pulmonale.

4. A 19-year-old man sustains a severe crush injury in an industrial accident. His injuries include a severe closed head injury, pelvic fracture, and crush injury to the right leg. Which one of the following statements is most correct regarding the evaluation and management of this patient?

a. Absence of a Cushing reflex (bradycardia and hypertension) virtually rules out significant elevations of intracranial pressure.

b. For laterally displaced pelvic fractures, using a bed sheet to circumferentially wrap and compress the pelvis with traction is as effective as external fixation in stopping blood loss.

c. Loss of a palpable pulse in the crushed extremity is an early sign of impending compartment syndrome.

d. Compartment pressures above 30 mm Hg in a crushed extremity indicate a need for close follow-up with serial compartment pressures measurement.

Answer: d. Intracranial hypertension can cause a Cushing reflex, resulting in a rise in blood pressure with a drop in the heart rate producing bradycardia. However, the absence of a Cushing reflex does not exclude intracranial hypertension. Pelvic fractures can be associated with massive blood loss producing shock. Closed pelvic fractures can cause a patient to lose 50% of his or her circulating blood volume. Laterally displaced (i.e., "open book") pelvic fractures need emergency stabilization of the fracture to achieve control of the blood loss. This can be accomplished with an external fixator. Alternatively, using a bed sheet to circumferentially wrap and compress the pelvis with traction is equally effective at stopping blood loss in the acute resuscitation setting. Continuing blood loss after fixation of the pelvic fracture likely requires angiographic embolization to stop the bleeding. In cases of compartment syndrome after a crush injury, loss of a palpable pulse is a late (not early) finding. Loss of a palpable pulse would be preceded by pain, pallor, paresthesias, and paralysis. A markedly elevated compartment pressure at 30 mm Hg would be an indication for performing fasciotomy, not serial examinations.

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Severe Heart Failure

FREDRIC GINSBERG AND JOSEPH E. PARRILLO

CHAPTER OUTLINE

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Acute Coronary Syndromes and Acute Heart Failure: Special Considerations

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Device Therapy for Heart Failure and Ventricular Tachyarrhythmias: Implanted Cardioverter Defibrillator and Cardiac Resynchronization Therapy
- Implanted Cardioverter Defibrillator Therapy
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Severe Heart Failure and Mechanical Circulatory Support
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Definition, Epidemiology, and Staging of Heart Failure

Heart failure is defined as the inability of the heart to provide cardiac output adequate to meet the metabolic demands of the body at a normal filling pressure. Normal cardiac output is maintained with mild heart failure, but more severe heart failure is associated with reduced cardiac output. Physiologic abnormalities lead to excessive salt and fluid retention and signs and symptoms comprising the heart failure syndrome. Heart failure is a progressive illness with a high mortality rate. Death can occur after chronic progressive worsening of heart failure, or suddenly and unexpectedly in patients who appear clinically stable. Appropriate therapies for heart failure, including medications, revascularization, and devices, have the potential to reverse the processes that cause heart failure and improve cardiac performance, stabilize the patient's symptoms, enhance functional status, and improve survival.

Heart failure is a very common illness. Approximately 6.5 million Americans are affected, females as frequently as males. It is estimated that 2.5% of the adult population of Americans are affected by heart failure, and more than 20% of hospital admissions in patients older than 65 years of age are due to heart failure. The population with heart failure is expected to increase to 8 million by 2030. Almost 1 million new cases are diagnosed annually. In those younger than 75 years, the incidence of heart failure is higher in black and Hispanic populations. In the United States, there are nearly 1 million hospital discharges yearly, a volume that did not change during the decade 2000 to 2010. There were 509,000 visits to the emergency department for heart failure in 2012. More than 56,000 people in the United States died in 2007 with heart failure as the

primary cause. The treatment of heart failure incurs a very large economic burden on the U.S. health care system. Estimated direct and indirect cost of heart failure in 2012 was estimated at $30.7 billion. The majority of this cost was related to the treatment of patients hospitalized with heart failure. Epidemiologic data show significant increases in both the incidence and prevalence of heart failure in the United States, likely influenced by the aging of the population, a high prevalence of hypertension, and improved treatment and survival of patients with ischemic heart disease.[1,2]

Patients hospitalized with acute heart failure are usually elderly, with a mean age in the early 70s. In the United States, roughly 80% of patients have a previous history of heart failure and in European studies one-third of patients had a new diagnosis of heart failure[3]; 40% to 55% of patients have normal or relatively normal left ventricular systolic function, which occurs more commonly in females than in males. Coronary heart disease is present in 50% to 60% of patients and hypertension in 72% of patients. Comorbidities are common, including renal disease in 30% of patients, diabetes mellitus in 43%, and chronic obstructive pulmonary disease in roughly 30%.[3,4] The prognosis of heart failure remains more serious than is generally appreciated. Only 50% of patients survive 5 years after the initial diagnosis of heart failure. Mortality is often due to associated noncardiac conditions. Risk factors for mortality include the presence of coronary artery disease, diabetes, hypertension, and cigarette smoking.[1]

In the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the diagnosis and management of chronic heart failure, four stages in the development of heart failure are recognized (Fig. 27.1). This staging system emphasizes the following details. (1) Heart failure may be preventable. Several common medical conditions, such as hypertension and diabetes mellitus, place patients at high risk for developing left ventricular dysfunction and heart failure. Appropriate management of these conditions may prevent the development of heart failure. (2) Left ventricular dysfunction and heart failure are conditions that worsen over time. (3) In patients with left ventricular dysfunction but who have not yet developed heart failure, medical therapy can delay or prevent the development of heart failure. (4) There are evidence-based guidelines for therapy for each stage.[5]

Stage A represents patients at high risk for heart failure but without structural heart disease or symptoms of heart failure. These include patients with hypertension, atherosclerotic heart disease, diabetes, obesity, patients exposed to cardiotoxic medications, or those with a family history of cardiomyopathy. Antecedent hypertension exists in 75% of patients who develop heart failure. Stage B patients have structural heart disease, but without signs or symptoms of heart failure. This group includes patients who have had a myocardial infarction, those with abnormal left ventricular ejection fraction (LVEF) but no symptoms of heart failure, and those patients with asymptomatic valvular heart disease. Stage C patients have structural heart disease with prior or current symptoms of heart failure. Stage D patients have refractory symptoms of heart failure at rest despite maximal medical therapy. They require specialized or extraordinary interventions, such as cardiac transplantation or mechanical circulatory support (MCS), or end-of-life care.

Pathophysiology

Heart failure can be due primarily to left ventricular systolic dysfunction or abnormal diastolic function, although both abnormalities are often present. In addition, right ventricular dysfunction may accompany left ventricular dysfunction or may be the primary problem. The syndrome of systolic heart failure—or "heart failure with reduced ejection fraction" (HFrEF)—results from depressed left ventricular contractility caused by loss of myocytes and myocardial fibrosis with reduced LVEF. The left ventricle is often dilated. Diastolic heart failure is now preferentially termed "heart failure with preserved ejection fraction" (HFpEF). It is caused by reduced left ventricular diastolic compliance and abnormal relaxation. Impaired diastolic filling leads to a higher left ventricular diastolic pressure to maintain cardiac output, with elevation of pulmonary capillary wedge pressure (PCWP) (Fig. 27.2).

Many conditions can cause damage to left ventricular myocardium and result in systolic heart failure. The most common are myocardial infarction and chronic myocardial ischemia caused by atherosclerotic coronary artery disease. Other common etiologies include hypertension, familial and idiopathic cardiomyopathy, viral myocarditis, and valvular heart disease, including aortic stenosis, aortic insufficiency, and mitral regurgitation. Peripartum cardiomyopathy, transient apical ballooning syndrome ("takotsubo" or stress cardiomyopathy), cardiomyopathy associated with prolonged tachycardia, and cardiomyopathy related to cardiotoxic cancer chemotherapy are less common. Uncommon causes are alcoholic cardiomyopathy, diabetic cardiomyopathy, and a cardiomyopathy seen in some patients with hyperthyroidism or severe obesity.[6–8]

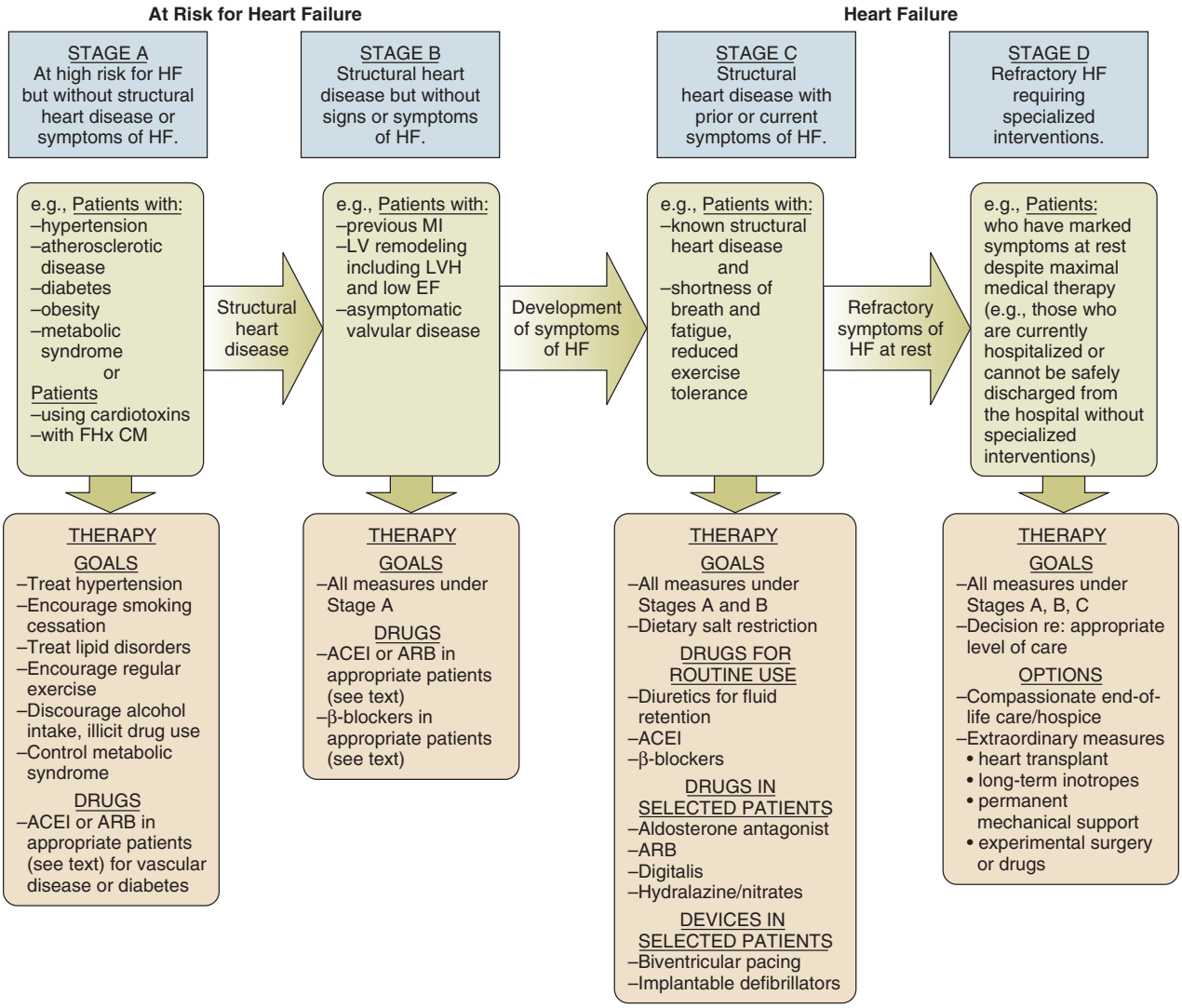
Myocardial damage and loss of myocytes result in a series of maladaptive systemic responses modulated by the autonomic and hormonal systems, termed *neurohormonal activation.* Two major systems involved in neurohormonal activation are the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Activation of the renin-angiotensin system leads to elevated levels of renin, angiotensin II, and aldosterone, which have deleterious consequences on cardiac structure, function, and hemodynamics.[2,9] Effects of neurohormonal activation include salt and fluid retention, endothelial dysfunction, myocyte hypertrophy, myocardial fibrosis, and myocyte apoptosis (programmed cell death). Sympathetic nervous system activation results in tachycardia, arrhythmias, increased myocardial oxygen consumption, and peripheral vasoconstriction.[10] Increased circulating norepinephrine levels contribute to myocyte injury and death. Renal effects of sympathetic nervous system activation lead to further activation of the RAAS.

Weakened left ventricular contractile force and neurohormonal activation lead to changes in cardiac structure termed *ventricular remodeling.* The left ventricular chamber becomes progressively more dilated, the shape of the left ventricle changes from ellipsoid to more spherical, and there is a reduction in LVEF.[2,9] In addition, the change in left ventricular geometry may lead to an increase in the size of the mitral annulus and altered coaptation of mitral valve leaflets, which causes mitral regurgitation and worsening heart failure (see Fig. 27.2). A detrimental positive feedback loop is established, where further left ventricular dysfunction leads to intensification of maladaptive responses, progressive deterioration in left ventricular structure and performance, and worsening heart failure.

Conditions commonly associated with HFpEF include hypertension, left ventricular hypertrophy, and acute coronary ischemia. HFpEF is common in elderly populations, especially in women, owing in part to progressive diastolic compliance abnormalities seen with aging. Uncommon conditions leading to diastolic heart failure include infiltrative and restrictive cardiomyopathies, such as amyloid cardiomyopathy, and chronic constrictive pericarditis.

Diagnosis and Serum Natriuretic Peptides

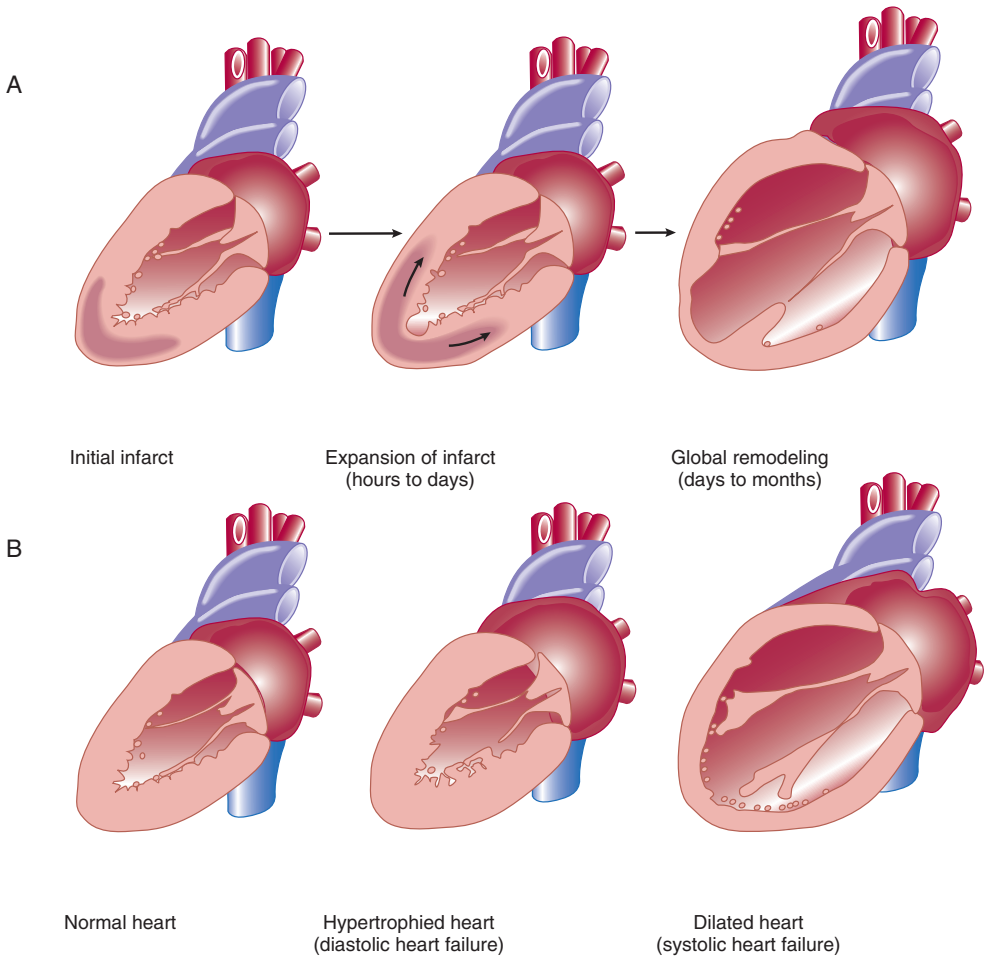
Heart failure is a clinical diagnosis, determined after evaluation of a patient's symptoms and physical examination and supported



• **Fig. 27.1** Stages in the development of heart failure and recommended therapy by stage. *ACEI,* Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *EF,* ejection fraction; *FHx CM,* family history of cardiomyopathy; *HF,* heart failure; *LV,* left ventricular; *LVH,* LV hypertrophy; *MI,* myocardial infarction. (Redrawn from Hunt S, Abraham WT, Chin M, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article. A report on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. *Circulation.* 2005;112: 1825–1852.)

by results of ancillary testing, including serum biomarkers, chest x-ray, and echocardiography. Symptoms of heart failure caused by pulmonary or systemic venous congestion are shortness of breath with exertion or at rest, cough, swelling of legs and/or abdomen, orthopnea, and paroxysmal nocturnal dyspnea. Fatigue, anorexia, and change in mental status are symptoms caused by low cardiac output. Physical examination findings include pulmonary rales, elevated jugular venous pressure, signs of cardiomegaly, cardiac murmurs (especially mitral regurgitation), S_3 gallop, hepatic enlargement, ascites, and edema. An S_3 gallop and elevated jugular venous pressure are the most specific signs of heart failure; absence of rales is not infrequent in patients with acute heart failure, and chest radiography may not show obvious congestion.[11] Manifestations of more severe heart failure on physical examination include marked dyspnea at rest possibly resulting in respiratory failure, cyanosis, cool extremities, and altered mental state. A careful evaluation for the presence of pulsus paradoxus is important if cardiac tamponade is suspected. However, these signs and symptoms are not specific for heart failure, and coexisting conditions, such as obesity, chronic lung disease, and deconditioning, can add uncertainty to the clinical diagnosis. Heart failure is often both underdiagnosed and overdiagnosed in outpatient and emergency department settings.

Studies have shown that serum assays of B-natriuretic peptide (BNP) and N-terminal pro-BNP (NTpro-BNP) improve the accuracy of diagnosing heart failure. BNP is a 32–amino acid

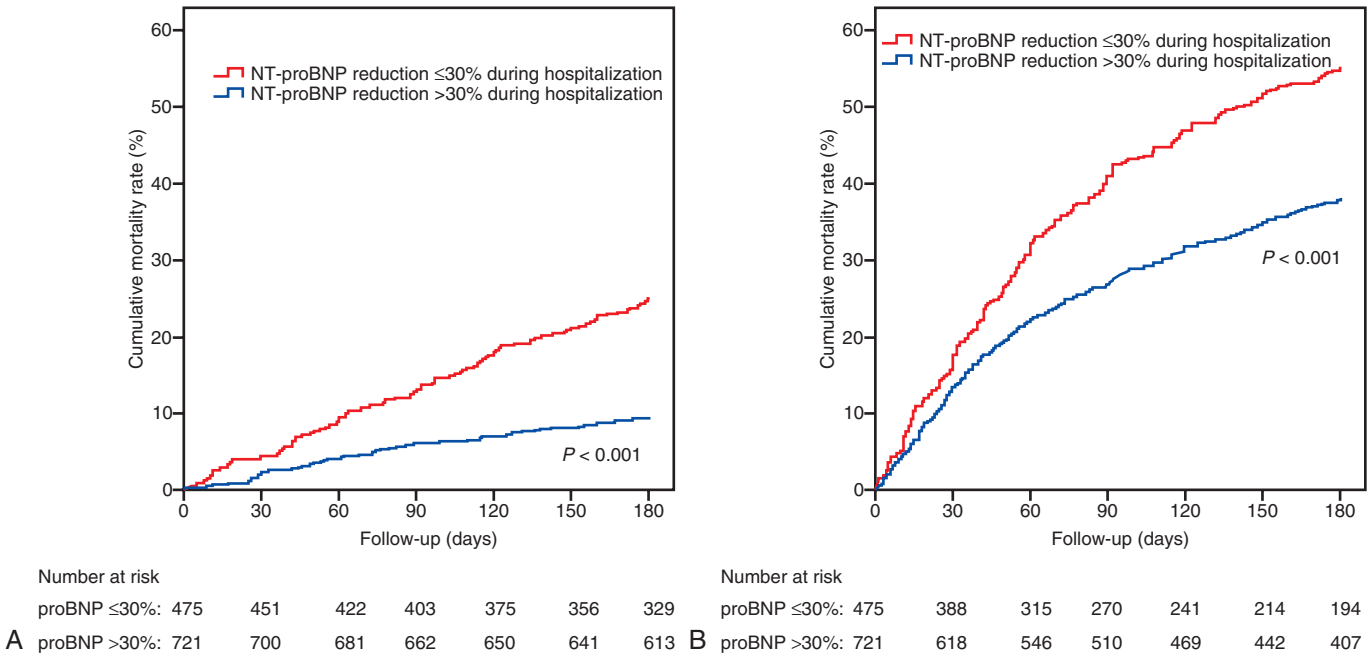


• **Fig. 27.2** A, Left ventricle (LV) remodeling after acute myocardial infarction, resulting in a dilated LV with global systolic dysfunction. B, Ventricular remodeling in diastolic and systolic heart failure. Note differences in LV morphology in diastolic versus systolic heart failure. (Redrawn from Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348:2007–2018.)

peptide produced by cardiac myocytes in response to pressure-induced wall stretch and tension.[12] Physiologic actions of BNP include arterial and venous dilation and natriuresis. A study of 1530 patients presenting to the emergency department with dyspnea showed that knowledge of BNP serum levels resulted in improved diagnostic accuracy of heart failure from 65% to 74% to 81% when compared with clinical judgment alone.[13] BNP levels above 100 pg/mL had a sensitivity of 90%, specificity of 76%, and diagnostic accuracy of 81.2% for the diagnosis of heart failure. Determination of BNP was very useful for discriminating patients with dyspnea owing to uncomplicated lung disease who had BNP values below 100 pg/mL.[14] Patients with BNP values below 100 pg/mL were very unlikely to have heart failure as the cause of dyspnea. Levels between 100 and 400 pg/mL can be seen in patients with primary right ventricular failure owing to cor pulmonale with chronic lung disease, idiopathic pulmonary hypertension, and acute pulmonary embolism. Left ventricular failure is the likely diagnosis when levels are above 400 pg/mL. BNP levels should always be interpreted in conjunction with all other clinical data to arrive at a correct diagnosis.

Evaluating BNP levels in heart failure patients in the emergency department was shown to decrease the need for hospitalization and decrease the need for intensive care unit (ICU) admissions, without affecting 30-day mortality rates. Total hospital stay was shortened by 3 days, cost of treatment was significantly reduced, and time to initiation of definitive therapy in the emergency department was shortened by 30 minutes.[15]

BNP levels correlate with disease severity. Higher levels are seen in patients with more severe heart failure and with worse left ventricular systolic function. Higher levels are correlated with a poorer prognosis and can predict an increased rate of functional deterioration and mortality.[16] In a study of 114 patients admitted to the hospital with class IV heart failure, of all variables evaluated, predischarge BNP level was most strongly associated with death or readmission within 6 months; BNP levels higher than 350 pg/mL had high sensitivity and specificity.[17] BNP is also elevated in patients with diastolic heart failure and renal failure. Stable patients with chronic left ventricular systolic dysfunction and compensated heart failure often have chronically elevated BNP levels; however, an increase of more than 30% over this "baseline" does reflect worsening heart failure status.[18] BNP levels may initially be low in patients with "flash" pulmonary edema, as they may present to the hospital more quickly than the time required for significant rises in serum BNP to occur. Obese patients tend to have lower levels of BNP and may have "falsely low" levels in the setting of heart failure.



• **Fig. 27.3** Kaplan-Meier curves for all-cause mortality (A) and composite endpoint (B) at 180 days according to NT-proBNP during hospitalization. *NT-proBNP,* N-terminal pro-B-type natriuretic peptide. (From Salah K, Kok WE, Eurlings LW, et al. Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure. *JACC Heart Fail.* 2015;3:751–761.)

NTpro-BNP can also be used for the diagnosis of heart failure. The precursor hormone pro-BNP is cleaved to form BNP and NTpro-BNP, which is physiologically inactive. NTpro-BNP has a longer half-life than BNP. It is cleared from the serum by the kidneys, so levels are higher in patients with coexisting renal disease. Levels of NTpro-BNP rise significantly in older populations. A cutoff level of NTpro-BNP below 300 pg/mL yielded a negative predictive value of 98% for exclusion of the diagnosis of heart failure.[19,20] The diagnosis of heart failure is very likely at levels above 450 pg/mL in patients younger than age 50, above 900 pg/mL in patients between 50 and 75 years, and above 1800 pg/mL in patients older than age 75. NT pro-BNP levels can also be used to guide therapy. In patients admitted to hospital with acute heart failure, a more than 30% reduction in NTpro-BNP predicted a reduction in the risk of mortality and readmission with heart failure (Fig. 27.3).[21]

Prognosis in Acute Heart Failure

Hospitalization for acute heart failure is associated with a poor prognosis. In-hospital mortality is high, with mortality rates of 4% to 8%. There is 9% mortality at 60 to 90 days, and 1-year mortality of 29%.[3,22–24] In a European heart failure database, in-hospital mortality was 6.9%, the 12-week readmission rate was 24%, and total mortality at 12 weeks was 13.5%.[4] More recent data indicate no major change in 30-day risk-standardized mortality after hospitalization for heart failure—11.5% in 2009–2010 and 11.3% in 2013.[25] Randomized trials of pharmacologic therapy reported an annual mortality of 10% in all patients with class II-III symptoms and 20% to 50% in class IV patients. Most recent data from the United States in the Medicare population show a 1-year mortality of 29.6% over 1 year after a heart failure hospitalization.[1] The mortality rate at 5 years continues to be around 50% despite recent advances in treatment. In the groups with the most severe chronic heart failure—patients awaiting cardiac transplantation—1-year mortality was 75% with 2-year mortality of 92%.[26] The prognosis for patients with cardiogenic shock caused by acute myocardial infarction (AMI) continues to be poor. Hospital mortality remains 40% to 50% even with aggressive supportive therapy and emergency revascularization strategies.[27] Rehospitalization rates are also high, averaging 20% to 25% at 30 days, although only half of rehospitalizations are caused by heart failure.

Several clinical factors have been shown to identify patients with a poorer prognosis. These include lower LVEF, low blood pressure on admission, and PWCP. In the United States the Acute Decompensated Heart Failure National Registry (ADHERE) database of 62,275 admissions for acute heart failure, blood urea nitrogen (BUN) more than 43 mg/dL, admission systolic blood pressure less than 115 mm Hg, and creatinine level more than 2.75 mg/dL were the three factors that indicated a higher in-hospital mortality. The presence of an elevated BUN was associated with a fourfold increase in hospital mortality to 8.35%. The presence of all three factors yielded an in hospital mortality of 19.8%[23] (Box 27.1).

Other factors that have been associated with increased mortality rates include hyponatremia, higher serum BNP level, and elevation of serum troponin.[28] In ADHERE, higher levels of serum BNP on admission were associated with a higher in-hospital mortality, ranging from 1.9% in the lowest quartile to 6.0% in the highest quartile (BNP > 1730 pg/mL). The ability of BNP to predict prognosis was present even after multivariate adjustment for coexisting conditions and was also true for patients with normal and abnormal LVEF.[29] Serum troponin is elevated in 6% to 10.4% of patients admitted with acute heart failure (with serum creatinine <2.0 mg/dL). Troponin elevation was associated with a lower blood pressure, lower ejection fraction, and longer hospital length of

• BOX 27.1 Factors Indicating a Poor Prognosis in Acute Heart Failure

Hypotension (systolic blood pressure <115 mm Hg on admission)
Presence of coronary artery disease
Elevated blood urea nitrogen and creatinine
Hyponatremia
Low left ventricular ejection fraction
Poor functional capacity
Marked elevation of B-natriuretic peptide, elevated troponin
Anemia
Diabetes mellitus

stay. Hypothetical mechanisms of troponin release in chronic heart failure include ischemia, cytokine activation, oxidative stress, and apoptosis. Hospital mortality was 8.0% in troponin-positive patients and 2.7% in troponin-negative patients. The ability of troponin elevation to predict mortality also was independent of other variables and was true even in patients with nonischemic etiologies of heart failure.[30] The coexistence of kidney disease significantly worsens the prognosis of patients with heart failure. Kidney disease aggravates the tendency to volume overload and heart failure decompensation, and heart failure often worsens renal function. Worsening renal function (WRF) during therapy and evidence of diuretic resistance also indicate patients with poorer outcomes. A meta-analysis of 16 large studies of heart failure patients revealed that 29% of heart failure patients had moderate to severe impairment of renal function. These patients had more than 100% increased relative mortality risk. Any degree of renal impairment had an approximately 50% increased relative mortality risk.[31]

Acute Heart Failure Syndromes

Initial Evaluation and Therapy

Acute heart failure is a common, life-threatening emergency. It is the cause of more than 1 million hospitalizations yearly in the United States. It is defined as either the new onset of sudden, severe heart failure symptoms or a gradual worsening of a chronic heart failure syndrome that has progressed in severity to require urgent and intensive therapy. Fifty percent to 60% of patients are male with an average age of 70 to 73 years.[32] Acute heart failure can occur in patients with systolic dysfunction or in patients with heart failure with HFpEF. Although in-hospital mortality and length of stay have been reduced, the prognosis remains poor, with 30% mortality at 1 year after hospitalization and 50% mortality at 5 years. This prognosis is affected by the high incidence of serious comorbid conditions as well as end-organ complications, including renal dysfunction, hepatic congestion, and thromboembolic conditions.

Acute heart failure requires urgent and simultaneous initiation of diagnostic testing and therapeutic interventions. Several different schemes are used to classify acute heart failure; these enable the clinician to assess the etiology and optimize initial diagnostic and therapeutic strategies. Blood pressure on presentation can often quickly differentiate the etiology, as acute heart failure with hypertension is considered a hypertensive emergency, mandating urgent blood pressure lowering. Acute heart failure with normal blood pressures suggests coronary artery disease as an etiology. Hypotension may indicate cardiogenic shock or advanced severe chronic heart failure. Another approach to the initial assessment is to evaluate for the likelihood of acute coronary ischemia as the etiology of acute heart failure to assess the need for and timing of revascularization strategies.[33,34]

A classification system recommended by the European Society of Cardiology identifies several distinct clinical syndromes of acute heart failure[22] (Table 27.1):

1. Acute worsening or decompensation of chronic heart failure symptoms, either in the setting of known chronic cardiovascular illness or de novo. These patients do not have shock or pulmonary edema. This is the most common presentation of acute heart failure requiring admission to hospital, occurring in approximately 70% of patients with acute heart failure.
2. Acute pulmonary edema with normal blood pressure, often caused by AMI or acute coronary ischemia.
3. Acute pulmonary edema associated with elevated blood pressure, often in the setting of chronic severe hypertension and chronic kidney disease. Pulmonary edema (syndromes 2 and 3) accounts for roughly 25% of acute heart failure admissions.
4. Cardiogenic shock with heart failure, usually the result of AMI. This is the most severe presentation of acute heart failure and is associated with high in-hospital mortality rates. This accounts for about 5% of acute heart failure cases.
5. High cardiac output heart failure in the setting of sepsis, hyperthyroidism, or cardiac arrhythmia. This is the least common presentation, occurring in a small percentage of patients.
6. Acute right ventricular failure, occurring with acute right ventricular myocardial infarction, massive pulmonary embolism, or cardiac tamponade. This presentation may be more subtle, marked by fatigue, dyspnea, hypotension, tachycardia, and signs of systemic venous congestion. This is also a relatively infrequent presentation of acute heart failure.

Symptoms of acute heart failure include severe shortness of breath, orthopnea, wheezing, and symptoms of hypoxemia including restlessness and confusion. Symptoms of tissue hypoperfusion, such as fatigue, weakness, mental status changes, nausea, and anorexia, may be subtle but are important to recognize as they may herald impending cardiogenic shock. Chest pain may indicate acute coronary ischemia. Physical examination often shows pulmonary rales and wheezes, an S_3 gallop, and elevation of jugular venous pressure. Peripheral pulses are weak and thready with diminished cardiac output states. A low cardiac output is reliably predicted by a low "proportional pulse pressure," which is calculated by the pulse pressure (systolic blood pressure minus diastolic blood pressure) divided by systolic blood pressure. A ratio below 0.25 predicts a cardiac index below 2.2 L/min per m^2.[35,36] The skin may be cool and clammy with cyanosis. Peripheral edema and ascites may indicate concomitant right ventricular failure of longer duration.

History and physician examination may not be sensitive or specific for the diagnosis of acute heart failure and is supplemented by urgent laboratory and radiologic testing. Complete blood cell count, electrolytes, renal and liver function, thyroid profile, and cardiac biomarkers (troponin I or troponin T) are routinely tested. Natriuretic peptide levels assist in the diagnosis of heart failure in patients presenting with dyspnea, and can be followed serially to assess effectiveness of therapy. An arterial line is helpful in managing patients with hypotension or cardiogenic shock. Electrocardiographic (ECG) evidence of acute ischemia or infarction will mandate a therapeutic approach targeted at optimizing myocardial blood flow. Chest radiography can show alveolar edema, interstitial edema, pleural effusions, and cardiomegaly, but may be unremarkable in

TABLE 27.1 Acute Heart Failure Symptoms

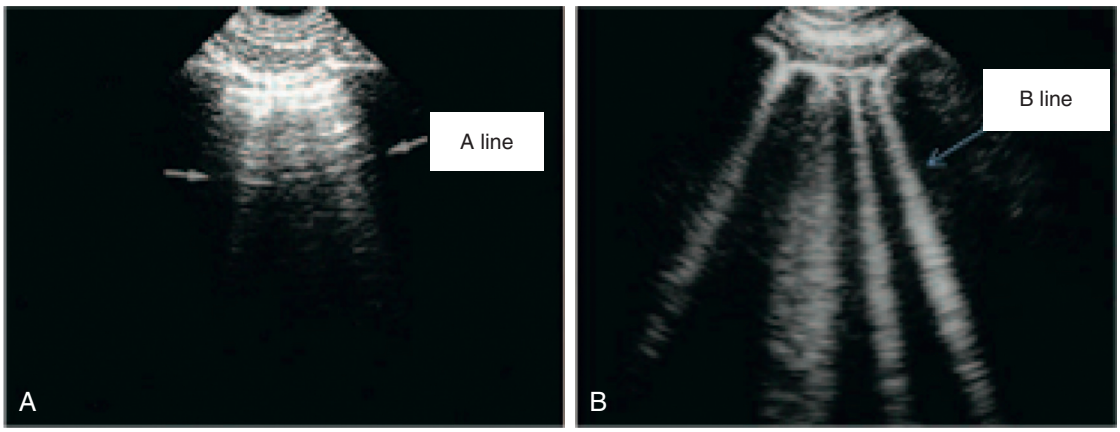
Syndrome	Onset	Signs and Symptoms	Hemodynamics
Acute decompensated heart failure	Days–weeks	Weakness Dyspnea Rales Third heart sound (S_3) gallop Edema	↑ PCWP ↓ CI Normal or ↑ RAP ↑ SVR
Acute pulmonary edema, normal BP	RV failure	Severe dyspnea Diffuse rales Cyanosis S_3 gallop	↑↑ PCWP Normal or ↓ CI Normal RA Normal or ↑ SVR
Acute pulmonary edema with hypertension	Acute	Severe dyspnea Diffuse rales	↑↑ PCWP Normal CI Normal RAP ↑↑ SVR
Cardiogenic shock	Acute	Hypotension Cyanosis Lethargy Cool, clammy	↑↑ PCWP ↑ RAP ↓↓ CI ↑ SVR
High-output heart failure	Days–weeks	Dyspnea Rales	↑ PCWP ↑ CI ↓ SVR
RV failure	Days–weeks	Hypotension Edema Ascites	Normal or ↑ PCWP ↑↑ RAP ↓↓ CI

BP, Blood pressure; *CI,* cardiac index; *PCWP,* pulmonary capillary wedge pressure; *RAP,* right atrial pressure; *RV,* right ventricular; *SVR,* systemic vascular resistance; ↑, increased; ↑, markedly increased; ↓, reduced; ↓↓, markedly reduced.

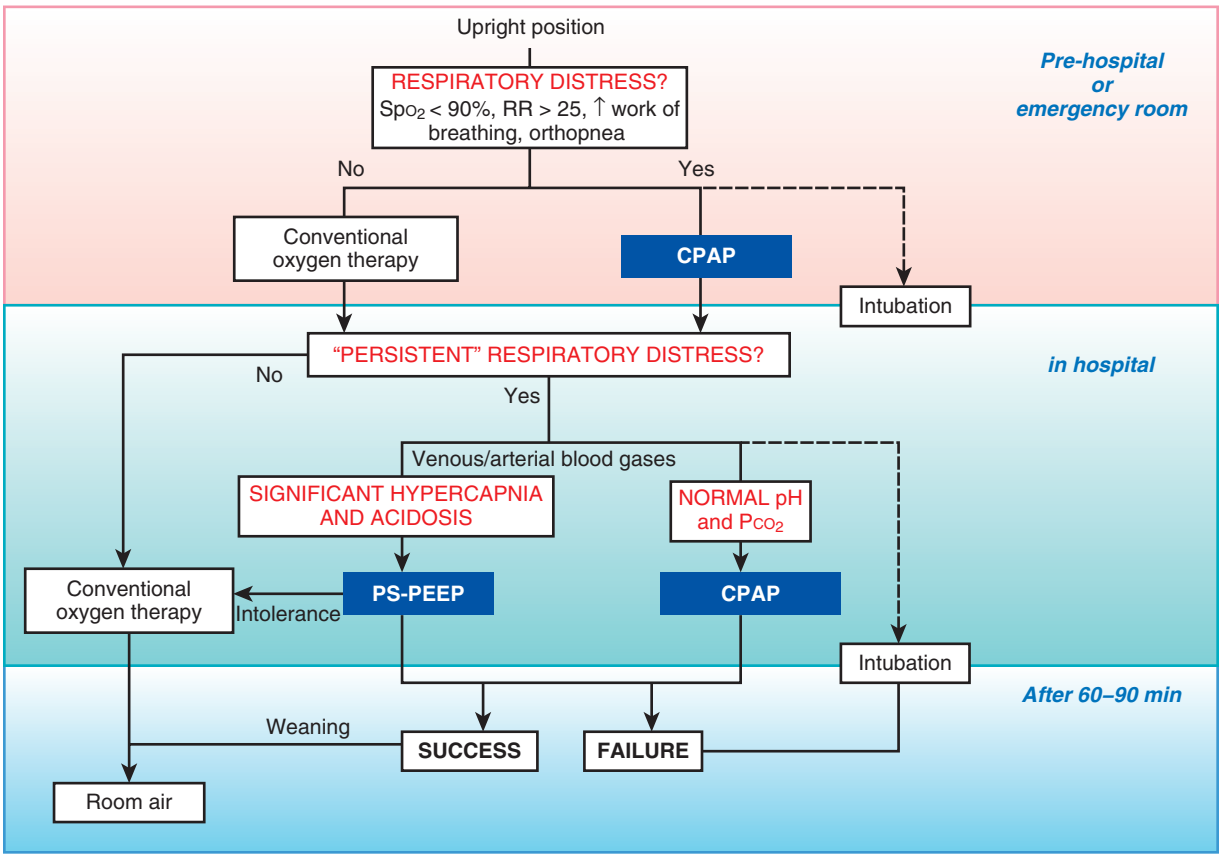
20% of patients with heart failure. Thoracic ultrasound is being used more frequently to assess for interstitial lung edema (Fig. 27.4).[32] Echocardiography should be performed emergently in unstable patients or can be performed after initial stabilization. It is essential to evaluate left ventricular size and function, right ventricular function, valve function, and the presence of pericardial effusion. Doppler echocardiography affords assessment of ventricular filling pressures, right ventricular systolic pressure, cardiac output, and the severity of valve lesions.

Rapid assessment of heart rate, blood pressure, cardiac rhythm, oxygen saturation, chest radiography, and ECG is necessary to initiate urgent therapies. Initial management is focused on providing adequate oxygenation and ventilation, optimizing blood pressure, stabilizing cardiac rhythm, treating myocardial ischemia when present, and reversing end-organ dysfunction. Initial therapy includes supplemental oxygen if the patient is hypoxemic. Patients with pulmonary edema often require ventilatory assistance with noninvasive positive airway pressure ventilation or endotracheal intubation. Noninvasive ventilation improves oxygenation and pulmonary compliance and decreases work of breathing. The use of continuous oxygen administration alone was prospectively compared with the use of continuous positive airway pressure ventilation (CPAP) and noninvasive intermittent positive pressure ventilation in 1069 patients who presented with acute cardiogenic pulmonary edema. No difference among these therapies was noted in the primary endpoint of death at 7 days or in the secondary endpoint of death plus endotracheal intubation at 7 days. Noninvasive ventilation did result in more rapid improvement in dyspnea, tachycardia, hypercapnia, and acidosis. There was no difference in safety or efficacy between CPAP and noninvasive intermittent positive pressure ventilation.[37] However, a Cochrane meta-analysis of 32 studies that enrolled 2916 patients concluded that in patients with acute cardiac pulmonary edema, the early use of noninvasive positive-pressure ventilation *was* associated with lower hospital mortality and lower need for subsequent endotracheal intubation. Noninvasive ventilation was associated with a shorter ICU stay and fewer neurologic complications.[38] Endotracheal intubation may be required for patients who demonstrate marked fatigue or severe hypercapnea and respiratory acidosis (Fig. 27.5).

There are few controlled trial data to arrive at evidence-based guidelines for the treatment of acute heart failure. Many recommendations are based on small studies, experience, observation, and consensus of opinion.[39] Initial medical therapy has historically included intravenous morphine because of its favorable vasodilator effect and relief of psychological distress. However, an analysis of registry data concluded that use of morphine was associated with increased need for endotracheal intubation and higher hospital mortality.[40] Therefore morphine should not be given routinely and its use should be individualized. Intravenous loop diuretics, such as furosemide, offer rapid and effective symptom relief and are almost always first-line therapy. Intravenous vasodilators are very useful, especially in patients with severe hypertension; intravenous nitroglycerin and intravenous nitroprusside are used most commonly. β-Blockers can be administered in the setting of acute myocardial



• **Fig. 27.4** Thoracic ultrasound images in normal and patients with acute heart failure. A, From the pleural line, one repetition of the pleural line, a horizontal line *(A line),* parallel to the pleural line, is visible, indicating normal lung with no pulmonary edema. Note some ill-defined vertical comet-tail artifacts, not to be confused with lung rockets. *Arrows* indicate A lines. B, Four or five B-lines arise from the pleural line, creating a pattern called lung rockets. *B lines* are vertical, long, well-defined artefacts erasing the A-lines and moving in concert with lung sliding. *B lines* indicate pulmonary edema. (From Lichtenstein DA. Whole body ultrasonography in the critically ill. Heidelberg: Springer Science, 2010; and Mebazza A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail.* 2015; 17:544–558.)



• **Fig. 27.5** Oxygen and ventilatory support in acute heart failure. *CPAP,* Continuous positive airway pressure; *P_{CO_2}*, partial pressure of carbon dioxide; *PS-PEEP,* pressure support–positive end-expiratory pressure; *RR,* respiration rate; *S_{PO_2}*, oxygen saturation. (From Mebazza A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail.* 2015; 17:544–558.)

ischemia, hypertension, or tachyarrhythmias. They should be withheld initially in patients with severe heart failure, hypotension, shock, bradycardia, or heart block. Calcium channel blocking agents are generally contraindicated in acute heart failure.

Urgent treatment of arrhythmias is often necessary. Rapid atrial fibrillation is a common problem in acute heart failure. In the EuroHeart Failure Study, 9% of patients hospitalized with acute heart failure had atrial fibrillation during the hospitalization, and 42% had a history of paroxysmal atrial fibrillation.[41] Other studies report atrial fibrillation in 25% to 30% of hospitalized heart failure patients.[31] Control of the ventricular response to atrial fibrillation is vitally important, especially in patients with diastolic heart failure. This can rapidly be achieved with the use of intravenous β-blockers such as metoprolol or esmolol, parenteral digoxin, or intravenous amiodarone. Intravenous diltiazem can be used in patients whose left ventricular systolic function is known to be normal or near normal.

Indications for Invasive Hemodynamic Monitoring:

Right heart and pulmonary artery (PA) catheterization enables accurate measurement of PWCP, right atrial pressure, cardiac output, and mixed venous oxygen saturation. This helps to more precisely define hemodynamic derangements because findings on physical examination are often nonspecific or misleading. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial evaluated the *routine* use of PA catheterization in patients hospitalized with acute exacerbation of chronic heart failure and left ventricular systolic dysfunction. There was no difference in the primary endpoint of days alive out of the hospital during the 6 months after discharge in groups managed with or without a PA catheter. Importantly, there were no significant adverse effects with PA catheter use. There were no subgroups identified in which use of the PA catheter was beneficial.[42] Based on this study and clinical experience, the routine use of PA catheters in the setting of acute heart failure is not recommended.

However, there are circumstances when the use of a PA catheter is of great assistance in the management of patients with acute severe heart failure, either for initial determination of hemodynamics or to better gauge response to therapy. Indications for PA catheter use include cardiogenic shock, differentiating pulmonary from cardiac causes of dyspnea or abnormalities on chest radiography, uncertainty of a patient's hemodynamic status by clinical assessment, severe heart failure with worsening renal function, managing parenteral vasodilator therapy, and in patients whose conditions are deteriorating despite therapy. PA catheter placement is also necessary as part of the evaluation for cardiac transplantation or the implantation of a ventricular assist device (Box 27.2).

Therapies with vasodilators and inotropes, tailored to the response in hemodynamic measurements, have been advocated as effective methods to obtain more rapid and sustained improvement in patients with the most severe heart failure.[43,44] Goals of treatment include lowering PCWP less than 16 mm Hg and right atrial pressure less than 8 mm Hg, reducing systemic vascular resistance to less than 1200 dynes/s per cm^{-5}, raising cardiac index to more than 2.6 L/min per m^2, and maintaining systolic blood pressure above 80 mm Hg. PCWP can be lowered to a normal value of 10 to 12 mm Hg in many patients with significant left ventricular dysfunction without untoward effects.[45] In a group of patients referred for cardiac transplantation, a combination of aggressive parenteral therapy, targeted to optimal hemodynamics, followed by conversion to appropriate oral therapy, resulted in clinical improvement so that 30% of these patients were able to be removed from transplant lists.[44]

• BOX 27.2 Indications for Invasive Hemodynamic Monitoring With a Pulmonary Artery Catheter in Acute Heart Failure

1. Cardiogenic shock
2. Cardiac versus pulmonary cause of dyspnea uncertain
3. Uncertainty regarding severity of heart failure
4. Worsening renal function during heart failure therapy
5. Guiding parenteral vasodilator therapy
6. Deteriorating clinical status despite appropriate therapy
7. Evaluation of concomitant pulmonary hypertension
8. Evaluation before cardiac transplantation

• BOX 27.3 Causes of Acutely Decompensated Heart Failure

Environmental Causes
Excess salt and fluid intake
Excess alcohol consumption
Medication noncompliance or misunderstanding
Emotional or physical stress

Adverse Medication Effects
Calcium channel blockers
Antiarrhythmic agents (types 1A, 1C)
Nonsteroidal antiinflammatory drugs
Corticosteroids
Metformin, thiazolidinediones
Cancer chemotherapy

Cardiovascular Conditions
Acute ischemia/infarction
Pulmonary embolism
Uncontrolled hypertension
Arrhythmia
Worsening valvular regurgitation
Endocarditis

Extracardiac Illness
Sepsis, infection, hypoxia
Renal failure, urinary obstruction
Thyroid disease
Anemia, blood loss
Obstructive sleep apnea
Bilateral renal artery stenosis
Worsening of chronic lung disease

Evaluation for Etiology of Heart Failure Exacerbation

In patients with chronic systolic heart failure who experience acute decompensation, the specific reason for deterioration must be searched for and corrected when possible (Box 27.3). Environmental

factors such as excessive salt and fluid intake or alcohol consumption are common. Lack of adherence with outpatient heart failure therapies is also common, as complex and expensive drug regimens pose obstacles to consistent adherence. Emotional and physical stressors should be corrected when feasible.

Concomitant administration of medications for noncardiac conditions may aggravate heart failure. The most common are corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs), which promote fluid retention and aggravate hypertension. NSAIDs also interfere with the beneficial renal effects of angiotensin-converting enzyme (ACE) inhibitors, and can lead to acute renal injury and interfere with the action of loop diuretics.[46] The use of NSAIDs has been reported to increase the risk of hospitalization for heart failure by 10-fold in patients with a history of heart failure.[4] In patients with diabetes, metformin and thiazolindinediones can contribute to water retention and exacerbate heart failure. Cardiac toxicity owing to anthracyclines or other chemotherapies such as tyrosine-kinase inhibitors, a newer class of cancer chemotherapy, may cause or aggravate heart failure by direct toxic effects on the myocardium.[47] Cardiac medications such as calcium channel blockers and type 1A and 1C antiarrhythmic drugs (propafenone, flecainide) and dronedarone are contraindicated in patients with acute decompensated heart failure.

Acute and chronic comorbid medical conditions often play a role in heart failure decompensation. Renal failure often has etiologies similar to heart failure (e.g., hypertension, vascular disease) and WRF will often aggravate heart failure. Other common conditions include infections, such as pneumonia, influenza or sepsis, pulmonary embolus, worsening anemia often owing to blood loss, hyperthyroidism or hypothyroidism, and obstructive sleep apnea. Progression of underlying cardiovascular conditions is often the cause of heart failure exacerbation. Examples include progression of coronary artery disease with acute ischemia, uncontrolled hypertension, and cardiac arrhythmias. Worsening valve regurgitation, endocarditis, and bilateral renal artery stenosis are less common causes of acute heart failure exacerbation.

Pharmacologic Management of Acute Heart Failure

Urgent, short-term goals of treatment of heart failure are to relieve dyspnea, reverse acute hemodynamic decompensation, and preserve myocardial function. After the patient's condition has stabilized and improved, then long-term objectives become paramount. These are preventing rehospitalization, improving functional status, and prolonging survival. Pharmacologic therapies shown to improve long-term survival by preventing or attenuating chronic left ventricular remodeling should be instituted or intensified before discharge from the hospital (Box 27.4).

Pharmacologic treatment of heart failure is aimed at achieving these goals by improving fluid balance and reversing the neurohormonal activation responsible for the progressive decline in left ventricular function. Therapy usually involves combinations of multiple medications. Several drugs have been shown to improve symptoms and functional capacity, decrease the need for repeated hospitalizations, and improve mortality. Careful serial assessment of patients is mandatory to guide pharmacologic therapy. In addition to assessment of symptoms, frequent assessment of weight, urinary output, blood pressure, cardiac rhythm, pulmonary rales, the presence of an S_3 gallop, jugular venous pressure, pulse oximetry, electrolytes, and renal function is mandatory.

• BOX 27.4 Goals of Therapy During Hospitalization for Acute Heart Failure

Clinical

1. Improve oxygenation, resolution of dyspnea and orthopnea
2. Decongestion: Effective diuresis, fluid weight loss, resolution of lung and peripheral edema

Laboratory

1. Normalized serum electrolyte levels
2. Optimized renal function
3. Reduce serum B-natriuretic peptide <30% from baseline

Hemodynamics

1. Reduce pulmonary capillary wedge pressure to <16 mm Hg
2. Reduce right atrial pressure <8 mm Hg
3. Optimize cardiac output, maintain systolic BP above 80 mm Hg

Improve Prognosis

1. Treat myocardial ischemia
2. Initiate guideline recommended pharmacologic therapy
3. Evaluation for device therapy (cardiac resynchronization, ICD)

TABLE 27.2 Loop Diuretics Used for the Treatment of Acute, Severe Heart Failure

Agent	Oral Dose (mg)	Initial Intravenous Dose (mg)	Maximum IV Bolus Dose (mg)	Continuous IV Dose (mg/h)
Bumetanide	0.5–2.0	1.0	4–8	0.5–2
Furosemide	20–80	40–80	160–200	5–40
Torsemide	10–40	10	100–200	5–20

Intravenous Diuretics

Although no randomized clinical trials exist, the use of loop diuretics is supported by a long history of clinical success. These agents increase renal excretion of salt and water. The onset of action of intravenous bolus furosemide is 30 minutes, with peak action at 1 to 2 hours. The half-life of the medication is 6 hours, so twice-daily dosing is usually required.[46] Other loop diuretics often used are bumetanide and torsemide (Table 27.2). Lower doses of loop diuretics are effective in patients with a new diagnosis of heart failure who are not using long-term diuretic therapy, but more aggressive initial diuretic dosing is recommended in patients with exacerbation of chronic heart failure to obtain effective pulmonary and systemic venous decongestion and to achieve more rapid symptom relief.[32,33] Subsequent dosing should be titrated to the response of the patient's fluid status and symptoms. Dosage reduction may be considered when clinical status improves. Hypokalemia, alkalosis, and hypomagnesemia are frequent side effects of loop diuretics and can potentiate the occurrence of arrhythmias, so electrolyte levels must be carefully monitored during aggressive diuretic therapy.

Several small clinical trials suggested that a constant infusion of a loop diuretic resulted in superior diuresis when compared with intermittent bolus dosing,[48,49] although other studies did not confirm this.[50] The Diuretic Optimization Strategies Evaluation (DOSE) trial (diuretic strategies in patients with acute decompensated heart failure) was a large, randomized controlled study performed in patients hospitalized with acute decompensated heart failure who

were taking a high dose of furosemide before admission. Patients were randomly assigned within 24 hours of admission to bolus dosing or constant infusion and were also randomly assigned to the usual daily outpatient dose (given intravenously) versus high dose (2.5 times the usual daily dose). No significant differences were noted in prespecified outcomes between bolus and infusion administration. However, the higher-dose group had better relief of dyspnea and more fluid and weight loss than the lower-dose group; 23% of the high-dose group had a significant deterioration in renal function, but at 60 days there was no difference in renal function between the two groups.[51]

An association between administration of high-dose loop diuretics and worse prognosis has been observed. There has been concern that this may be mediated by adverse renal effects and further activation of the RAAS by loop diuretics. However, in one retrospective analysis using propensity matching, hospital mortality was not different between low-dose and high-dose diuretic groups.[52] In another study, greater RAAS activation at baseline, as defined by higher levels of renin and aldosterone, was associated with worse initial heart failure status. However, higher diuretic doses did not correlate with further RAAS activation, and RAAS activation was not predictive of worse outcomes at 60 days.[53] In another study, daily furosemide doses of more than 160 mg were not associated with poorer outcomes after multivariate analysis and adjustment for disease severity.[54] Thus it is likely that poorer outcomes associated with high-dose diuretic are not due to the drug itself but reflect a greater severity of heart failure illness.[55]

The complex interaction of severe heart failure and WRF is called the *cardiorenal syndrome.* Up to 50% of patients hospitalized with heart failure demonstrate a glomerular filtration rate (GRF) less than 60 mL/min per m^2. WRF is often defined as a rise in serum creatinine of more 0.3 mg/dL or a 30% increase over baseline. This is seen in approximately one-third of hospitalizations for acute heart failure.[56] There is increasing evidence that the most common hemodynamic alterations that lead to WRF in heart failure are elevated systemic venous pressure and increased intraabdominal pressure.[57] In a retrospective study of patients with acute heart failure who had right heart catheterization, elevated central venous pressure was associated with reduced GFR and higher all-cause mortality. These findings were independent of the measured cardiac output.[58] Patients at particular risk for developing WRF are those with lower LVEF, lower blood pressure, diabetes mellitus, a history of hypertension, and older age. These patients have longer hospital stays and higher readmission and mortality rates. The best treatment strategy for these patients is not clear, as patients with significant renal impairment have generally been excluded from large randomized pharmacologic heart failure trials. Aggressive diuresis is often associated with WRF but is often necessary to relieve congestion. WRF is associated with worse outcomes only when accompanied by persistent congestion.[59] Indeed, poorer outcomes have been associated with failure to achieve adequate decongestion at hospital discharge, which may be present in 24% to 44% of patients. WRF with persistent congestion is associated with more severe hemodynamic abnormalities.[40,54,60]

Patients with chronic heart failure with or without renal dysfunction may exhibit resistance to loop diuretics, defined as an acute reduction in diuretic efficacy after repeated loop diuretic dosing. With chronic loop diuretic use, there is an increase in sodium reabsorption in the distal nephron and stimulation of aldosterone release. In edematous states there is delayed oral absorption of the drug. With renal dysfunction there may be reduced levels of drug delivered to the renal tubule. This resistance is associated with a poorer prognosis. Diuretics that act distally in the renal tubule, such as metolazone or hydrochlorothiazide, or aldosterone blockers such as spironolactone, can be added. Combination diuretic therapy induces a greater diuresis than simply increasing the dose of loop diuretic further. The response may be delayed for 48 to 72 hours. Combining diuretics often augments diuresis even in the setting of significant chronic kidney disease, and a good response can be expected in more than 70% of patients. Particular attention must be given to monitoring renal function and electrolytes when combination diuretic therapy is prescribed[61] (Table 27.3).

TABLE 27.3 Treatment of Refractory, Diuretic-Resistant Heart Failure

Supplemental Diuretic	Usual Dose
Hydrochlorothiazide	20–50 mg once or twice daily
Metolazone	2.5–5.0 mg once or twice daily
Spironolactone	12.5–50 mg once daily

Vasopressin Inhibitors

The use of vasopressin inhibitors has been evaluated in clinical trials of treatment of acute heart failure.[62] Vasopressin is a hormone synthesized in the hypothalamus; its major effect is to control free water clearance. It acts through V1a receptors in vascular smooth muscle and myocardium, leading to peripheral and coronary vasoconstriction, myocyte hypertrophy, and positive inotropy. Vasopressin also acts through V2 receptors at the renal tubule collecting ducts to cause free water retention and hyponatremia. Levels of vasopressin are increased in patients with chronic heart failure, and higher vasopressin levels correlate with worse heart failure severity. Vasopressin release is stimulated by changes in serum osmolality and cardiac output and leads to further vasoconstriction and retention of free water.[63,64] Inhibition of vasopressin's effects would have theoretic benefits in patients with heart failure. In contrast to loop diuretics, inhibition of vasopressin theoretically would not cause hypotension or neurohormonal activation and would not aggravate cardiac arrhythmias owing to electrolyte depletion.

Conivaptan is a vasopressin antagonist that inhibits V1a and V2 receptors. Tolvaptan and lixivaptan are antagonists selective for the V2 receptor. These medications increase urine volume and free water excretion, with a rise in the serum sodium concentration. The use of conivaptan in patients with class III-IV heart failure was associated with increased urine output, and decreases in PCWP and right atrial pressure, without changes in cardiac output.[4] Oral use of tolvaptan was associated with fluid loss and diuresis without change in heart rate, blood pressure, or serum creatinine. Hemodynamic effects of tolvaptan included rapid reduction in PCWP and right atrial pressure.[65]

In a large, multicenter, placebo-controlled randomized trial, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), tolvaptan was administered to patients hospitalized with heart failure. There were no adverse consequences on heart rate, blood pressure, or serum electrolytes and there was more rapid improvement in dyspnea and signs of heart failure compared with usual therapy. Hyponatremia improved. However, at 10 months' follow-up after hospitalization, there was no improvement in mortality or readmission rates.[66,67] A more recent trial in patients hospitalized with dyspnea caused by systolic

heart failure or HFpEF evaluated administration of 2 doses of 30-mg tolvaptan at 24 and 48 hours after hospital admission, compared with standard diuretic therapy. Despite greater fluid loss in the patients receiving tolvaptan, there was no improvement in dyspnea relief, and there was an increased risk for WRF. There also was no difference in posthospitalization outcomes.[68]

Currently tolvaptan is approved for treatment of heart failure if there is hypervolemia and severe hyponatremia (i.e., serum sodium < 125 mEq/L) or less severe hyponatremia if associated with symptoms and not responding to fluid restriction. Cases of severe liver injury have been reported. A course of therapy with tolvaptan should not exceed 30 days, and its use is contraindicated in patients with significant liver disease.

Parenteral Vasodilators (Table 27.4)

Intravenous vasodilator therapy is often added to diuretic therapy to obtain more rapid improvement in severe heart failure. There is limited controlled trial evidence on which to base recommendations for their use.[69] The Acute Heart Failure Global Registry of Standard Treatment (ALARM-HF) enrolled patients hospitalized with heart failure in eight countries. A retrospective analysis of unadjusted and propensity-matched data studied in-hospital mortality related to use of vasodilators. The adjusted data showed a lower in-hospital mortality when a vasodilator was combined with a diuretic, compared with diuretic therapy alone (hospital mortality 7.8% vs. 11.0%, $P = 0.016$).[70] In the European Society of Cardiology 2012 Heart Failure Guidelines, a IIa indication (level of evidence B) is given to intravenous nitrates administered for relief of dyspnea, whereas the ACC Foundation/AHA 2013 guidelines give a IIb indication (level of evidence A) to vasodilators.[5,22] A clear indication for vasodilators is acute pulmonary edema with severe hypertension. Their use should also be considered in patients who are not responding to intravenous diuretics combined with standard oral heart failure medications. Blood pressure response to these medications needs to be carefully monitored as hypotension is common. Improvement in hemodynamics has been obtained with aggressive intravenous vasodilator therapy using intravenous nitroprusside, intravenous nitroglycerin, or nesiritide. The choice of agents depends on matching the patient's clinical picture and hemodynamics with the predicted effects of each vasodilator.[71,72]

Nitroglycerin

Intravenous nitroglycerin is an effective systemic and coronary vasodilator. It is very useful in heart failure caused by acute coronary ischemia because it improves coronary blood flow. Intravenous nitroglycerin acts as a venodilator at lower doses, lowering preload and PCWP, thereby reducing pulmonary congestion, without increasing oxygen demand. It is also an arterial dilator at high doses, but it is less effective at reducing afterload than nitroprusside.[33] Dose ranges between 5 and 200 μg/min. Headache is a frequent side effect. A major limitation of the use of intravenous nitroglycerin is tachyphylaxis, the rapid development of tolerance to the drug's effect, which often occurs after only 24 hours of therapy. Prescribing a "nitrate-free" period during the daily dosage regimen has been advocated to limit the development of tolerance, but this is not feasible in patients receiving parenteral therapy. Nitrates have not been shown to improve long-term prognosis.

Nitroprusside

Intravenous sodium nitroprusside is a powerful venous and arterial dilator. It is a drug of choice in treating hypertension-related heart failure with pulmonary edema and severe heart failure owing to acute mitral regurgitation. The use of nitroprusside requires hospitalization in the ICU and invasive monitoring with a PA catheter and arterial line. This drug causes a significant reduction of afterload and preload, lowering right atrial pressure, systemic vascular resistance, mean systemic blood pressure and PCWP, and increased cardiac output in patients with heart failure owing to left ventricular systolic dysfunction. Limitations of nitroprusside use include inducing a coronary "steal" syndrome in patients with active coronary ischemia and facilitating pulmonary ventilation-perfusion mismatch.[46] Accumulation of the toxic metabolites thiocyanate and cyanide may occur with more prolonged administration in patients with renal or hepatic disease. The dosage range is 0.3 to 5.0 μg/kg per minute.

Nesiritide (B-Naturetic Peptide)

Human BNP manufactured by recombinant DNA technology is available as an intravenous medication, nesiritide, for heart failure therapy. BNP is a hormone produced by ventricular and atrial

TABLE 27.4 Hemodynamic Effects of Parenteral Vasodilators

	Nitroglycerin	Nitroprusside	Nesiritide
Starting dose	10–20 μg/min	0.3 μg/kg/min	
Infusion	May increase up to 200 μg/min	May increase up to 5 μg/kg per minute	0.01 μg/kg per minute
Right atrial pressure	Reduced	Reduced	Reduced
LV end-diastolic pressure	Moderately reduced	Moderately reduced	Mildly reduced
Mean arterial pressure	Reduced	Moderately reduced	Reduced
Systemic vascular resistance	Moderately reduced	Moderately reduced	Mildly reduced
Cardiac index	Increased	Increased	Increased
Other considerations	Headache common, tachyphylaxis common	Increased cyanide and thiocyanate levels with prolonged use	Cannot follow serum BNP level during use

BNP, B-natriuretic peptide; *LV*, left ventricular.

myocytes in response to stretch from cardiac chamber dilatation. Hemodynamic effects include venous and arterial dilation, coronary vasodilation, and natriuresis. Initial trials showed greater reduction in PCWP and right atrial pressure compared with intravenous nitroglycerin.[71] It is not proarrhythmic and does not induce tolerance.[73] It may potentiate the effects of loop diuretics. Significant hypotension may limit its use in some patients.[46] Because the hypotensive effects of nesiritide are less marked than those of nitroprusside, nesiritide can be used without invasive hemodynamic monitoring and can be initiated in emergency department settings. Nesiritide is initiated as an intravenous bolus dose of 2 μg/kg followed by infusion of 0.01 μ/kg per minute.

Nesiritide was compared with dobutamine in patients with severe heart failure. Nesiritide infusion was associated with less tachycardia and ventricular arrhythmia.[74] A meta-analysis of three randomized trials of nesiritide suggested a slight increase in mortality in patients given nesiritide versus a placebo control group, possibly mediated through an adverse effect on renal function.[75,76] A retrospective review of patients receiving intravenous vasoactive medications for acute heart failure indicated mortality rates, adjusted for clinical variables, were equivalent for patients receiving nitroglycerin or nesiritide. Patients who received intravenous nesiritide or intravenous nitroglycerin had a lower in-hospital mortality compared with patients who received dobutamine or milrinone.[77]

A randomized, placebo-controlled international study, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), was performed to evaluate the effect of nesiritide on relief of dyspnea, mortality, and renal function in patients hospitalized with acute heart failure; 7141 patients were enrolled. More than 90% of patients received loop diuretics and 15% received vasodilator therapy. Patients who received nesiritide had slightly better relief of dyspnea at 6 and 24 hours, although this did not meet a prespecified significant improvement in dyspnea score. There was no significant difference in hospital mortality, 30-day mortality, or death or rehospitalization at 30 days. There was no significant worsening of renal function in the nesiritide group. Hypotension was significantly more common in the nesiritide group (26.6%) compared with the control group (15.3%). The authors concluded that nesiritide was not useful for routine use in the management of patients with severe heart failure.[78] The Renal Optimization Strategies Evaluation (ROSE) trial evaluated the use of a low dose of nesiritide (0.005 μg/kg per minute) with diuretic therapy, compared to low-dose dopamine and diuretics alone, in patients with decompensated systolic heart failure. The study showed no improvement in urine volume, change in renal function (as measured by serum cystatin C level), or improvement in decongestion using nesiritide dosing strategy.[79] Nesiritide thus is used only in patients with acute decompensated heart failure to relieve dyspnea when more conventional therapies are ineffective.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are of limited use as parenteral therapy in patients with acute severe heart failure in the urgent setting. *Enalaprilat* is an intravenous bolus formulation that can be used in patients with chronic heart failure who are taking chronic oral ACE inhibitor therapy and who are unable to take oral medication. The maximal action occurs 1 to 4 hours after administration, with a six-hour duration of action.

Inotropic Drugs (see Table 27.5)

Dobutamine is a potent β_1-agonist. It also has β_2-agonist properties. Its major effects are increased myocardial contractility and increased cardiac output. It increases myocardial oxygen demand. It also has venodilator properties. At doses of 2.5 to 15 μg/kg per minute, dobutamine will lower systemic vascular resistance and PCWP and cause a slight increase in heart rate. It has rarely been associated with eosinophilia and fever.

In patients with heart failure, β-receptors may be chronically downregulated. Therefore the effects of dobutamine may be attenuated in patients with chronic heart failure. Dobutamine may be detrimental in patients with severe coronary artery disease or after myocardial infarction, as it increases myocardial oxygen demand and can aggravate ischemia and increase heart rate and induce arrhythmias.[74] Tolerance to the effects of dobutamine has been demonstrated in patients with infusions lasting more than 24 to 72 hours, theoretically owing to induction of β-receptor downregulation.[80] In studies of more prolonged dobutamine use, mean 14 days, a higher 6-month mortality

TABLE 27.5 Hemodynamic Effects of Inotropic Drugs and Vasopressors

	Dobutamine	Milrinone	Levosimendan	Dopamine	Norepinephrine
Bolus dose	No	25–75 μg/kg over 10–20 min	12 μg/kg over 10 min (optional)	No	No
Infusion dose	2–20 μg/kg per minute	0.375–0.75 μg/kg per minute	0.05–2.0 μg/kg per minute	3–10 μg/kg per minute	0.2–1.0 μg/kg per minute
Heart rate	Increased	Increased		Increased	Increased
Cardiac output	Increased	Increased	Increased	Increased	Increased
Systemic vascular resistance	Reduced at lower doses	Reduced	Reduced	Increased at higher doses	Increased
Other considerations	Increased myocardial oxygen demand, arrhythmia	Hypotension, arrhythmias, renal metabolism	Not available in United States, improved lusitropy, hypotension	Increased myocardial oxygen demand, arrhythmia	Administer via central venous access, increased myocardial oxygen demand

was observed with dobutamine when compared with a vasodilator, without improvement in quality of life.[81]

Milrinone is an inhibitor of myocyte phosphodiesterase. This leads to increased intracellular cyclic adenosine monophosphate and calcium. It is a noncatechoamine inotropic agent that acts "downstream" from the β-receptor, so it is more useful than dobutamine in patients being treated with β-blockers. It may improve diastolic function. Hemodynamic effects include reduction of right atrial pressure and vasodilation with reduction in pulmonary and systemic vascular resistance. In heart failure, stroke volume and cardiac output are increased with a slight fall in mean systemic arterial pressure. Milrinone acts as a coronary vasodilator, and there is no net increase in myocardial oxygen consumption. Arterial blood pressure and PCWP tend to be lowered more than with dobutamine, and milrinone's action is more prolonged. There is no tolerance or attenuation of its effect. Milrinone is started as an infusion at 0.125 μg/kg per minute, avoiding bolus doses, with a maintenance infusion of 0.375 to 0.75 μg/kg/minute. It is cleared through the kidneys, so doses need to be reduced in patients with renal disease. Its use is limited in patients with hypotension or severe kidney disease.

Levosimendan is available for use in Europe but not in the United States. It is an inotropic drug that acts by enhancing sensitivity of troponin C to calcium. It also improves diastolic function and has vasodilator properties. Initial dose is 0.1 μg/kg per minute, which can be increased to 0.4 μg/kg per minute over 4 hours. In one trial, levosimendan was associated with more short-term clinical improvement compared with placebo, but with more hypotension and arrhythmias and without improvement in 90-day mortality.[82] Another trial compared levosimendan use to dobutamine and found no difference in 180-day mortality and no improvement in other secondary outcomes.[83]

The choice of milrinone versus dobutamine depends on specific clinical circumstances. Dobutamine tends to cause a slight rise in heart rate and has little effect on mean arterial pressure, whereas milrinone often lowers systemic arterial pressure owing to more prominent lowering of systemic vascular resistance.[84–86] Patients who do not respond to dobutamine may have a favorable response to milrinone. In the setting of acute heart failure, milrinone is used more often than dobutamine in view of its more potent vasodilator properties. In addition, its effects are not primarily mediated through β-receptors, which is an important consideration in patients receiving concomitant β-blocker therapy. However, dobutamine has a much shorter half-life than milrinone, so dobutamine-induced hypotension can be more rapidly reversed by discontinuing the drug.

Vasopressors (Table 27.5)

Dopamine effects include vasodilation and increased renal blood flow at low doses, 1 to 3 μg/kg per minute, via stimulation of dopaminergic receptors. At moderate doses, 3 to 10 μg/kg per minute, increased myocardial contractility and increased heart rate are seen via stimulation of β-receptors. High-dose dopamine, 10 to 20 μg/kg per minute, is associated with vasoconstriction owing to α-adrenergic activation.[81] Dopamine is a less useful agent for treatment of heart failure because it causes tachycardia, coronary vasoconstriction, increased afterload, and increased oxygen consumption. Dobutamine generally will lead to a greater rise in cardiac output than dopamine in systolic heart failure. Dopamine can be used when significant hypotension is present and it is necessary to restore adequate arterial pressure for end-organ perfusion. Although dopamine at low doses had been advocated to be used as add-on therapy to inotropic agents in an attempt to increase renal blood flow and augment diuresis, no controlled trials have demonstrated significant improvement in heart failure outcomes with this strategy. The ROSE trial demonstrated no improvement in urine output, decongestion, or protection of renal function in heart failure patients treated with "renal dose" dopamine, 2 μg/kg per minute.[79] No significant benefit of low-dose dopamine has been shown in preventing acute renal failure in high-risk patients or in the treatment of established renal failure.[80]

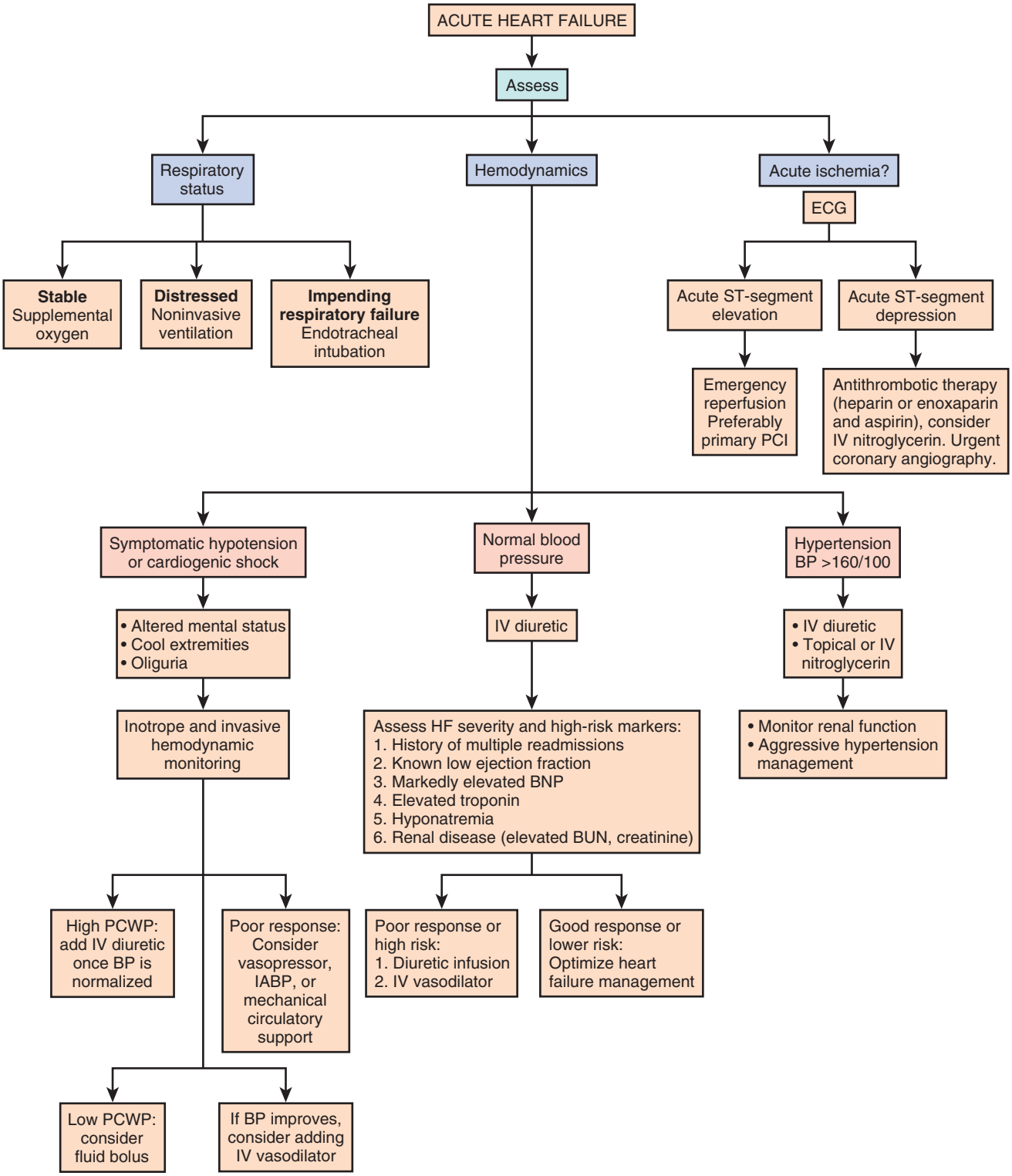
Norepinephrine is a sympathomimetic agent with strong α-agonist and weaker β-agonist effects. In patients with heart failure, the main effect of norepinephrine is to raise blood pressure by causing vasoconstriction with little effect on cardiac output. It will increase inotropy somewhat and increase myocardial oxygen demand. Its use in the setting of heart failure is restricted to patients with the most severe hypotension, unresponsive to dopamine, or in patients with complicating illnesses such as sepsis.[80] Norepinephrine should be weaned and discontinued as early as possible. The dosage range is 0.2 to 1 μg/kg per minute.

Norepinephrine and dopamine were compared in a randomized, controlled trial of 1679 patients with shock, 280 (16.7%) of whom had cardiogenic shock. In the entire group, there was no difference in survival at 28 days if patients were treated with norepinephrine or dopamine. However, in a predefined subgroup analysis of patients with cardiogenic shock, dopamine use was associated with a significantly increased mortality. In addition, in the entire group, dopamine was associated with significantly higher rates of arrhythmia, especially atrial fibrillation (24% vs. 12.4% with norepinephrine), which led to stopping the vasopressor more frequently. There was also a higher rate of severe arrhythmia with dopamine (6.1%) compared with norepinephrine (1.6%).[87] Based on the results of this study, norepinephrine is the preferred vasopressor in patients with cardiogenic shock.

An algorithm for the approach to the evaluation and therapy of acute heart failure is presented in Fig. 27.6.

Considerations Regarding the Use of Inotropes and Vasopressors

There is clear evidence that inotropic drugs are associated with more coronary ischemia, more arrhythmia, poorer outcomes, and increased mortality. Several clinical studies that evaluated the usefulness of routine inotropic therapy, comparing milrinone or dobutamine with placebo, showed no evidence for improved short-term or medium-term outcomes with inotropic therapy. In fact, the use of inotropic agents has been consistently associated with a *worse* prognosis for survival.[46] In the Flolan International Randomized Survival Trial (FIRST) study of patients with class III–IV heart failure, an average 14-day infusion of dobutamine was associated with an increased risk of morbid events and higher short-term mortality.[88] The use of a 48-hour infusion of milrinone was evaluated as routine therapy in patients admitted with class III–IV heart failure, when inotropic therapy was not considered essential. In The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) when compared to standard therapy without milrinone, no improvement in symptom relief, hospital length of stay, or rehospitalization rate within 60 days was demonstrated. Milrinone was associated with more hypotension and atrial arrhythmia than placebo, without improvement in short-term or 60 day mortality.[86] The ALARM-HF registry showed that adjusted in-hospital mortality was 1.5 times higher in patients treated with dobutamine or



• **Fig. 27.6** Algorithm for the treatment of acute heart failure. *BP,* Blood pressure; BNP, *B-natriuretic peptide; BUN, blood urea nitrogen; ECG,* electrocardiogram; *HF,* heart failure; *IABP,* intraaortic balloon pump; *IV,* intravenous; *PCI,* percutaneous coronary intervention; *PCWP,* pulmonary capillary wedge pressure. (Adapted from Pang PS. Acute heart failure syndromes. *Emerg Med Clin North Am.* 2011;29:675–688.)

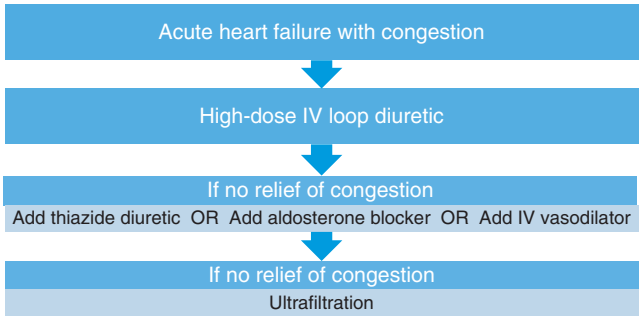
dopamine and 2.5 times higher in patients treated with norepinephrine. Levosimendan therapy had a minimally higher mortality.[70] These negative outcomes with inotropic agents are thought to be related to their propensity to stimulate sympathetic nervous system activation, increase myocardial oxygen demand, aggravate myocardial ischemia, increase the risk of serious cardiac arrhythmias, and cause myonecrosis by stimulation of chronic hibernating myocardium.

Therefore inotrope use is limited to patients in a critical care unit who have symptomatic low cardiac output and hypotension owing to reduced left ventricular systolic function and signs of end-organ hypoperfusion or cardiogenic shock.[81,89] If use of an inotrope is necessary, the shortest duration of therapy should be attempted (i.e., <72 hours) or the addition of MCS should be considered. Patients with end-stage heart failure may become inotrope-dependent, when weaning the drug leads to aggravation of the heart failure syndrome. Inotropes can be used as a bridge to heart transplantation or MCS. ACC/AHA guidelines for evaluation and management of chronic heart failure indicate that long-term intermittent infusions of a positive inotropic drug as therapy for symptomatic systolic dysfunction is *contraindicated.*[5] Continuous inotrope infusion can also be recommended for palliation of symptoms in patients with refractory end-stage heart failure (stage D). These patients will have been deemed poor candidates for advanced therapies such as MCS or heart transplantation. In this setting, quality of remaining life takes precedence over prolonging life. In one report of patients with refractory end-stage heart failure, median survival of patients receiving continuous inotrope infusion was 3.4 months, with 26% of patients surviving to 6 months.[90] The decision to use inotropic agents in this circumstance is one that should be carefully individualized.

Ultrafiltration

Venovenous ultrafiltration has been advocated for use in treating severe heart failure. This process removes iso-osmolar extracellular fluid via a convection process and is not associated with changes in serum electrolytes.[91] Newer ultrafiltration systems use peripheral arm veins without the need for central venous access. Systemic anticoagulation is necessary. In a pilot study of 40 patients admitted with heart failure, usual care for heart failure with diuretic therapy was compared with usual care combined with ultrafiltration. At 24 hours, average fluid loss with diuretic therapy was 2838 mL compared with 4650 mL with ultrafiltration. Weight loss and improvement in dyspnea was similar with the two therapies. Ultrafiltration was not associated with significant changes in heart rate or blood pressure.[92]

More recent larger trials have failed to demonstrate long-term survival benefit or renal sparing effects with ultrafiltration. The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial investigated the use of ultrafiltration compared with intravenous diuretic therapy in 200 patients admitted with acute decompensated heart failure. Ultrafiltration was associated with more rapid weight loss and fluid loss. At 90 days, there were fewer rehospitalizations for heart failure in the ultrafiltration group, without change in mortality. There was no difference with respect to renal function in the 2 groups.[93] In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, patients with acute decompensated heart failure, worsening renal function, and persistent congestion were treated with either ultrafiltration for 28 to 67 hours or aggressive diuretic therapy. No advantage was seen with ultrafiltration. Primary endpoint analysis showed that ultrafiltration was associated with a slight worsening of renal function, significantly more than with diuretic therapy. Fluid weight loss was similar in the two groups. Serious adverse events were common in both groups but slightly more frequent in the ultrafiltration group (72% vs. 57%, $P = 0.03$).[94]



• **Fig. 27.7** A systematic approach to decongestion therapy. *IV,* Intravenous.

Additional factors to consider are the higher cost, need for anticoagulation, potential vascular access complications, and greater nursing training and support with ultrafiltration.[40,95] Current ACC heart failure guidelines give a IIb recommendation (level of evidence B) for ultrafiltration in patients with severe heart failure for the relief of severe congestion.[5] It should not be used routinely as a substitute for diuretics. European Society of Cardiology guidelines also give a IIa indication for ultrafiltration in the setting of refractory volume overload in the setting of acute kidney injury.[22] A systematic approach to decongestion therapy is presented in Fig. 27.7.

Transition to Chronic Pharmacologic Therapy for Severe Heart Failure

After improvement in acute heart failure status is achieved, drug regimens for treating chronic heart failure are initiated and optimized, depending on the etiology of heart failure. The medical treatment of chronic systolic heart failure is based on results of many large, randomized, placebo-controlled trials (see following text). Long-term prognosis is directly related to reduction in left ventricular size, improvement in left ventricular systolic function and restoration of more normal left ventricular geometry, a process called "reverse remodeling." Optimal drug regimens combining several classes of medication help to achieve these ends by reversing the neurohormonal activation responsible for left ventricular remodeling and progressive decline in left ventricular function. Clinical goals of medical therapy include improved survival, reduction in the rate of rehospitalization, and improvement in functional capacity, exercise tolerance, and quality of life. It has been shown that initiating these medical therapies while patients are in the hospital improves long-term adherence.

Oral Diuretic Therapy (Table 27.6)

Loop diuretics are routinely used in patients with signs or symptoms of fluid retention. Diuretics are continued even after patients are euvolemic to prevent reaccumulation of fluid and symptoms of congestion. A flexible dosing schedule, based on daily weights, assessment of symptoms, and close telephone contact with a heart failure treatment team member, can be very effective in maintaining a euvolemic state while reducing the frequency of side effects.

TABLE 27.6 Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
Loop Diuretics			
Bumetanide	0.5–1.0 mg once or twice	10 mg	4–6 h
Furosemide	20–40 mg once or twice	600 mg	6–8 h
Torsemide	10–20 mg once	200 mg	12–16 h
Thiazide Diuretics			
Chlorothiazide	250–500 mg once or twice	1000 mg	6–12 h
Chlorthalidone	12.5–25 mg once	100 mg	24–72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6–12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12–24 h
Potassium-Sparing Diuretics			
Eplerenone	12.5 mg once	20 mg	24 h
Spironolactone	12.5–25 mg once	50 mg[a]	2–3 days
Triamterene	50–75 mg once	200 mg	7–9 h

[a]Higher doses may occasionally be used with close monitoring of serum creatinine and potassium levels.

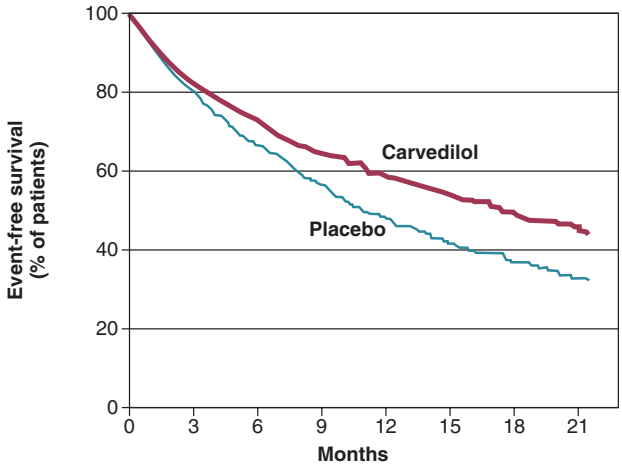
Modified from Hunt S, Abraham WT, Chin M, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article. A report on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society of Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. *Circulation. 2005*;112:1825–1852.

Furosemide is the most common loop diuretic used. Bumetanide or torsemide may be helpful in patients with suboptimal responses to furosemide owing to their more consistent absorption after oral administration. Metolazone or a thiazide diuretic can be used in addition to a loop diuretic in patients with more severe heart failure because of their synergistic effects. Patients must be periodically monitored for side effects of these agents, including azotemia, hypokalemia, alkalosis, hyponatremia, and hypomagnesemia.

β-Blockers

Catecholamine levels are increased in heart failure, and higher levels correlate with worse disease severity. Catecholamines have direct negative effects on the myocardium, including induction of myocyte hypertrophy and apoptosis.[10] Clinically these effects are evident as left ventricular dilation, increased ischemia, peripheral vasoconstriction, and arrhythmia. β-Blockers interfere with catecholamine-mediated activation of cardiac β-receptors, and thereby attenuate β-receptor–mediated increases in heart rate and oxygen consumption. Sympathetic nervous system–mediated effects on remodeling can be prevented or attenuated. In addition, carvedilol blocks β-receptors and α-receptors, which mediate vasoconstriction and increased cardiac contractility.

Multiple large trials using β-blockers in thousands of patients with chronic heart failure, or in post–myocardial infarction patients with reduced LVEF, have demonstrated significant and consistent improved survival and reductions in the need for repeat rehospitalization for heart failure. The Beta-Blocker Heart Attack Trial (BHAT) showed a relative 26% reduction in mortality at 2 years in post–myocardial infarction patients treated with propranolol.[96,97] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial using bisoprolol showed a 34% relative risk reduction at 16 months of therapy in the combined endpoint of hospitalizations and mortality.[98] The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) study showed a relative reduction of 33% in these endpoints at 12 months using metoprolol succinate.[99] Patients with more severe heart failure, symptom class III-IV, with severely reduced ejection fractions (< 25%) were studied in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. These patients began therapy with carvedilol during hospitalization. At mean follow-up of 10.4 months, a 35% relative mortality reduction was seen, with improvement in mortality beginning as early as 3 weeks after initiation of therapy (Fig. 27.8).[100]



No. of Patients at Risk

Placebo	1133	767	513	377	262	154	88	55
Carvedilol	1156	789	559	431	318	208	122	81

• **Fig. 27.8.** All-cause mortality rate in patients with class III to class IV heart failure, ejection fraction less than 25%, demonstrating significant survival benefit with carvedilol. (Redrawn from Packer M, Coats A, Fowler M, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344:1651-1658.)

In these trials, β-blockers were well tolerated, with a frequency of side effects not different from placebo; there was also no increased risk of heart failure exacerbation owing to β-blocker therapy even in the early phases of drug administration.[101] Trials have shown an approximate 6% absolute increase in LVEF after 2 years of therapy with carvedilol.[102]

The specific β-blockers recommended as supported by clinical trial evidence are metoprolol succinate, bisoprolol, and carvedilol. They should be initiated once patients are stable and euvolemic. Doses should be titrated up to maximal recommended doses (e.g., metoprolol succinate 200 mg daily or carvedilol 25 mg bid) or maximally tolerated doses as heart rate and blood pressure permit. They are useful in patients with both ischemic and nonischemic cardiomyopathy. β-Blockers are recommended for left ventricular dysfunction even in the absence of symptoms (stage B patients) and in patients who appear compensated and stable while not using this medication, as these patients have a high likelihood of disease progression to symptomatic heart failure within 12 months. This therapy should be combined with other recommended heart failure pharmacologic therapy. Contraindications to β-blocker use include severe bradycardia or bronchospastic lung disease (Table 27.7).

For patients who are already using β-blocker therapy and who are hospitalized with acute decompensation of heart failure, β-blocker therapy should be continued unless hypotension, shock, severe bradycardia, or advanced heart block is present. In patients with a severe heart failure exacerbation, temporary reduction of the chronic dose by 50% can be considered. Discontinuation of this medication has been associated with higher short-term mortality and more frequent rehospitalizations for heart failure in observational studies.[103] In a meta-analysis of 6 trials that included 2554 patients, stopping β-blocker therapy was associated with an increased risk of in-hospital mortality (relative risk 3.72) and mortality at 6 months (relative risk 1.78)[104] (Fig. 27.9). If β-blockers are temporarily withheld, they should be reinstituted before discharge unless there are ongoing specific contraindications, as patients who are not using this drug at hospital discharge tend to not have it resumed at subsequent outpatient visits.[105,106]

TABLE 27.7 Treatment for Patients With Heart Failure and Low Ejection Fraction

Drug	Initial Dose	Target Maximal Dose
β-Blockers		
Metoprolol succinate	25 mg daily	200 mg daily
Carvedilol	3.125 mg bid	25 mg bid
Bisoprolol	1.25 mg daily	10 mg daily
ACE Inhibitors		
Captopril	6.25 mg tid	50 mg tid
Lisinopril	2.5 mg daily	40 mg daily
Enalapril	2.5 mg bid	20 mg bid
Ramipril	2.5 mg daily	10 mg daily
Angiotensin Receptor Blockers		
Losartan	25 mg daily	100 mg daily
Valsartan	40 mg bid or 80 mg daily	160 mg bid or 320 mg daily
Candesartan	4 mg daily	32 mg daily
Aldosterone Antagonists		
Spironolactone	12.5 mg daily	50 mg daily
Eplerenone	12.5 mg daily	50 mg daily
ARNI		
Valsartan/sacubitril	24/26 mg bid	97/103 mg daily
Hydralazine + isosorbide dinitrate	37.5 mg + 20 mg tid	75–100 mg + 40 mg tid
Selective Sinus Node Inhibitor		
Ivabradine	5 mg bid	7.5 mg bid

ACE, Angiotensin-converting enzyme; *ARNI*, angiotensin receptor blocker valsartan plus the neprilysin inhibitor sacubitril; *bid*, twice a day; *tid*, three times a day.

Angiotensin-Converting Enzyme Inhibitors

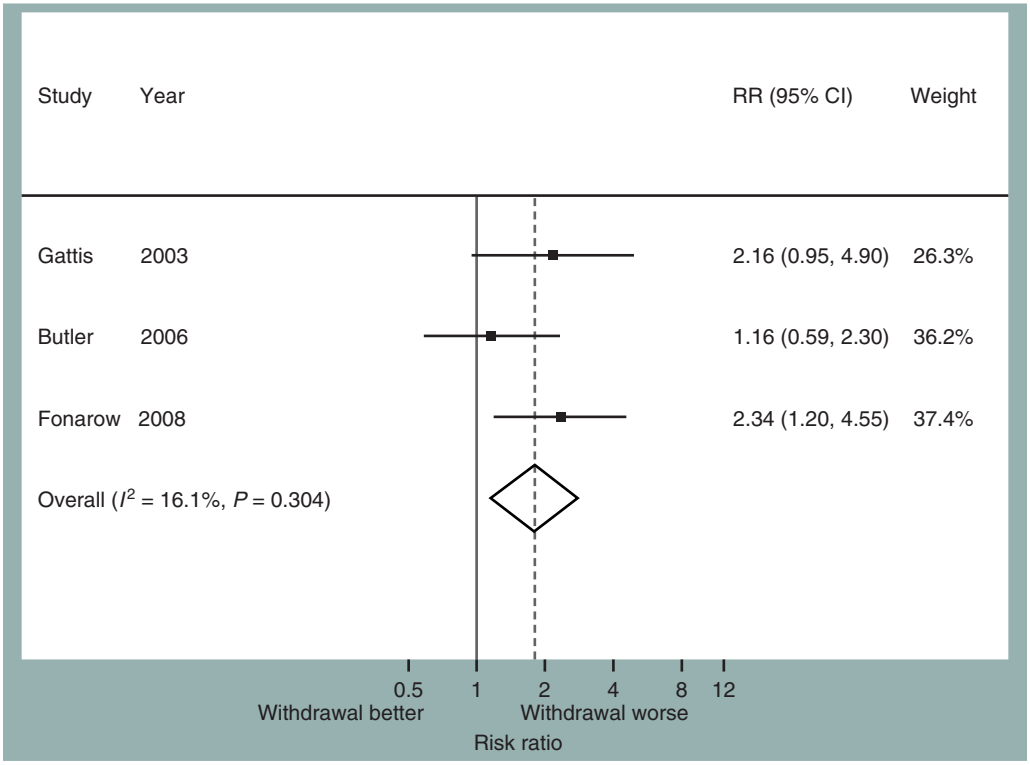
Many studies have shown benefits of ACE inhibitor therapy in post–myocardial infarction patients as well as patients with cardiomyopathy and heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) trial using enalapril in patients with class II-III heart failure and LVEF below 35% showed a 10% relative risk reduction in mortality at 3.5 years.[107] Enalapril given to patients less ill, with asymptomatic left ventricular dysfunction (ejection fractions <35%) in the companion SOLVD trial showed a reduction in the clinical diagnosis of heart failure and a statistically significant reduction in heart failure hospitalizations at 3 years.[108] A meta-analysis performed of 32 trials, involving 7105 patients, using captopril, enalapril, ramipril, quinapril, or lisinopril found that ACE inhibitors reduce the risk of death and hospitalization caused by heart failure.[109] These results indicate that the positive effects of ACE inhibitors are likely to be a class effect and not specific to a particular agent (see Table 27.7).

Side effects of these agents include cough, WRF in patients with underlying renal disease or renal artery stenosis, angioneurotic edema, and hyperkalemia. The dose of ACE inhibitors should be increased as renal function and blood pressure allow. Studies have shown that medium doses of ACE inhibitors, compared with low doses, significantly reduce hospitalization rates for heart failure. However, higher doses given routinely do not significantly reduce cardiovascular events further.[110] Additional improvement in symptoms and mortality is thus best achieved by adding β-blocker and other heart failure therapy rather than increasing ACE inhibitors to the highest doses.[111]

Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) work to counter the effects of angiotensin II at the tissue level by blocking angiotensin II receptors. Multiple studies have shown benefits of these medications in patients with heart failure. Large numbers of patients in controlled trials have been studied, and these drugs have been as well studied as the ACE inhibitors. Trials included use of ARBs as a substitute for ACE inhibitors or in combination with ACE inhibitors and β-blockers.

The RESOLVD trial, using candesartan in heart failure patients with a mean ejection fraction of 27%, showed equivalent mortality rates and similar exercise tolerance and functional class to patients treated with enalapril at 3.5 years.[112] The Evaluation of Losartan in the Elderly II (ELITE II), a study using losartan compared with captopril in patients with ejection fractions less than 40%, showed no difference in mortality or congestive heart failure admissions. Losartan was better tolerated because of the lower incidence of problematic cough.[113] The Valsartan Heart Failure Trial (Val-HeFT



• **Fig. 27.9** Discontinuation of β-blockers was associated with a significantly increased risk of death. (From Prins KW, Neill JM, Tyler JO, et al. Effects of Beta-blocker withdrawal in acute decompensated heart failure: a systematic review and neta-analysis. *JACC Heart Fail.* 2015;3:647–653.)

2001) showed that valsartan as a substitute for ACE inhibitor therapy was associated with a relative 33% risk reduction in mortality when compared with placebo.[114] In the Candesartan in Heart failure-Assessment of moRtality and Morbidity (CHARM) study, candasartan was prescribed for patients with ejection fractions less than 40%. A 17.5% relative risk reduction in cardiovascular death and congestive heart failure admissions was seen when this ARB was used as a substitute for ACE inhibitors.[115] When candesartan was added to therapy with ACE inhibitors and β-blockers, a small 10% relative risk reduction in rehospitalizations was seen without improved mortality[116] (see Table 27.7).

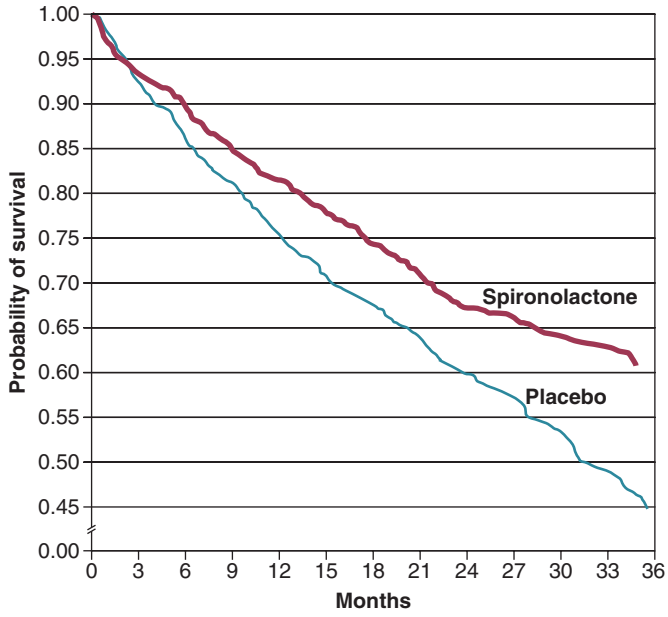
ARBs are an appropriate choice for patients who cannot be maintained with ACE inhibitors because of side effects such as cough. Patients with angioneurotic edema during ACE inhibitor therapy can often be successfully treated with ARBs without developing this complication.[117] Adding ARB therapy to ACE inhibitors and β-blockers is not generally recommended, and only small additional benefit may be achieved with a greater risk of renal dysfunction and hyperkalemia.

Combination Angiotensin Receptor-Neprilysin Inhibitor

Sacubitril is an inhibitor of the neutral peptidase called neprilysin, which degrades and inactivates the natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of the actions of neprilysin results in greater activity of these vasoactive peptides, causing vasodilation and reduced sodium retention in patients with heart failure. A trial of 8442 patients with class II, III, and IV systolic heart failure with LVEF less than 40% compared enalapril with the combination of the ARB angiotensin receptor blocker valsartan plus the neprilysin inhibitor sacubitril (ARNI). Patients had to be able to tolerate the medication during a run-in phase before enrollment. After 27 months of therapy, treatment with ARNI was associated with an absolute reduction in the primary endpoint of all-cause mortality and hospitalization for heart failure by 4.7% (26.5% compared with 21.8%, $P < 0.001$). The rates of all-cause death and death from cardiovascular cause were also significantly reduced by ARNI.[118] In the updated ACC/AHA/Heart Failure Society of American 2016 Heart Failure Guidelines, use of ARNI in place of ACE inhibitors or ARBs was given a class I indication for patients with chronic systolic heart failure to reduce symptoms and improve mortality. A class I indication is also given for ARNI as a replacement of ACE inhibitor or ARB therapy in patients with chronic symptomatic systolic heart failure, functional class II or III, to further reduce morbidity and mortality. When switching from an ACE inhibitor to ARNI, a washout period of at least 36 hours is indicated to prevent the occurrence of angioedema, which is common with concomitant use of ARNI and ACE inhibitors. ARNI should not be administered to patients with a history of angioedema.[119] If heart failure biomarkers are being followed during ARNI therapy, NTpro-BNP should be used as BNP levels rise as a result of this therapy.

Aldosterone Antagonists

Aldosterone antagonists counteract the salt and water retention caused by aldosterone. In addition, aldosterone is considered to be involved in the progressive myocardial fibrosis that occurs as part of the remodeling process. In the Randomized Aldactone



No. at risk

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

• **Fig. 27.10** Kaplan-Meier analysis of the probability of survival among patients in the placebo group and patients in the spironolactone group, treated for class III to class IV heart failure and left ventricular dysfunction. The risk of death was 30% lower among patients in the spironolactone group than among patients in the placebo group ($P < 0.001$). (Redrawn from Pitt B, Zannad F, Remme W, et al The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med.* 1999;341:709–717.)

Evaluation Study (RALES), the aldosterone antagonist spironolactone was given to patients with severe, class III-IV heart failure with ejection fraction below 35%. A 24% relative risk reduction in mortality was seen in treated patients over 2 years, with reduced cardiovascular death and reduced need for rehospitalization[120] (Fig. 27.10). Thus these agents are effective at improving outcomes in patients with the most severe chronic heart failure. Aldosterone antagonists are contraindicated in patients with renal insufficiency and creatinine levels above 2.5 mg/dL (or GFR <30 mL/min) or in patients with baseline potassium levels above 5.0 mmol/L. Spironolactone should be initiated at low doses, such as 12.5 mg daily or every other day, especially in elderly patients.

An analysis of a large Canadian health care database showed a substantial increase in the frequency of spironolactone use after the RALES trial was published. This increased use was temporally associated with a twofold to threefold increased rate of hospitalization for hyperkalemia.[121] This highlights the need for careful monitoring of serum electrolytes after aldosterone blockers are initiated.

Eplerenone is an aldosterone blocker similar to spironolactone except that it has fewer antiandrogen effects and thus is free of the side effect of gynecomastia in men. It has been found effective in treating heart failure after AMI (see later text). It was subsequently tested and found to be very effective in patients with chronic heart failure. In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study, a placebo-controlled randomized study of 2737 patients with LVEF below 35% and class II heart failure, eplerenone was added to therapy with ACE inhibitors and β-blockers at a target dose of 25 to 50 mg daily. Mean follow-up was 21 months. Eplerenone reduced the occurrence of the primary endpoint of cardiovascular death plus hospitalization for heart failure from 25.9% to 18.3% ($P < 0.001$), with improvement in other clinical endpoints. Serious hyperkalemia that necessitated drug discontinuation occurred in only 1.1% of patients.[122]

Aldosterone blockade appears to result in beneficial effects in heart failure independent of its potassium-sparing and diuretic effects.[123] Aldosterone blockers are an important therapy for heart failure and should be routinely added to ACE inhibitors and β-blockers in patients with symptomatic heart failure with low LVEF (see Table 27.7).

Combination Hydralazine/Isosorbide Dinitrate

Combination therapy with the vasodilators hydralazine and isosorbide dinitrate (ISDN) was associated with improvement in mortality when compared with placebo in one study in the era preceding the advent of ACE inhibitors and β-blocker therapy for heart failure.[123] A retrospective analysis of this study suggested that African American patients may have benefited preferentially. To evaluate this finding prospectively, the African-American Heart Failure Trial (A-Heft) study enrolled more than 1000 self-described African American patients with class II-IV heart failure and ejection fractions below 45%. The use of the combination of hydralazine with ISDN, titrated to a dose of 75 mg hydralazine plus 40 mg ISDN given 3 times daily, was associated with a 40% relative risk reduction in mortality at 10 months and a 33% relative risk reduction in first hospitalization for heart failure. This therapy was added to treatment with β-blockers, ACE inhibitors, and spironolactone.[124] Hydralazine-ISDN is approved for treatment of African American patients with heart failure and left ventricular systolic dysfunction.

Digoxin

Digoxin is a relatively weak inotropic agent. It works by inhibiting the myocyte sarcolemmal sodium-potassium pump, leading to increased intracellular calcium levels and increased inotropy. It also has vagotonic effects.[81] The use of digoxin in heart failure was studied in large numbers of patients in sinus rhythm and LVEF <45% in the Digitalis Investigation Group (DIG) trial. A decreased

need for rehospitalization for heart failure was seen with this therapy. However, there was no improvement in overall mortality.[125] A post hoc analysis of this data concluded that patients with lower serum digoxin levels (0.5–0.9 ng/dL) did have lower mortality and lower rates of heart failure hospitalization when compared with those with levels above 1.2 ng/mL.[126] Serum digoxin levels should be obtained more than 6 hours after a dose. It is hypothesized that lower digoxin doses may have beneficial neurohormonal (sympatholytic) effects without the detrimental effects of inotropic stimulation. Another post hoc analysis of the DIG trial results suggested that women (who made up 22% of the study population) assigned to treatment with digoxin had a higher cardiovascular and heart failure mortality compared to those assigned to placebo.[127]

Digoxin is indicated only for patients with symptomatic heart failure, stages C and D, to reduce the rate of hospitalization and not to improve mortality.[5] It is also useful in heart failure patients with atrial fibrillation to help control the ventricular rate. Digoxin is not useful in the setting of acute heart failure, and it should be avoided in patients with hypokalemia, bradycardia, or heart block.

I_f Channel Blocker

Ivabradine is a selective sinus node inhibitor that works via the I_f channel to slow heart rate. It has no effect on atrioventricular node conduction or myocardial contractility. Epidemiologic studies have shown that in patients with chronic heart failure a higher resting heart rate is associated with increased mortality. Therefore ivabradine was used to treat 6505 patients with chronic heart failure, mostly functional class II and III, with LVEF below 35% and in sinus rhythm with resting heart rate above 70 beats/min. This therapy was in addition to β-blockers and RAAS inhibition. At 2 years, treatment with ivabradine significantly reduced heart failure hospitalizations (from 21% to 16%), with a slight reduction in heart failure deaths (5% to 3%, not statistically significant). Average heart rate reduction with this medication was 15 beats/min. These results support the hypothesis that reducing resting heart rate is an important therapeutic goal in patients with chronic systolic heart failure.[128] The 2016 ACC Foundation/AHA guidelines give a IIa indication for the use of ivabradine to reduce heart failure hospitalizations for patients with symptomatic stable chronic systolic heart failure.[119]

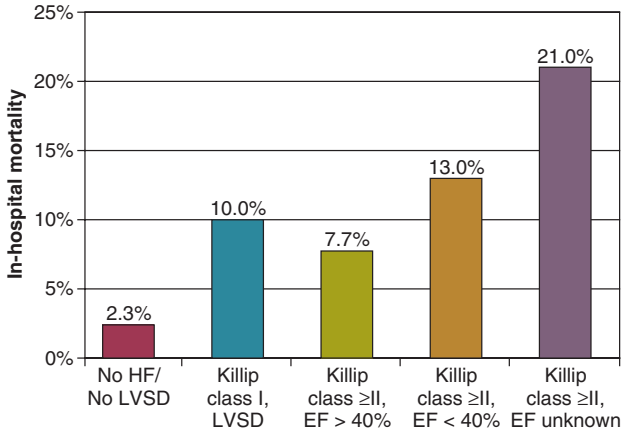
Acute Coronary Syndromes and Acute Heart Failure: Special Considerations

Coronary artery disease can lead to acute heart failure via several different mechanisms. (1) Acute ischemia leads to impaired myocardial relaxation, acute diastolic dysfunction, and sudden elevation of left ventricular filling pressure. (2) Acute ischemia can cause "stunning," defined as myocardial dysfunction caused by severe, prolonged ischemia without infarction. After normal blood flow is restored, normal function recovers in days or weeks. (3) AMI and necrosis lead to acute left ventricular systolic dysfunction owing to loss of contractile tissue. (4) Mechanical complications of AMI include acute, severe mitral regurgitation and papillary muscle ischemia, infarction, and rupture. Another mechanical complication is infarction and rupture of the interventricular septum with acute left-to-right shunting. (5) AMI involving the right ventricle causes acute right ventricular heart failure. (6) Chronic ischemia can cause myocardial dysfunction that can be reversed with revascularization, a process termed "hibernation."

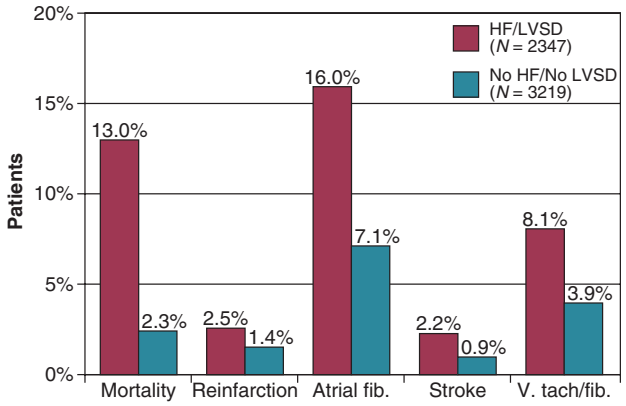
Acute myocardial ischemia is often superimposed on a ventricle impaired by chronic ischemia and infarction, so that multiple mechanisms are often present in patients with chronic coronary disease presenting with acute heart failure.[129] Acute heart failure may develop even without evidence for significant left ventricular systolic dysfunction on echocardiography and without acute necrosis documented by myocardial enzyme determinations. With effective therapy, the majority of patients with heart failure owing to an acute coronary syndrome do not have left ventricular systolic dysfunction at discharge, and only a minority will develop chronic heart failure.

In a European observational study of acute heart failure complicating acute coronary syndromes (ACS), in patients without previous history of heart failure, 13% of ACS patients presented with heart failure on admission.[130] Heart failure developed later during hospitalization in an additional 5.6% of patients. The incidence of acute heart failure of 15.6% was identical in patients with ST-segment elevation myocardial infarction (STEMI) and non–STEMI. Eight percent of patients with unstable angina developed heart failure.

Acute heart failure accompanying ACS identifies patients who are at high risk for adverse outcome. In-hospital mortality and postdischarge morbidity and mortality are worse. In a large registry of patients with AMI, event rates, therapies, and outcomes between 1996 and 2008 were analyzed. The overall incidence of heart failure in ACS declined from 46% in 1996 to 28% in 2008. In the most recent years, incidence of heart failure was identical if patients presented with STEMI or nSTEMI. In 2008, in-hospital mortality and 30-day mortality were 17% and 31%, respectively. 30% of these patients had normal LVEF. Women represented about 46% of the AMI with heart failure population, a higher proportion than in AMI without heart failure. Risk factors for developing heart failure included female gender, older age, a history of prior myocardial infarction, diabetes, hypertension, and the presence of chronic heart failure. In-hospital mortality rate for these patients was 13%, versus 2.3% for patients with AMI but without heart failure or left ventricular dysfunction (Fig. 27.11). Mortality rates



• **Fig. 27.11** In-hospital mortality rate in patients admitted with acute myocardial infarction, according to the presence of heart failure and left ventricular ejection fraction. *EF,* Ejection fraction; *HF,* heart failure; *Killip class I,* patients without evidence of heart failure on physical examination; *Killip class II,* patients with evidence of heart failure on physical examination; *LVSD,* left ventricular systolic dysfunction. (Redrawn from Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT Registry. *Eur Heart J.* 2004;25:1911–1919.)



• **Fig. 27.12** In-hospital clinical events among patients with and without heart failure *(HF)* or left ventricular systolic dysfunction *(LVSD)* ($P < 0.001$ for all events except reinfarction). *Atrial fib.,* Atrial fibrillation; *V. tach/fib,* ventricular tachycardia/ventricular fibrillation. (Redrawn from Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT Registry. *Eur Heart J.* 2004;25:1911–1919.)

remain three times higher during the first year in the heart failure group. Other complications also occurred more commonly in these patients, including atrial and ventricular arrhythmias, reinfarction, and stroke[131] (Fig. 27.12).

Therefore early aggressive pharmacologic therapies are necessary, including intravenous diuretics, intravenous nitroglycerin, and β-blockers. Urgent cardiac catheterization ("early invasive" approach) is usually indicated. Intraaortic balloon counterpulsation or other MCS should be used in patients with signs and symptoms of continued ischemia despite aggressive medical therapies or who have cardiogenic shock. In patients with acute heart failure owing to AMI, rapid reperfusion is the cornerstone of therapy. This may be achieved with thrombolytic therapy (in the minority of patients with STEMI), percutaneous coronary intervention (PCI), or urgent coronary artery bypass surgery. Percutaneous or surgical reperfusion should always be considered when coronary anatomy is appropriate. In the Global Registry of Acute Coronary Events (GRACE) study, revascularization therapies were associated with lower mortality in patients with ACS and acute heart failure.[130]

In patients in whom heart failure develops or who have significant left ventricular systolic dysfunction after myocardial infarction, several medications have been shown in large placebo-controlled randomized studies to improve mortality and reduce the risk of repeat hospitalizations. β-Blockers should be part of standard post–myocardial infarction heart failure therapy. In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study, the use of carvedilol led to a significant reduction in all cause and cardiovascular mortality.[132] The SAVE study was the first trial to show that the use of an ACE inhibitor (captopril) was beneficial in post–myocardial infarction patients with ejection fraction below 40%.[133] There was a 5% absolute mortality reduction after 42 months of follow-up. In the Acute Infarction Ramipril Efficacy (AIRE) trial, treatment with the ACE inhibitor Ramipril, started 3 to 10 days after myocardial infarction in patients with heart failure, resulted in a significant mortality benefit at an average of 15 months of follow-up.[134] In the Valsartan in Acute Myocardial Infarction (VALIANT) study, the ARB valsartan was as effective as an ACE inhibitor in improving survival and reducing cardiovascular morbidity in patients with left ventricular dysfunction after myocardial infarction.[135] Therefore β-blockers and ACE inhibitors should be started early and continued over the long term in patients with reduced LVEF after AMI. Angiotensin receptor blockers are recommended in patients who are intolerant to ACE inhibitors.

Aldosterone blockers have also been shown to be effective in improving prognosis in patients with heart failure or left ventricular dysfunction after myocardial infarction and are recommended for these patients. The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) showed that eplerenone significantly reduced all-cause mortality and repeat hospitalizations at 16 months after AMI.[136] Reduction in mortality and sudden cardiac death was noted as early as 30 days after initiation of eplerenone.[137]

In the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy) data, the use of dual antiplatelet therapy, β-blockers, ACE inhibitors, and statins all increased between 1996 and 2008. In the latter years of the analysis, more than 90% of revascularizations were performed by PCI. More frequent utilization of these effective therapies resulted in improved outcomes, with in-hospital mortality declining from 19% in 1996 to 13% in 2008, with 1-year mortality also declining from 36% to 31%.[131]

Heart Failure With Preserved Left Ventricular Ejection Fraction (Diastolic Heart Failure)

Heart failure can occur in patients with normal or relatively normal left ventricular systolic function. HFpEF is diagnosed when patients present with typical signs and symptoms of heart failure, with LVEF above 50%, and evidence of abnormal diastolic function on Doppler echocardiography or cardiac catheterization. Some studies of HFpEF have included patients with LVEF between 40% and 50%. These patients are now considered a "borderline group" between heart failure with reduced and normal ejection fraction. HFpEF is common, occurring in approximately 50% of patients hospitalized with acute heart failure. Reported prevalence rates vary and are related to the demographics of study populations, including age, inpatient and/or outpatient status, the proportion of African Americans and females, and whether patients were evaluated at an academic referral center or in a community-based setting. The incidence appears to be increasing at a rate of approximately 1% per year.[34,138]

Compared with HFrEF, patients with HFpEF tend to be older, are more often female; have hypertension, atrial fibrillation, chronic kidney disease, obesity, and obstructive sleep apnea more often; and have significant coronary artery disease less often.[1,139] In a meta-analysis of 31 population-based studies in Europe that analyzed 41,972 patients, the average age of patients with HFpEF was 71 years compared with 66 years in HFrEF patients. Fifty percent of patients were women (compared with 28% with HFrEF), hypertension was present in 51%, and ischemic heart disease in 43% (41% and 59% in HFrEF, respectively).[140] Other studies have estimated hypertension prevalence in 60% to 89% of patients with HFpEF.[138,141–144]

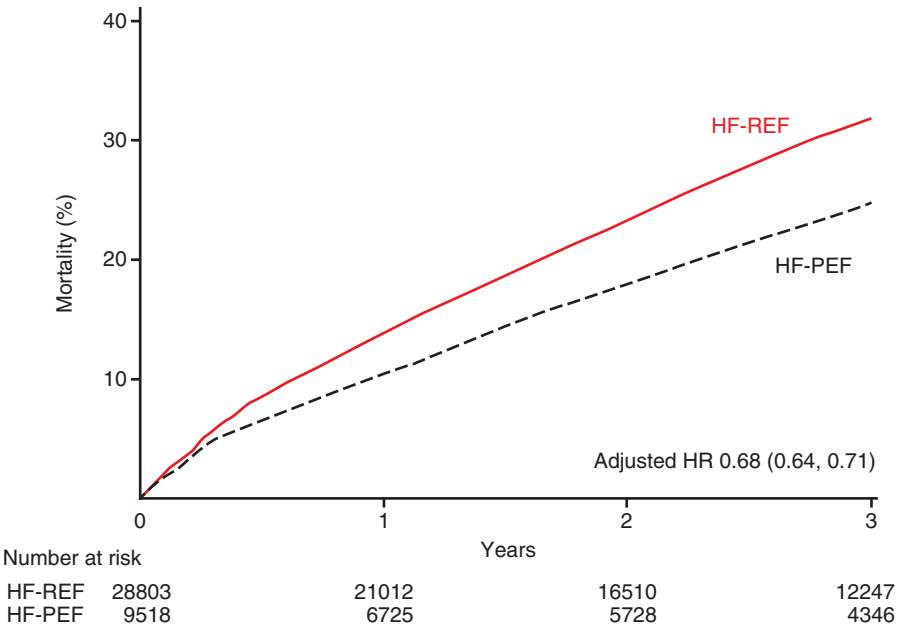
The traditional view of pathophysiology in HFpEF focused on increased left wall thickness and abnormal left ventricular geometry with increased left ventricular mass/volume ratio. Diastolic performance abnormalities included impaired ventricular filling owing

to increased wall stiffness with reduced compliance and abnormal relaxation. Myocyte hypertrophy, myocardial fibrosis, and increased collagen in extracellular matrix were responsible for the physiologic abnormalities. The hemodynamic and anatomic abnormalities include increased left ventricular end diastolic pressure, increased left atrial pressure, left atrial dilation, pulmonary venous hypertension, and pulmonary congestion.[115,117] Some patients then develop chronic pulmonary hypertension, elevated right ventricular diastolic pressure, and right atrial dilation. Patients with HFpEF usually demonstrate normal indices of left ventricular systolic performance and contractility at rest, but often the ejection fraction does not increase appropriately during exercise.[34,138,140,145,146]

A newer view of the pathophysiology of HFpEF involves systemic inflammation, coronary artery endothelial dysfunction, and primary renal abnormalities. Evidence for this includes higher levels of plasma biomarkers of inflammation in patients with HFpEF compared with HFrEF.[138] Systemic inflammation may result in pulmonary vasoconstriction and abnormal skeletal muscle oxygen utilization during exercise, and decreased renal excretion of sodium leading to plasma volume expansion. Patients with HFpEF are more sensitive to changes in volume, as heart failure is more likely to occur with volume expansion and hypotension more likely with volume contraction. Systemic inflammation may also cause oxidative stress, leading to coronary microvascular dysfunction and myocyte hypertrophy, increased numbers of myofibroblasts, increased collagen production, increased left ventricular wall stiffness, and left ventricular remodeling.[138,145]

Patients who present with heart failure owing to HFpEF have a history and physical examination indistinguishable from patients with systolic heart failure. Presenting blood pressure may be higher, and acute "flash" pulmonary edema often occurs. Common exacerbating factors include severe hypertension, medication noncompliance, myocardial ischemia, renal dysfunction, and valve dysfunction. In one study, no precipitating factors could be identified in 50% of these patients.[147] Serum BNP levels are elevated but tend to be lower than in patients with HFrEF, reflecting lower left ventricular wall stress. Up to 30% of patients with symptomatic HFpEF may have normal BNP levels, related to obesity or the presence of symptoms occurring only during exercise.[34] Diagnosis is made more difficult by the frequent coexistence of obesity and deconditioning. Common ECG abnormalities in HFpEF include atrial fibrillation, left atrial abnormality, and left ventricular hypertrophy, but these are not specific for HFpEF. Echocardiography is invaluable for determining LVEF and assessing Doppler parameters of diastolic function. Exercise testing is often helpful in the evaluation exercise tolerance and exercise-related symptoms, blood pressure response to exercise, and inducible ischemia. Invasive hemodynamic assessment is often invaluable in making the diagnosis in many patients when clinical signs are indeterminate. However, some hemodynamic findings may be misleading, as pulmonary hypertension may be due to elevated left atrial pressure or fixed pulmonary venous hypertension, and large v waves in the pulmonary capillary tracing may be due to abnormal left atrial compliance rather than severe mitral regurgitation.[34]

The prognosis of patients with HFpEF is serious. Mortality is probably not as poor as in patients with HFrEF, although one study found similar adjusted and nonadjusted mortality rates at 30 days and 1 year for hospitalized patients with heart failure and LVEF below 40% or above 50%.[148] A large European meta-analysis showed a 32% lower risk of death over 3 years in patients with HFpEF compared with HFrEF: 121 of 1000 patient-years compared with 141 of 100 patient-years (Fig. 27.13).[140] In-hospital mortality is around 4% or four times age-matched controls.[120,141,149] Annual mortality is variable and likely depends on the frequency of comorbid conditions in the cohort of patients studied; it has been reported in the range of 1.3% to 17.5%.[150] Readmission rates are



• **Fig. 27.13** Mortality for patients with heart failure with preserved left ventricular ejection fraction *(HF-PEF)* and heart failure with low left ventricular ejection fraction *(HF-REF)*, adjusted for age, gender, etiology of heart failure, hypertension, diabetes, and atrial fibrillation. *HF,* Heart failure; *HR,* heart rate. (From Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J.* 2012;33:1750–1757.)

similar to those with HFrEF: as high as 50% at 1 year. Factors that identify patients with a worse prognosis include renal dysfunction, worse functional class, male gender, and advanced age.[149] Patients with HFpEF and hypertension have a worse prognosis than those with hypertension without heart failure.[146]

Unlike systolic heart failure, there are no placebo-controlled randomized studies that have demonstrated effective therapy for diastolic heart failure. The 2013 Guidelines for Treatment of Heart Failure give class I recommendations to controlling hypertension and using diuretics to control symptoms of fluid overload. A class IIa recommendation is revascularization for patients with ischemia as the major cause of HFpEF.[5]

The evidence base includes the Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved Study, which compared the use of the ARB candesartan with placebo for treating HFpEF. After an average 3-year follow-up, the combination of death from cardiovascular cause or admission for heart failure was similar in the two groups. There was a modest impact on preventing hospitalizations due to heart failure in patients treated with candesartan.[151] The Irbesartan in Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial testing irbesartan in more than 4000 patients with heart failure and LVEF above 45% showed no beneficial effect on mortality or heart failure rehospitalizations.[152] The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial evaluated treatment with spironolactone in patients with heart failure and LVEF above 45%, with follow-up for 3.3 years. There was no benefit in the primary composite endpoint of cardiovascular death, aborted cardiac arrest, or hospital admission for heart failure. There was a statistically significant benefit for spironolactone in the isolated endpoint of heart failure hospitalizations.[153] A post hoc analysis of the TOPCAT data analyzing only those patients enrolled in the Americas (the United States, Brazil, Argentina, and Canada) showed a fourfold difference compared with patients enrolled in Russia and Asian Georgia, with the rates of the primary outcome significantly improved by spironolactone in the Americas.[154] The prognostic effect of aldosterone blockade in HFpEF is still debated. Another trial showed no improvement in exercise tolerance or quality of life in HFpEF patients treated with isosorbide mononitrate.[155]

Several basic recommendations are widely agreed on. Medical therapy of HFpEF is primarily focused on alleviating symptoms. Diuretics are effective at improving pulmonary congestion. Lower doses of diuretics are generally used, as usual doses often lead to volume depletion and hypotension. Effective treatment of underlying conditions, including hypertension, diabetes mellitus, and coronary artery disease, is essential. Control of elevated blood glucose may help retard myocardial fibrosis by lessening cross-linking of myocardial collagen. Control of myocardial ischemia is important, although there are no convincing controlled data that revascularization will reliably prevent recurrences of diastolic heart failure. Maintenance of sinus rhythm and avoidance of tachycardia are also important.

β-Blockers can be useful to reduce heart rate and improve diastolic filling time. They are also effective medications for hypertension and coronary ischemia. Similarly, calcium channel blockers may improve symptoms of diastolic heart failure by treating hypertension and ischemia and improving diastolic relaxation. The use of ACE inhibitors and ARBs is indicated to lower blood pressure, reduce myocardial fibrosis, and block the adverse effects of the activation of the renin-angiotensin system. In a retrospective study of patients hospitalized with heart failure and ejection fraction below 40%, patients who were prescribed an ACE inhibitor had better quality-of-life scores, improved functional class, and lower adjusted mortality.[143] The aldosterone antagonists spironolactone and eplerenone can be used to treat hypertension and they may reduce left ventricular fibrosis (see previous text). Weight loss in obese patients and treatment of obstructive sleep apnea are important. Therapy with positive inotropic drugs or digoxin is not useful in patients with diastolic heart failure (Box 27.5).

• BOX 27.5 Treatment of Heart Failure With Preserved Left Ventricular Ejection Fraction

- Effective control of systemic hypertension
- Diuretics should be used for decongestion and symptom relief
- Evaluate for and treat myocardial ischemia, with revascularization when indicated
- Control atrial fibrillation
- Consider spironolactone use

Myocarditis and Acute Heart Failure

Myocarditis is defined as inflammation of heart muscle and is an uncommon cause of acute heart failure. Although most patients with acute myocarditis are not critically ill and make a complete recovery, a minority can develop severe left ventricular dysfunction, acute heart failure, and even cardiogenic shock.[156,157] Viral myocarditis may also cause chronic activation of immune mechanisms that over time may lead to dilated cardiomyopathy and chronic heart failure.

In most patients with myocarditis a specific cause is not found, but lymphocytic inflammation owing to a viral etiology is assumed in most cases. Coxsackie B enterovirus was considered the most common cause up to the 1990s, but human herpesvirus 6, cytomegalovirus, and parvovirus B19 have been implicated as causative agents more frequently over the past 20 years.[158] Other viral causes include influenza, Epstein-Barr virus, hepatitis C, and herpes simplex 1 and 2. The protozoa *Trypanosoma cruzi* is the cause of Chagas disease, a form of myocarditis that can lead to chronic heart failure, endemic in Central and South America. Another cause of myocarditis is autoimmune disease, including myocarditis associated with progressive systemic sclerosis, systemic lupus erythematosus, and polymyositis. Other types of myocardial inflammation are characterized by giant cells, in myocarditis complicating giant cell arteritis or isolated giant cell myocarditis, or eosinophils, seen in hypersensitivity or eosinophilic myocarditis, an uncommon entity caused by a systemic allergic reaction.

Myocarditis is a diagnosis made on clinical grounds and should be suspected in patients who present with new-onset heart failure, with or without antecedent flulike symptoms. Chest pain is often but not always present. Laboratory abnormalities include elevated leukocyte count, elevated sedimentation rate, and elevated troponin levels; sensitivity of troponin I in myocarditis is reported as 34% to 53% with specificity of 89%.[159,160] ECG changes suggestive of myocardial ischemia or infarction may be seen but are not always present. The presence of severe coronary disease often needs to be specifically excluded.

Pathologic specimens show both infiltration with inflammatory cells and myocyte necrosis. Endomyocardial biopsy (EMB) has been the traditional method used to diagnose acute myocarditis

but it has significant limitations. EMB is insensitive for diagnosis and a high degree of interobserver diagnostic variability has also been reported. In patients in whom myocarditis was suspected on clinical grounds, only 10% to 67% of patients had positive biopsies in reported series.[156,157] An AHA/ACC/European Society of Cardiology scientific statement offered recommendations concerning the appropriate use of EMB based on patients' clinical presentations. EMB was deemed useful, beneficial, and effective (class I indication) in patients with acute heart failure with severe heart failure or arrhythmias after other causes are excluded. EMB is necessary to diagnose giant cell myocarditis and eosinophilic myocarditis, as immunosuppressive therapy is mandated in these conditions. A class I indication for EMB was also given in new-onset, subacute heart failure with duration of illness of 2 weeks to 3 months, in those whose condition fails to improve with medical therapy for heart failure or who demonstrate severe ventricular arrhythmia or advanced heart block.[161] EMB should be considered if causes such as sarcoidosis or autoimmune disease are suspected.

Cardiac magnetic resonance has more recently been shown to be an important tool in the diagnosis of myocarditis.[162,163] This technique offers a noninvasive means to make this diagnosis but may be difficult to use in critically ill patients. Diagnostic criteria include (1) focal or diffuse myocardial edema in T2-weighted images; (2) early gadolinium enhancement on T1 imaging indicating inflammation and cell damage; and (3) late gadolinium enhancement in subepicardial or midmyocardial areas indicating noncoronary-related necrosis and fibrosis. Myocardial edema may be subepicardial, transmural, or global and is not always associated with late gadolinium enhancement. Signs of inflammation may be diffuse or patchy and are often confined to the lateral free wall of the left ventricle or the base of the interventricular septum (Fig. 27.14). Diagnostic accuracy of cardiac magnetic resonance is reported at 78% when two or three criteria are present and 68% when only late gadolinium enhancement is present.[164,165]

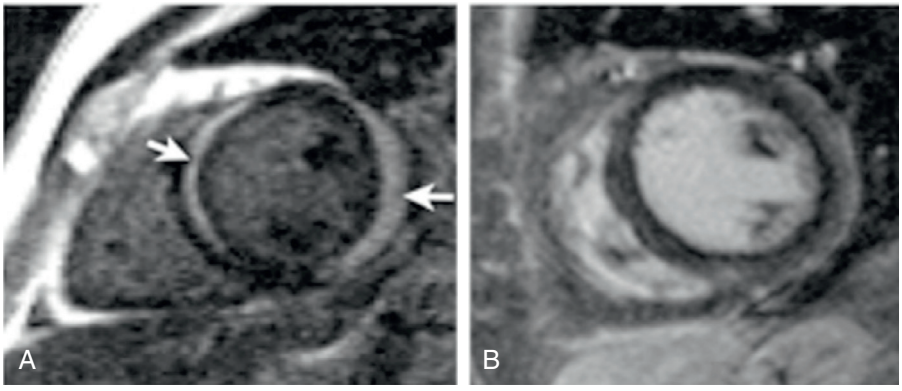
Pharmacologic management of heart failure caused by myocarditis is similar to the management of heart failure from other causes. Diuretics, ACE inhibitors, β-blockers, and aldosterone blockade should be prescribed. Many patients experience significant improvement in left ventricular function during the first 6 months after diagnosis. NSAIDs should be avoided because they may worsen myocarditis.[166] The use of immunosuppressive drugs for acute myocarditis is controversial; there is no evidence that *routine* treatment with immunosuppression is beneficial. It should be considered in patients with acute, severe heart failure or whose condition continues to worsen despite heart failure therapy. Immunosuppressive therapy should be also used in patients with myocarditis associated with autoimmune diseases. EMB should be performed and should show active inflammation and necrosis prior to initiating immunosuppressive therapy.

Fulminant Myocarditis

Myocarditis with acute, severe heart failure and cardiogenic shock is termed fulminant myocarditis. Most often there is a history of fever and other symptoms of a viral illness for several weeks, and with a distinct time of onset of heart failure symptoms. This presentation is contrasted with that of other patients with acute, severe myocarditis who have acute heart failure without cardiogenic shock with a less distinct time of onset of heart failure symptoms. Patients with fulminant myocarditis are critically ill and require intensive pharmacologic support with vasodilators and inotropes. In the most critically ill patients, mechanical circulatory may be necessary to use as a bridge to recovery or to cardiac transplantation. When supported aggressively, many patients recover fully with normal ventricular function. Therefore aggressive supportive therapy is indicated, even in gravely ill patients.[167]

Device Therapy for Heart Failure and Ventricular Tachyarrhythmias: Implanted Cardioverter Defibrillator and Cardiac Resynchronization Therapy

Sudden death is a frequent occurrence in heart failure patients, especially in patients with coronary artery disease. Sudden death is presumed to be due to sustained ventricular tachycardia or ventricular fibrillation in the majority of cases. It is estimated that 30% of patients with heart failure and ejection fractions below 30% die suddenly. In patients with heart failure and significant ventricular tachyarrhythmias, treatment with antiarrhythmic drug therapy alone is not recommended as this has been shown to be ineffective therapy (see later text). Evaluation and correction of hypoxia, electrolyte abnormalities (hypokalemia, hypomagnesemia), and ischemia is the initial approach. The medications recommended for systolic heart failure have been shown to reduce the incidence



• **Fig. 27.14** A, Subepicardial enhancement of lateral and midwall enhancement of the septal wall *(arrows)*. B, Diffuse subepicardial enhancement. (From Friedrich MG, Sechtem U, Shulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol.* 2009;53:1475–1487.)

of sudden death. However, prophylactic therapy with antiarrhythmic drugs therapy aimed at preventing sudden arrhythmic death has been shown to be ineffective and may even worsen prognosis. In the Cardiac Arrhythmia Suppression Trial (CAST), patients with coronary artery disease, a history of myocardial infarction, and frequent premature ventricular contractions on baseline Holter monitoring had an increased mortality when treated with the antiarrhythmic drugs encainide or flecainide, despite effective suppression of the occurrence of arrhythmia on follow-up Holter monitoring.[168] This adverse effect on mortality is presumably due to the potential for these drugs to actually worsen arrhythmia ("proarrhythmia"), especially in patients with left ventricular dysfunction. Therefore class IA and IC antiarrhythmic drugs quinidine, procainamide, disopyramide, flecainide, and propafenone are not useful for prevention of sudden death and are contraindicated in patients with heart failure.

Amiodarone was also studied as primary prevention of sudden death, as the propensity for proarrhythmia is less than with type I antiarrhythmics. Six-hundred seventy-five patients with heart failure and ejection fractions below 40% were randomly assigned to treatment with amiodarone or placebo, with no survival difference between the two groups at 45 months.[169] There was a trend toward reducing mortality with amiodarone in patients with nonischemic cardiomyopathy. In another study, 1486 post–myocardial infarction patients with ejection fractions below 40% were randomly assigned to amiodarone or placebo with no difference in mortality in 21 months, although there was a suggestion of a reduction in deaths caused by arrhythmia.[170] Unlike the findings in CAST, there was no observed increased risk of death with amiodarone. Thus this medication is not helpful in the prevention of sudden cardiac death, but it is considered safe for treatment of supraventricular arrhythmias in heart failure patients.

Implanted Cardioverter Defibrillator Therapy

The implanted cardioverter defibrillator (ICD) is standard therapy for both primary and secondary prevention of life-threatening ventricular arrhythmias and sudden cardiac death in patients with severe left ventricular systolic dysfunction. This therapy is supported by the results of several large, randomized controlled trials. The use of an ICD was compared to antiarrhythmic drugs for secondary prevention of sudden cardiac death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) study. These patients had been resuscitated from cardiac arrest or survived ventricular tachycardia associated with syncope and had LVEFs below 40%. A total of 1016 patients were randomly assigned to receive an ICD or antiarrhythmic drugs (>90% received amiodarone). There was a statistically improved survival with ICD therapy at 1, 2, and 3 years of follow-up.[171] Published guidelines recommend ICDs as first-line therapy in patients with ischemic and nonischemic cardiomyopathy who have survived a cardiac arrest or an episode of sustained ventricular tachycardia (secondary prevention).[5]

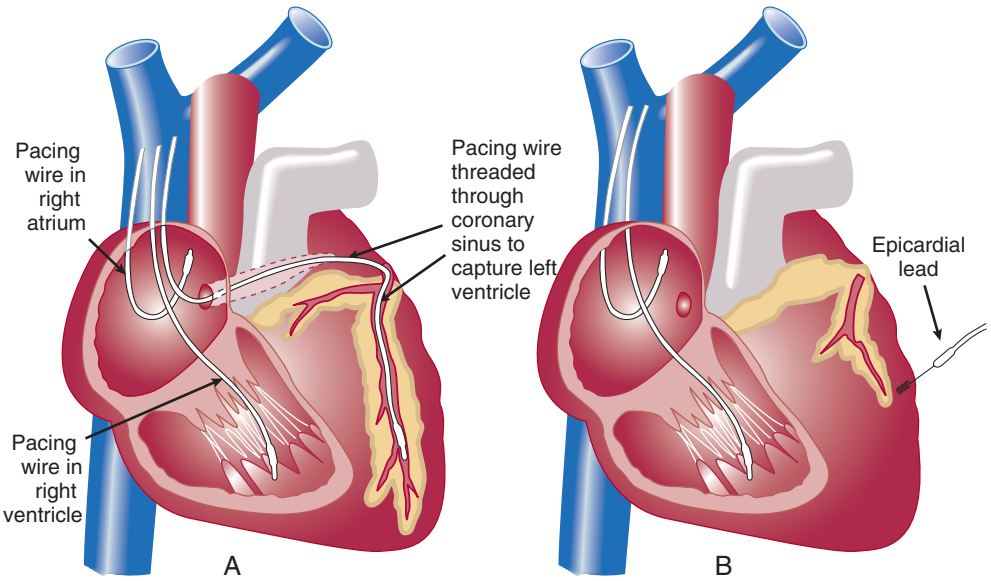
ICD therapy is also recommended as primary prevention of sudden cardiac death in patients with systolic heart failure owing to coronary heart disease and in patients with nonischemic cardiomyopathy. In the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I), patients who had had a myocardial infarction, with ejection fractions below 35%, and asymptomatic nonsustained ventricular tachycardia on monitoring, were studied with electrophysiologic testing; if inducible ventricular tachycardia was present and not suppressed with antiarrhythmic therapy, then patients were enrolled and randomly assigned to ICD versus medical therapy (standard medical therapy with or without amiodarone). At 2 years of follow-up, total mortality was significantly reduced from 39% in the medically treated group to 15% in the ICD group.[172] In the Multicenter Unsustained Tachycardia Trial (MUSTT), a similar cohort of patients showed an improvement in 5-year mortality from 55% in the medication-only group to 24% in patients treated with ICDs.[173] In MADIT II, the patient population was extended to include patients with a history of myocardial infarction and ejection fractions below than 30%. Importantly, in this study, neither ventricular arrhythmias seen on monitoring nor induced at electrophysiologic study were necessary for inclusion. A statistically significant improvement in total mortality was seen in patients treated with ICDs, from 19.8% to 14.2% at 4 years.[174] Class IV heart failure patients were not included in these studies.

The Sudden Cardiac-Death-Heart Failure Trial (SCD-HeFT) enrolled patients with functional class II and III heart failure with LVEFs below 35%. This study differed from MADIT I and II in that a greater number of patients (48%) had nonischemic cardiomyopathy. Primary prevention of sudden cardiac death was compared among standard heart failure pharmacologic therapy, standard therapy combined with amiodarone, and standard therapy plus an ICD. After a mean follow-up of 45.5 months, mortality was improved from 29% in the medical group and 28% in the amiodarone group to 22% in the ICD group, which was statistically significant. This improvement was particularly notable in patients with class II heart failure.[175] Benefits of ICD therapy were seen in patients with both ischemic and nonischemic cardiomyopathy. A meta-analysis of all studies in which ICDs were used as primary prevention in patients with nonischemic cardiomyopathy indicated a statistically significant 31% relative risk reduction in favor of ICDs.[176] A more recent European study evaluated ICD therapy in 1116 patients with heart failure owing to nonischemic cardiomyopathy. Compared with the initial trials evaluating ICDs, patients enrolled in this trial had more modern heart failure medical therapy and 58% had cardiac resynchronization therapy (see later text). At an average follow-up of 67 months, there was no difference in all-cause mortality in the ICD group versus the control group (21.6% vs. 23.4%, $P = 0.28$). The incidence of sudden cardiac death was significantly decreased from 8.2% in the non-ICD group to 4.3% in the ICD group. A subgroup analysis suggested benefit from ICD therapy in younger patients (<age 59 years).[177]

The guideline-approved use of ICD therapy for prevention of sudden cardiac death includes patients with LVEF below 35%, caused by ischemic as well as nonischemic cardiomyopathy, with functional class II–III heart failure, at least 40 days after myocardial infarction, who have anticipated survival of longer than 1 year.[5]

Cardiac Resynchronization Therapy

In many patients with heart failure, there is a lack of coordination of systolic motion of the interventricular septum and left ventricular free wall, termed dyssynchrony. This often coexists with His-Purkinje conduction system disease, with QRS prolongation on ECG.[178] A left bundle branch block (LBBB) pattern with long QRS duration is associated with an increase in all-cause mortality in patients with heart failure. Pacemaker therapies have been developed to correct left ventricular dyssynchrony. This is termed biventricular pacing or cardiac resynchronization therapy (CRT). Standard transvenous pacing leads are placed in the right atrium (in the absence of chronic atrial fibrillation) and right ventricle. The left ventricular free wall is paced via a third electrode passed



• **Fig. 27.15.** A, Placement of pacing wires in biventricular pacing. B, Lack of coronary sinus venous branch necessitates epicardial placement of third lead via minimally invasive surgical procedure.

transvenously via the coronary sinus into an epicardial lateral cardiac vein. Alternatively, a left ventricular lead can be placed directly on the epicardium of the lateral wall of the left ventricle via thoracoscopy. The pacemaker is programmed to coordinate timing of septal stimulation via the right ventricular lead with left ventricular lateral wall stimulation via the coronary sinus lead (Fig. 27.15).[178,179]

In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, 453 patients with LVEF below 35%, class III-IV heart failure, and QRS duration longer than 130 msec were treated with standard medical therapy or resynchronization therapy plus medical therapy. At 6 months of follow-up, CRT resulted in a statistically significant improvement in 6-minute walking distance, quality-of-life score, and functional class, with fewer hospitalizations for recurrent heart failure.[178] In the Cardiac Resynchronization in Heart Failure (CARE-HF) study, CRT (without ICD) was evaluated in 813 patients with class III–IV heart failure caused by left ventricular systolic dysfunction, with ejection fraction below 35% and QRS duration longer than150 msec or QRS duration longer than 120 msec with signs of dyssynchrony on echocardiography. Mean follow-up was 29.4 months. The primary endpoint of all-cause mortality plus unplanned hospitalization for cardiovascular causes was reduced from 55% in medically treated patients to 39% with CRT ($P < 0.001$). All-cause mortality was reduced from 30% to 20% with CRT ($P < 0.002$). Quality-of-life scores improved and ejection fractions improved.[180] A meta-analysis of three major resynchronization trials in 1634 patients concluded that chronic resynchronization therapy was associated with a statistically significant 51% reduction in death from progressive heart failure.[181] Thus CRT can reduce mortality as well as improve symptoms in patients with chronic heart failure. The success rate of left ventricular lead placement is high. There is a low incidence of serious complications of device implantation including coronary sinus dissection or perforation.

Devices combining biventricular pacing and ICD capability were evaluated in patients with systolic heart failure and low ejection fraction. The rationale is to decrease morbidity and mortality associated with progressive heart failure as well as to decrease mortality associated with sudden life-threatening ventricular arrhythmia. Biventricular pacing does not interfere with appropriate ICD detection and termination of ventricular arrhythmias.[182] The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial enrolled 1520 patients with advanced heart failure, functional class III-IV, in sinus rhythm, with QRS duration longer than 120 msec. Therapies compared were best pharmacologic heart failure therapy, best therapy with CRT, and best therapy with combination CRT plus ICD. The primary endpoints of all-cause death or hospitalization for any cause, followed over 12 months, were 68% in the drug therapy group, and 56% in both device groups, a significant difference. Death or hospitalization owing to cardiovascular cause after 1 year were 60% in the drug-alone group, with a relative risk reduction of 25% in the biventricular pacing group and 28% in the CRT plus ICD group. The authors concluded there was a significant reduction in heart failure hospitalizations with biventricular pacing, and there was an additional significant reduction in mortality when ICD therapy was added. Improvement occurred in both in patients with ischemic and nonischemic cardiomyopathy.[183]

CRT has also been studied in less ill patients, patients with functional class II and III heart failure with ejection fraction less than 30%; 1798 patients with QRS duration longer than 120 msec during native conduction, or 200 msec during ventricular pacing, were treated with an ICD alone or with ICD plus CRT. At a mean follow-up of 40 months, there was a significant improvement with CRT in the primary endpoint of all-cause mortality plus hospitalization for heart failure (33.2% with CRT-ICD vs. 40.3% with CRT alone, $P < 0.001$).[184] A meta-analysis of studies using CRT in patient with mild heart failure showed significant favorable effects on left ventricular remodeling and reduction in the progression of heart failure.[185]

Optimal response to CRT occurs more often in the presence of longer QRS duration. Current guidelines give a class I indication for CRT to patients with LVEF below 35%, functional class II-IV symptoms despite optimal medical therapy, and LBBB on ECG with QRS duration longer than 150 msec, as well as functional class I patients with LVEF below 30%. A class IIa indication is given to patients with QRS duration longer than 150 msec without

LBBB and LVEF below 35%, or in patients with LBBB with QRS duration of 120 to 149 msec.[5] CRT with ICD results in left ventricular remodeling provides symptomatic benefit and improves survival in patients with heart failure.

Severe Heart Failure and Mechanical Circulatory Support

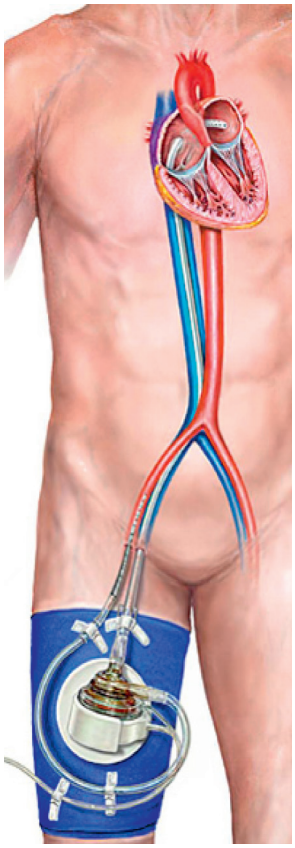
Temporary "Nondurable" Support

In patients with cardiogenic shock or refractory, severe heart failure, treatment with pharmacologic measures including inotropic agents and vasodilators is often not effective in reversing severe hemodynamic derangements. In these patients, MCS is required. Goals of mechanical supports include improved end-organ perfusion, lowering high cardiac filling pressures and relieving pulmonary edema, and preserving myocardial function by increasing coronary artery perfusion, reducing myocardial oxygen consumption, and unloading the left ventricle.[186,187] Temporary circulatory support systems can be delivered percutaneously in the cardiac catheterization laboratory or in the operating room when larger-bore cannulation is required. These systems can be placed urgently in unstable patients and can support the circulation until negative cardiac function improves or a decision is made regarding more durable mechanical support.[188] Causes of severe heart failure and cardiogenic shock in which temporary, or "nondurable," mechanical support can be considered include AMI, fulminant myocarditis, severe peripartum cardiomyopathy, stress-induced cardiomyopathy, after cardiac surgery, and for the mechanical complications of AMI.

The intraaortic balloon pump (IABP) is a form of temporary circulatory support with the longest clinical experience. This balloon catheter is placed percutaneously in the descending aorta via the femoral artery. The catheter size is 7.5F to 8.0F. Balloon inflation is timed to occur with the onset of diastole, resulting in diastolic augmentation of cardiac output and improved coronary perfusion pressure. The IABP offers modest hemodynamic support, an additional 0.5 to 1.0 L/min flow. Because timing of balloon inflation is synchronized to the ECG, marked tachycardia or frequent ventricular tachyarrhythmias results in poor augmentation of cardiac output. Complications are reported in 2.6% to 4.2% of patients and include stroke, limb ischemia, vascular injury, thrombocytopenia, or mesenteric ischemia. An IABP cannot be used in patients with moderate or severe aortic insufficiency or severe peripheral arterial disease.

The TandemHeart system (TandemLife, Pittsburgh, PA) is a form of temporary circulatory support that can offer 3.5 L/min of augmented flow via a larger, 15F catheter or 5 L/min of flow via a 19F catheter. The catheter is placed in the femoral vein and advanced to the left atrium via a transatrial septal puncture. Blood is removed from the left atrium, circulated via an extracorporeal centrifugal pump, and returned via the femoral artery (Fig. 27.16). The duration of support is approved for 6 hours (U.S. Food and Drug Administration) to 30 days (CE Mark in Europe). Hemodynamic effects include reduction of left ventricular preload and left ventricular end-diastolic pressure, decreased oxygen demand and left ventricular work, and increased afterload. Systemic anticoagulation is required. Severe peripheral arterial disease (PAD) is a contraindication.[186,187]

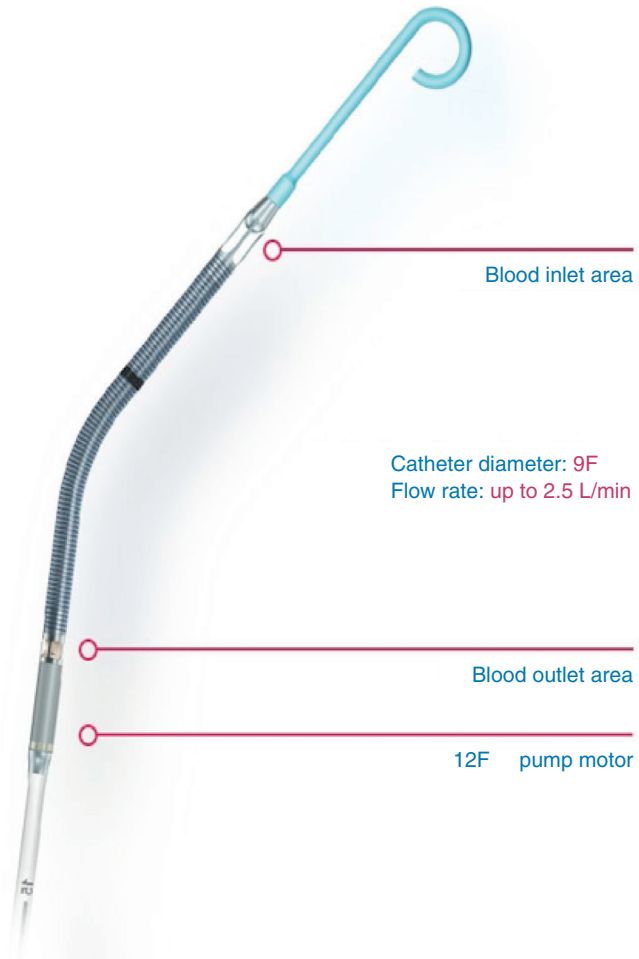
The Impella device (Abiomed, Danvers, MA) is a catheter on which is mounted a microaxial rotary pump. The catheter is placed retrograde into the left ventricle via percutaneous femoral artery catheterization. A pigtail tip stabilizes catheter position in the left ventricle. Blood is pulled from the left ventricle into an inlet area and then is expelled into the descending aorta. Flows of 2.5 L/min or 4 L/min can be delivered via percutaneously inserted 12F- or 14F-diameter catheters. A larger device delivering 5 L/min is placed via a femoral artery cutdown. Impella is approved for duration of use of 6 hour (U.S. Food and Drug Administration) to 5 days (CE Mark) (Fig. 27.17). This support system also requires cardiac electrical stability and adequate right ventricular function. Contraindications to its use include severe aortic valve disease and severe PAD. Limb ischemia and vascular injury are complications, similar to other systems using large-bore cannulas. Catheter migration, kinking, and obstruction of inflow have been reported.



• **Fig. 27.16** The TandemHeart system. (TandemHeart, Pittsburgh, PA.)

There are few data from randomized, controlled clinical trial with large numbers of patients to guide the use of these devices. In the IABP-SHOCK trial, the use of IABP was tested in 600 patients with cardiogenic shock caused by AMI who underwent urgent PCI; 83% of patients had IABPs placed after PCI was performed. There was no effect of IABP on 30-day mortality, a primary endpoint, or other secondary endpoints.[189] In another trial, the use of IABPs in patients with large anterior myocardial infarction but without shock, placed before PCI was performed, resulted in no difference in infarct size or survival at 6 months.[190] The 2013 ACC Foundation/AHA Guidelines for AMI give a IIa indication ("weight of evidence in favor of usefulness/efficacy") to the use of IABPs in cardiogenic shock because acute ST-elevation MI.[191]

Extracorporeal membrane oxygenation (ECMO) is a form of temporary circulatory support that uses an extracorporeal circuit, a centrifugal pump, and a membrane oxygenator. ECMO is not new, but improvements in technology and greater experience have resulted in more frequent use. A form of ECMO (VA ECMO



• **Fig. 27.17** The Impella device. (Abiomed, Inc., Danvers, MA.)

[venoarterial ECMO]) is used to support patients with severe heart failure. Venous blood is drawn through a femoral catheter, circulated by the pump through an oxygenator, and returned via the femoral artery. Large cannulas (19F- to 21F-diameter) are required. Additions to this circuitry are often required to ensure adequate cerebral and coronary oxygenation as well as adequate perfusion of the leg distal to catheter insertion. Systemic anticoagulation is required. Support with ECMO can be delivered for days to weeks. ECMO results in improved end-organ perfusion without increased myocardial oxygen demand. Left ventricular preload is reduced but afterload is increased. This may have deleterious effects on left ventricular function and may result in further left ventricular dilation. If this results in worsening lung edema, then unloading of the left ventricle via a left atrial or left ventricular vent catheter may be necessary.[186] Complications include bleeding (40% major or significant), thrombosis of circuitry or cannulae, infection, limb ischemia or compartment syndrome, hemolysis, and thrombocytopenia. A 5.9% incidence of stroke and 4.7% risk of amputation owing to limb ischemia have been reported (Fig. 27.18).[192]

Compared with other temporary support modalities, VA ECMO improves arterial oxygenation. Reported experience with ECMO includes the following. In an observational study of patients with cardiogenic shock caused by ST-elevation myocardial infarction, a 39% mortality was observed using ECMO, compared with 72% mortality in historical controls. Survival of 68% to ICU discharge was reported in patients with fulminant myocarditis supported with ECMO. Its use has also been reported in patients with septic shock and postcardiotomy shock. ECMO can be used as a bridge to recovery or to more durable mechanical support.[191]

Specific indications for and timing of temporary circulatory support (TCS) are evolving as technology improves and a wider experience is garnered. TCS offers greater improvements in systemic flow compared with inotropes and vasopressors, without the cost of increasing myocardial oxygen demand or increasing the risk of arrhythmia. Because the mortality associated with cardiogenic shock remains high, earlier use of TCS should be considered in patients whose conditions are not stabilizing or not improving with medical therapy and before the occurrence of severe end-organ damage or irreversible shock. Immediate use of TCS should be strongly considered in patients who present with profound shock.[187] In patients with refractory pulmonary edema or lung injury, ECMO improves oxygenation as well as support the circulation. TCS is relatively contraindicated in patients with a poor quality of life before their acute illness, a poor prognosis owing to severe comorbidities, established multiorgan system failure, severe neurologic impairment, sepsis, or high bleeding risk.

• BOX 27.6 Patients Who May Benefit From Ventricular Assist Device Therapy

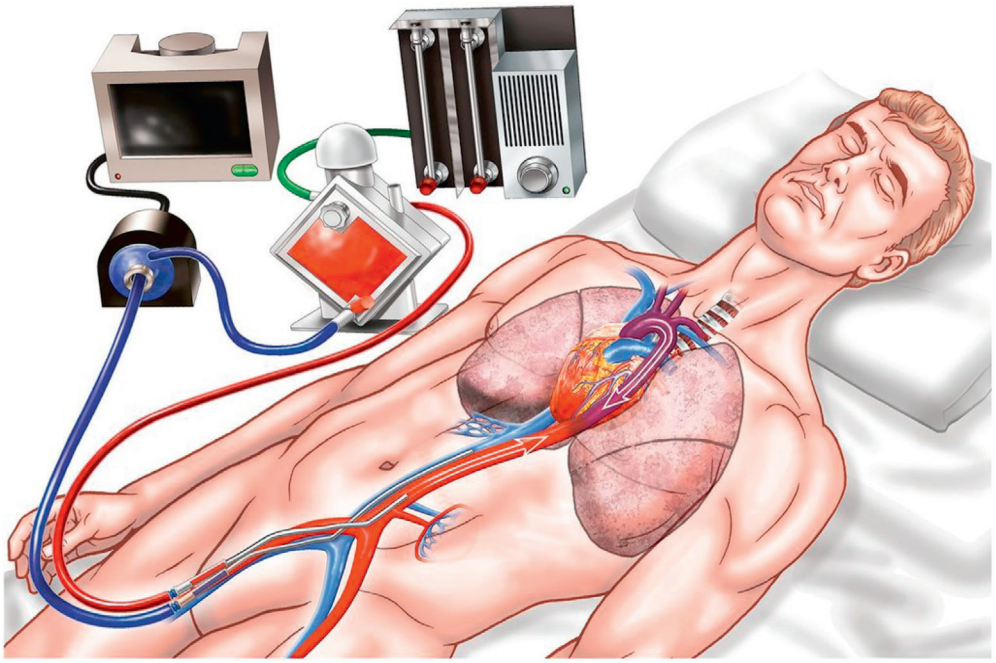
- Symptomatic functional class IV heart failure for longer than 2 months despite optimal medical and device therapy
- Two or more hospitalizations for decompensated heart failure in prior 12 months without obvious precipitating reason
- LVEF below 25%, or peak oxygen consumption less than 14 mL/kg per minute on CPET
- Dependence on inotropic therapy for more than 2 weeks
- Worsening end-organ function (renal, hepatic)
- Inability to tolerate β-blocker and/or ACE-I therapy because of hypotension
- Absence of severe RV dysfunction

ACE, *Angiotensin-converting enzyme;* CPET, *cardiopulmonary exercise testing;* LVEF, *left ventricular ejection fraction;* RV, *right ventricular.*

Durable Mechanical Support

It is estimated that more than 600,000 patients in the United States have chronic stage D, class IV heart failure. These patients have a very poor prognosis, even with appropriate pharmacologic and device therapy.[192] Cardiac transplantation offers an effective therapy for many patients with end-stage heart failure and is currently associated with a 1-year survival of more than 80% and median survival of 10.7 years.[193] However, the pool of donor hearts is currently less than 3000 per year in the United States and is not increasing.[194,195] Therefore durable MCS with ventricular assist devices (VADs) is being used with increasing frequency to support the function of the failing heart and provide normal cardiac output and flow to vital organs.

Patients considered for VAD therapy include those with refractory cardiogenic shock, patients dependent on and unable to be weaned from parenteral inotropic drugs for 14 days, those with persistent class IV symptoms despite optimal medical and device therapy for the prior 45 to 60 days, progressive cardiorenal dysfunction precluding the use of ACE inhibitors or hypotension preventing the use of ACE inhibitors and/or β-blockers, peak oxygen consumption of less than 14 mL/kg per minute on cardiopulmonary stress testing, or inability to perform this test[192,193] (Box 27.6).



• **Fig. 27.18** Femoral venoarterial extracorporeal membrane oxygenation (ECMO). When ECMO is implemented via femoral venous drainage and femoral arterial return in patients with residual native cardiac function and impaired lung function, reinfused oxygenated blood *(red arrow)*, flowing retrograde through the aorta, may meet resistance from poorly oxygenated blood flowing antegrade from the left ventricle *(purple arrow)*. Depending on the amount of cardiac function, the location of the interface between antegrade and retrograde flow will vary, and the reinfused oxygenated blood may not reach the cerebral and coronary vascular beds. (From Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol*. 2014;63:2769–2778.)

MCS can be used in clinical scenarios including the following:

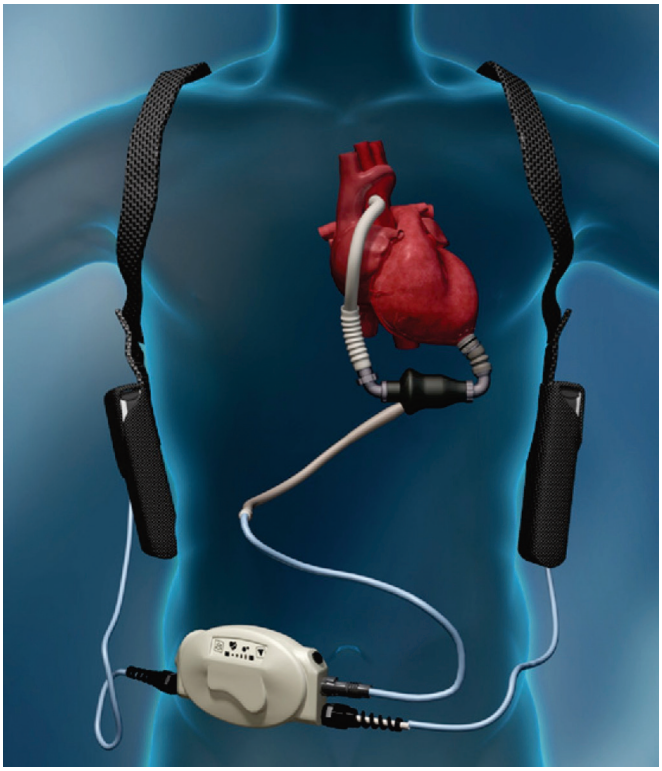
1. Bridge to cardiac transplantation. A mortality rate of 30% has been reported in patients listed for and awaiting heart transplantation, so MCS may enable many patients to survive to obtain transplantation.
2. Bridge to decision. These patients have an urgent need for support but have end-organ impairment exacerbated by heart failure, which makes transplantation a poor initial option. End-organ function may improve after a period of improved circulation with MCS, so that transplantation becomes feasible.
3. Bridge to recovery. Approximately 10% of patients have significant improvement in cardiac function during MCS such that survival is expected after removal of MCS. Examples include patients with severe peripartum cardiomyopathy and fulminant myocarditis.[167]
4. Destination therapy: long-term support with MCS. The HeartMate II (Thoratec Corp., Pleasanton, CA) continuous-flow VAD was approved for use as destination therapy in 2010. In 2014, 45.7% of VADs were implanted as destination therapy devices.[1]

Current VADs are small, implanted intracorporeally, and provide continuous, nonpulsatile flow. These continuous-flow devices function are much more durable and are associated with improved outcomes when compared with first-generation pulsatile-flow VADs. Current devices are suitable for long-term support. Battery packs are small and wearable, so that patients with VADs have freedom of movement and can participate in rehabilitation and normal daily activities (Fig. 27.19). These devices require systemic anticoagulation and antiplatelet therapy.

Appropriate patient selection for VAD use is vital. Exclusions to VAD therapy as destination therapy include the following[192,193,196]:

- Small body surface area (<1.2 m^2 or obesity with body mass index >45 kg/m^2)
- High pulmonary vascular resistance (>8 Woods units)
- Poor right ventricular function (defined by low right ventricular stroke work index or right atrial pressure/PCWP ratio >0.63),
- Serum creatinine above 3 mg/dL
- Elevated BUN
- Moderate to severe pulmonary disease
- Current cancer chemotherapy
- Inability to undergo anticoagulation
- Restrictive cardiomyopathy as cause of heart failure
- Poor social support
- Advanced liver disease (elevated transaminase, bilirubin, and international normalized ratio)
- Poor nutritional state (low albumin)
- Coagulopathy
- Neurologic deficits
- Severe anemia

Contraindications to the use of VADs include severe chronic obstructive pulmonary disease, need for hemodialysis, aortic insufficiency, or aortic valve mechanical prosthesis. Risk scores have been developed to attempt to define appropriate patient selection but need prospective validation. The incidence of major



• **Fig. 27.19** A continuous-flow left ventricular assist device. The axial, continuous-flow device is implanted within the chest and is attached to an external power source. (From Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol.* 2009;54:312–321.)

complications of VAD therapy at 2 years include right ventricular failure (18%), sepsis (19%), stroke (11.7%), and bleeding (54%). Gastrointestinal bleeding is associated with an acquired von Willebrand factor deficiency and gastrointestinal arteriovenous malformations. Other complications include pump thrombosis, right ventricular failure, and left ventricular underfilling, which may cause syncope and be due to hypovolemia or a "suction event" within the left ventricle. The most common causes of death in VAD patients are multiorgan system failure, neurologic dysfunction, sepsis, and VAD removal.[188]

In patients with VADs implanted as destination therapy, current survival is 75% at 1 year and 50% at 3 years. In 2013 and 2014, there were approximately 2400 continuous-flow VAD implants per year in the United States. A classification system (the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profile) is used to identify the severity of heart failure and to define suitability for VAD implantation (Fig. 27.20). Currently 80% of patients receiving VADs are in profiles 1 to 3 (critical cardiogenic shock, progressive decline despite continuous intravenous inotrope therapy, or stable on inotrope therapy). Patients in profiles 1 and 2 have a higher mortality. Current actuarial 1-year survival in all VAD recipients is 80%, with 2-year survival of 70%.[197] Device failure requiring replacement occurs in 4% to 9% of patients, most often because of pump malfunction, infection or pump thrombosis.[197] Patients with VADs have a rehospitalization rate at 1 year of 70%.[193] However, quality-of-life scores assessments shows continued improvement at 12 and 24 months after implantation.

Extending the indication for VAD therapy to less sick heart failure patients was studied in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial. Two hundred patients with low functional class 3 or ambulatory class 4 chronic heart failure were randomly assigned to receive optimal medical therapy versus VAD therapy. At 1 year, VAD patients had improved survival on assigned therapy (80% vs. 63%) and improved 6-minute walking distance. However, VAD therapy was associated with a higher rate of adverse events (1.9 events per patient-year), most often for bleeding, with an 80% rehospitalization rate. Optimal medical therapy was associated with an adverse event rate of 0.83 events per patient-year, predominantly heart failure exacerbation, and rehospitalization rate of 63%.[198]

Future refinements in design will include further miniaturization of pumps; providing some degree of pulsatile flow, which may reduce bleeding complications; total implantability without externalized drive lines, which will reduce the risk of infection; and remote monitoring of devices. Patients can now be supported with mechanical devices for many years with satisfactory quality of life.

Key Points

- Factors that identify patients with acute heart failure who have a poorer prognosis include elevated BUN and creatinine, low systolic blood pressure, hyponatremia, markedly elevated BNP, elevated serum troponin, and lower LVEF.
- When patients with chronic heart failure are admitted to the hospital with acute decompensation, it is important to determine the reason for the acute change in status to attempt to reduce the risk of future episodes of decompensation and rehospitalization.
- Although controlled trial evidence is lacking, the use of vasodilators in combination with diuretics for acute severe heart failure is often useful, especially in patients with hypertension or those who are not adequately responding to diuretics alone.
- The use of inotrope therapy is reserved for patients with symptomatic low cardiac output and signs of end-organ hypoperfusion or cardiogenic shock.
- Defining hemodynamics with a PA catheter is often useful, especially in patients in cardiogenic shock, worsening renal function, or in whom hemodynamic status is uncertain.
- Pharmacologic therapy of chronic heart failure caused by left ventricular systolic dysfunction has been shown to improve adverse left ventricular remodeling. Medical therapies shown to improve mortality include β-blockers, ACE inhibitors, angiotensin receptor blockers with or without neprilysin inhibitors, aldosterone antagonists, and a combination of hydralazine with isosorbide dinitrate.
- Acute ischemia caused by coronary artery disease should always be considered as a potential etiology in patients presenting with acute heart failure. When ischemia is identified, aggressive revascularization therapies should be strongly considered to improve prognosis.
- Although randomized controlled trial data are lacking, the treatment of HFpEF includes aggressive control of hypertension, treating cardiac ischemia, controlling arrhythmias including atrial fibrillation, and considering the use of spironolactone.
- In patients with cardiogenic shock, newer percutaneous devices are now available that provide effective hemodynamic support for days to assess whether cardiac function is improving or if more permanent mechanical support is indicated.

INTERMACS profile descriptions	Time frame for intervention
Profile 1: Critical Cardiogenic shock	
Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. *"Crash and burn."*	Definitive intervention needed within hours.
Profile 2: Progressive decline	
Patient with declining function despite intravenous inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance *"Siding on inotropes."* Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3: Stable but inotrope dependent	
Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction *"Dependent stability."*	Definitive intervention elective over a period of weeks to few months.
Profile 4: Resting symptoms	
Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over period of weeks to few months.
Profile 5: Exertion intolerant	
Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS 4 and require definitive intervention.	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
Profile 6: Exertion limited	
Patient without evidence of fluid overload is comfortable at rest and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment. *"Walking wounded."*	Variable, depends upon maintenance of nutrition, organ function, and activity level.
Profile 7: Advanced NYHA II	
A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Transplantation or circulatory support may not currently by indicated.
Modifiers for Profiles	
TCS-Temporary Circulatory Suppor—can modify only patients in hospital (other devices would be INTERMACS devices) includes IABP, ECMO, TandemHeart, Levitronix, BVS 5000 or AB5000, Impella.	Possible Profiles to Modify 1, 2, 3 in hospital.
A-Arrhythmia—can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise. This includes frequent ICD shock or requirement for external defibrillator, usually more than twice weekly.	Any profile.
FF-Frequent Flyer—can modify only outpatients, designating a patient requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy.	3 if at home, 4, 5, 6. A frequent flyer would rarely be profile 7.

• **Fig. 27.20** A classification of heart failure syndromes, with level 1 representing the most critical illness with an urgent need for mechanically assisted circulatory support. Levels 1 through 5 include patients with New York Heart Association *(NYHA)* class IV heart failure. Levels 5 and 6 describe patients with advanced NYHA class III heart failure. (From Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant.* 2009;28:535–541.)

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Review Questions

1. In patients with severe, chronic systolic heart failure who are being considered for durable mechanical support with a left ventricular assist device (LVAD), which of the following would be considered a contraindication to device implant?
   - **a.** Severely abnormal left ventricle (LV) systolic function with LV ejection fraction below 10%
   - **b.** Inability to wean from inotropic medications
   - **d.** Severe pulmonary hypertension with pulmonary vascular resistance (PVR) less than 2 Woods units
   - **d.** Poor right ventricular function

   Answer: d. LVAD therapy supports only left ventricular function. Severe right ventricular dysfunction is not effectively treated with an LVAD, and if present can result in severe right ventricular failure after LVAD implantation. Severe LV systolic function (choice a) and inability to wean from inotropic therapy (choice b) are indications for LVAD therapy, not contraindications. Severe pulmonary hypertension is a contraindication to LVAD therapy in the presence of severe elevation of pulmonary vascular resistance greater than 3 Woods units. Pulmonary hypertension with less severe elevation of PVR (choice c) may reflect pulmonary hypertension caused by left heart failure and would not preclude LVAD implantation.
2. Which of the following is true regarding the use of intravenous vasodilator therapy for the treatment of acute, severe heart failure?
   - **a.** Vasodilator therapy is useful for emergency management of heart failure caused by acute severe mitral regurgitation complicating acute myocardial infarction.
   - **b.** Vasodilator therapy has been shown to preserve renal function in patients with acute heart failure.
   - **c.** Neseritide is preferred over intravenous nitroglycerin or nitroprusside.
   - **d.** Vasodilator therapy is contraindicated in acute heart failure caused by acute coronary ischemia.

   Answer: a. In patients with acute severe mitral regurgitation (for instance, caused by rupture of chordae tendineae or ruptured head of papillary muscle complicating acute myocardial infarction) vasodilator therapy can lower preload, improve pulmonary edema, and improve cardiac output by lowering LV afterload. Vasodilator therapy is an appropriate temporizing measure while preparing patients for cardiac surgery. Vasodilators have not been shown to result in consistent improvement in renal function in heart failure patients (choice b incorrect), and neseritide does not offer consistent benefits over other vasodilator drugs (choice c incorrect). In patients with acute heart failure caused by acute coronary ischemia, treatment with intravenous nitroglycerin is an effective therapy (choice d incorrect).
3. Which is the most common presentation of acute heart failure in the hospital setting?
   - **a.** Acute worsening of chronic heart failure
   - **b.** Acute pulmonary edema caused by acute coronary ischemia
   - **c.** Acute pulmonary edema caused by severe hypertension
   - **d.** Cardiogenic shock

   Answer: a. Roughly 75% of hospital admissions for acute decompensated heart failure involve acute worsening of chronic heart failure, either heart failure with normal or reduced LV ejection fraction. Acute pulmonary edema, caused by either acute ischemia or severe hypertension, accounts for roughly 25% of heart failure admissions (choices b and c incorrect). Cardiogenic shock accounts for 5% of acute heart failure admissions (choice d incorrect).

28

Anaphylaxis and Anaphylactic Shock

DANIEL DE BACKER

CHAPTER OUTLINE

Pathophysiology

Symptoms and Clinical Diagnosis

Treatment and Management
- Initial Management
- General Management
- Steroids and Antihistaminic Agents
- Other Agents

What Should Be Done After Recovery for Anaphylactic Shock?

The severe forms of anaphylaxis include severe cutaneous lesions, respiratory failure and upper airway obstruction, and circulatory failure (anaphylactic shock). Although respiratory symptoms or cutaneous lesions may be life-threatening, the most severe cases of anaphylaxis are related to the rapid progression into a generalized systemic reaction.

Pathophysiology

Mast cells and basophils play a prominent role in anaphylaxis. Mast cells are based primarily in tissues (skin, respiratory, and gastrointestinal tract) but are also in the blood. When these cells are activated by immunoglobulin E (IgE) and allergen, these cells degranulate and release numerous mediators, including histamine but also leukotrienes, prostaglandins, and other inflammatory mediators. Mediators from polymorphonuclear leukocytes and platelets are responsible for late-phase reactions after the initial anaphylactic event. These mediators are associated with endothelial dysfunction (manifested mostly by increased vascular permeability leading to loss of intravascular volume in conjunction with swelling and interstitial edema, and abnormal vascular reactivity leading to hypotension associated with marked skin vasodilation) and bronchial smooth muscle constriction.

Anaphylactic reactions are in many instances mediated by IgE but some severe episodes can also be related to non-IgE–mediated mechanisms (sometimes called anaphylactoid reaction). The World Allergy Organization suggested that the term *anaphylactoid* be abandoned and that all events should be called *anaphylactic episodes*, regardless of the mechanism of production.[1] They further suggested to divide these into immunologic and nonimmunologic events. Nonimmunologic anaphylactic events could be considered synonymous with the term anaphylactoid, and the immunologic events were further subcategorized as mediated and not mediated by IgE. A separate category was further added that is neither immunologic nor nonimmunologic, but rather "idiopathic."[1]

The immune-mediated IgE-dependent or IgE-independent and nonimmune-mediated mast cell degranulation-mediated anaphylactic reactions have similar clinical features. In IgE-mediated anaphylaxis, the IgE ligated to the antigen activate surface receptors that induces the release of mediators. In non-IgE–mediated anaphylactic reactions, the direct activation of surface receptors on mast cells and basophils by antigen is responsible for similar mediator release. Among the agents able to directly activate these surface receptors, iodinated contrast agents, opiates, and some antibiotics are the most common (Box 28.1).

Symptoms and Clinical Diagnosis

The symptoms of anaphylaxis are quite variable and can affect the following:
- Skin (flushing, itching, urticaria, angioedema, morbilliform rash)
- Eyes and orbits (periorbital itching, erythema and edema, conjunctival erythema, tearing)
- Mouth and mucosa (itching of lips and tongue, swelling of lips and tongue)
- Upper respiratory system (rhinorrhea, sneezing, dysphonia, hoarseness, stridor, dry cough)
- Lower airways (tachypnea, dyspnea, cough, wheezing and bronchospasm, respiratory arrest)
- Cardiovascular system (tachycardia, bradycardia [less common], hypotension and shock, cardiac arrest)

The clinical features associated with severe anaphylaxis are often associating cutaneous (rash and edema), respiratory symptoms (stridor, bronchospasm), and circulatory symptoms (hypotension or shock).

Several clinical criteria can be used to diagnose anaphylaxis (Box 28.2). These clinical criteria are mostly based on respiratory and/or circulatory compromise that occurs very acutely in the context of known or potential exposure to a causal agent.

The differential diagnosis includes vasovagal/neurocardiogenic reactions, pulmonary embolism, and septic shock for the cardiovascular symptoms. For the respiratory symptoms, the differential diagnosis includes acute respiratory decompensation from severe asthma attacks, foreign body aspiration, and vocal cord dysfunction.

When hemodynamic evaluation is available, it typically shows decreased systemic vascular resistance and low filling pressures.[2,3] Cardiac output is often low before volume replacement. Of note, the heart is often involved in anaphylaxis, either directly or under

• BOX 28.1 Agents Frequently Associated With Immune and Nonimmune Types of Anaphylaxis

Immunologic Mechanisms

IgE-mediated
- Food (nuts, shellfish, fruits, and so on)
- Venoms (stinging insects)
- Medications (β-lactam antibiotics, NSAIDs, neuromuscular blocking agents, and so on)
- Natural rubber latex
- Seminal fluid
- Radioconstrast media (in some cases)

IgE-Independent
- Radioconstrast media (in most cases)
- Dextrans
- Monoclonal antibodies (Rituximab)
- Medications (β-lactam antibiotics, NSAIDs, and so on)
- Natural rubber latex
- Seminal fluid

Nonimmunologic Mechanisms

Medications (opioids, protamine, and so on)

NSAIDs, *Nonsteroidal antiinflammatory drugs.*

• BOX 28.2 Clinical Criteria for Diagnosing Anaphylaxis[1]

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips/tongue/uvula) and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia collapse, syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia collapse, syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

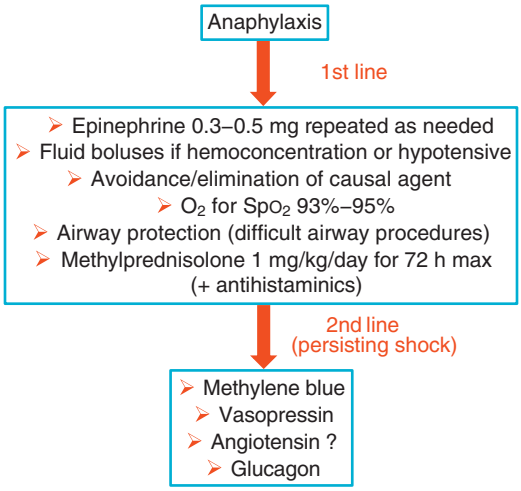
OR

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   a. Infants and children: low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure
   b. Adults: systolic blood pressure of <90 mm Hg or >30% decrease from that person's baseline

PEF, *Peak expiratory flow.*

the influence of high levels of endogenous and exogenous catecholamines. The heart is rich in mast cells, and mediators released from activated human heart mast cells strongly influence ventricular function, cardiac rhythm, and coronary artery tone.[4] Cases of myocardial ischemia (sometimes related to coronary spasm[2] and/or stent thrombosis or occlusion by mast cells and eosinophils—the Kounis syndrome[5]) and cases of Takotsubo syndromes have been described[2,6–8]; these can be accompanied by severe depression of myocardial contractility. Arrhythmic events can also frequently occur.[2] Given this potential cardiac involvement, it is recommended to perform echocardiography to evaluate cardiac function of these patients, as in other causes of shock.[9,10]

When in doubt that the clinical pattern corresponds to anaphylaxis, it is recommended to measure mast cell tryptase as an indicator of mast cell degranulation.[11,12] Serial mast cell tryptase measurements are obtained and anaphylaxis is considered when the rise in tryptase is higher than a given threshold (peak tryptase should be >1.2 × baseline tryptase + 2 mg/L). Although this measure is not specific to the causative agent or to a mechanism (IgE-mediated or not), it allows confirmation of the anaphylactic process.[12]



• **Fig. 28.1** Management of a patient with severe anaphylaxis. O_2, Oxygen; Spo_2, oxygen saturation measured by pulse oximetry.

Treatment and Management

Case fatality register studies have demonstrated that deaths can occur within minutes of the onset of an anaphylactic reaction and that the severity of the reaction is often difficult to predict initially.[13,14] It is therefore consistently advocated by guidelines that all reactions are promptly managed by initiating a range of pharmacologic and nonpharmacologic interventions.[15] These actions are summarized in Fig. 28.1.

Initial Management

Anaphylactic shock is characterized by vasoplegia and capillary leak. Hence, initial management should include volume replacement and vasopressors. In opposition perhaps with other types of shock, prioritization is given to vasopressor and in particular to epinephrine.

Epinephrine

Epinephrine is the drug of choice as it interacts with pathophysiologic mechanisms of anaphylaxis.[16] The β-adrenergic effects of epinephrine inhibit mast cell degranulation by increasing intracellular levels of cyclic adenosine monophosphate. In addition, β-adrenergic stimulation reverses bronchospasm, whereas the

α-adrenergic vasoconstrictive properties of epinephrine may increase vascular tone and improve venous return by constriction of capacitance veins.[17] Accordingly, it increases cardiac filling and improves cardiac output. By its action on diastolic pressure, epinephrine also enhances coronary flow. Of note, epinephrine also increases myocardial contractility and increases heart rate, and these effects are not always warranted in the early phase, as it can led to obstruction of the left ventricular outflow tract. In this situation, fluid loading would help to relieve the symptoms.[18]

Even though the effect of epinephrine on mortality remains unproven by large-scale randomized studies, it is widely accepted that epinephrine should be administered as soon as possible after the onset of severe anaphylaxis,[14–16] even when shock is not present.[14] Epinephrine is recommended for self-administered therapy as an intramuscular injection[14] (usual dose 0.3–0.5 mg repeated at 5- to 10-minute intervals depending on the symptoms). In the hospital and under the supervision of emergency physicians, anesthesiologists, and/or intensivists, epinephrine should be administered intravenously in patients with shock (boluses of 0.3–0.5 mg that can be increased to 1 mg, repeated as needed).

When shock persists in the hospital setting, after administration of several boluses of 1 mg epinephrine, what would be the vasopressor agent of choice? Data are lacking to decide whether prolonged epinephrine infusion should be used or whether another vasopressor agent should be used. In many instances, physicians use either continuous infusion of epinephrine or norepinephrine. In addition, alternative agents may be considered (see additional measures).

Fluids

Fluids are also a key part of the management of anaphylactic shock. Because of the increased permeability and vascular dilation, hypovolemia is an important component of anaphylactic shock. Hemoconcentration is often present as an index of the severity of hypovolemia. Fluid replacement should thus be generous in patients with anaphylactic shock. Crystalloids should be used as a first choice, especially in patients presenting with hemoconcentration. Colloids may also be used, in combination with crystalloids. The exact amount of fluids to administer is highly variable, especially when capillary leak is ongoing. Fluid boluses are usually indicated as long as hemoconcentration persists. After correction of hemoconcentration, administration should be guided using classic hemodynamic guidance, preferring dynamic variables to predict fluid responsiveness when these can be applied.[9]

General Management

Avoidance of the causal agent is mandatory. In patients with venom exposure, it is recommended to closely look at the skin to ensure that retained stingers should not be extracted. For in-hospital exposure, it is important to stop administration of the causative agent (contrast media, antibiotic, dextran, gelatins, exposure to latex, and so on).

Airway management is crucial, and difficult intubation procedures should be used for patients with suspected laryngeal edema. Oxygen is administered to ensure a pulse oxygen saturation between 93% and 96%.

Steroids and Antihistaminic Agents

Systematic reviews are inconclusive on the use of steroids and antihistaminic agents.[19] However, these agents are used very frequently, especially in the most severe cases. Their effect on the initial insult may be limited but these seem mostly useful in limiting the secondary phase. Steroids inhibit the synthesis of histamine and therefore may limit the protraction of symptoms or biphasic reactions.[20] Methylprednisolone (1 mg/kg per 24 hours) mays be administered up to 72 hours.

Other Agents

Modulation of Guanylate Cyclase

Methylene blue inhibits guanylate cyclase and as such may not only stabilize endothelial dysfunction but also limit mastocyte degranulation. The use of methylene blue is mostly supported by experimental evidence and case reports.[21–25] In an experimental model of protamine-induced anaphylactic shock, methylene blue administration attenuated hypotension and improved cardiac function, without affecting nitric oxide levels.[26] Experimental data also suggest that the effects of the combination of epinephrine and methylene blue are much better than the effects of methylene blue in isolation.[25] Several case studies reported beneficial effects of methylene blue in epinephrine-refractory hypotension associated with anaphylactic shock.[22,23] Methylene blue may also be beneficial for respiratory symptoms refractory to epinephrine in severe anaphylaxis without hypotension.[24]

Nitric Oxide Modulation?

As anaphylactic shock is a form of severe vasodilation, inhibition of nitric oxide may sound attractive. Inhibition of nitric oxide attenuates hypotension and hemoconcentration but fails to improve myocardial contractility.[27] In an experimental model of anaphylactic shock, nitric oxide inhibition improved blood pressure but resulted in impaired myocardial function, an increase in bronchospasm and pulmonary vascular resistance, and increased mortality rate.[28] On the other hand, nitric oxide donors improve bronchospasm.[28,29] These experimental results highlight the dual role of nitric oxide in anaphylactic shock.

Vasopressin

Experimental data suggest that vasopressin levels are initially increased in anaphylactic shock in response to hypotension and that vasopressin inhibition worsens the outcome of anaphylactic shock.[30] However, when direct comparison with epinephrine is provided, epinephrine improved bronchospasm and cerebral oxygenation, whereas vasopressin had minimal effects on these aspects.[31,32] Accordingly, vasopressin should not replace epinephrine. However, combination of epinephrine and vasopressin may be considered. Administration of vasopressin in epinephrine-resistant anaphylactic shock resulted in a prompt hemodynamic stabilization in a small series of cases.[33]

Angiotensin

Angiotensin is a promising agent for refractory hypotension in septic shock.[34] Experimental data suggest that angiotensin levels are initially increased in anaphylactic shock in response to hypotension.[30] Also, patients treated with angiotensin-converting enzyme inhibitors have a worse outcome when anaphylactic shock develops,[35] possibly because angiotensin-converting enzyme inhibitors prime mast cells.[36] Hence, angiotensin administration may appear attractive, but data are lacking at this stage to support its use.

Glucagon

Glucagon inhibits histamine release.[37] In an isolated heart model submitted to anaphylaxis, glucagon provided protection from anaphylaxis-induced arrhythmias and improved coronary perfusion.[37]

In humans, the use of glucagon has been described successfully in case reports[38] but series, even retrospective, are lacking.

What Should Be Done After Recovery for Anaphylactic Shock?

The causative agent, if not yet known, should be identified by review of case history. When the cause is not identified, delayed evaluation should be conducted by an allergist or immunologist. For some of the causative agents (some foods, pollens, penicillins, venoms of stinging insects, and so on), the cause of anaphylaxis may be supported by the results of skin tests and/or in vitro IgE tests. Unfortunately, these tests are not available for the majority of medications, and the causative agent often remains speculative. The file of the patient should clearly identify the allergic agent and the patient should carry a notice of this allergy in a wallet. When the cause is not fully avoidable or when the causative agent cannot be determined, the patient should be supplied with an autoinjectable epinephrine pen.

Key Points

- Anaphylaxis is related to degranulation of mast cells and basophils after contact to an antigen.
- Classic IgE-mediated allergic reaction (type I), IgE-independent, and nonimmune anaphylactic reactions are clinically identical and respond similarly to treatment.
- The clinical consequences of anaphylaxis are related to endothelial activation with vasoplegia and increased microvascular permeability.
- Hemodynamic characteristics of anaphylaxis include tachycardia, hypotension, decreased cardiac filling pressures, and decreased systemic vascular resistance.
- Cardiac involvement is frequent in anaphylaxis. Echocardiography should be performed in severe cases to assess cardiac function.
- Anaphylaxis management includes the following actions: securing airway patency, removing the causative agent, administering epinephrine, and administering fluid to correct hypovolemia.
- Corticosteroids should be given in severe cases to prevent late-phase reactions.
- Methylene blue and vasopressin can be considered as second-line agents in addition to epinephrine.
- All patients who have experienced anaphylaxis should be referred for appropriate follow-up. These patients may require allergy testing, desensitization, and premedication strategies.

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Review Questions

1. Which one of the following hemodynamic patterns is *most* likely to be found in a patient with anaphylactic shock?

	MAP	CVP	SVR	CO	HCT
a.	85	15	↑	8.0	53
b.	45	15	↓	3.5	35
c.	45	2	↓	5.5	55
d.	85	2	↑	8.0	35

CO, Cardiac output; *CVP*, central venous pressure; *HCT*, hematocrit; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance.

Answer: c. Anaphylactic shock is characterized by severe vasodilation and hemoconcentration. Even though cardiac output is usually increased, volume repletion is often required to achieve this hyperdynamic pattern.

2. A patient develops anaphylactic shock in the radiology suite. Which one of the following is the *most* appropriate first-line treatment for the patient's hypotension?

a. Norepinephrine
b. Epinephrine
c. Hydrocortisone
d. Dobutamine
e. Vasopressin

Answer: b. Epinephrine is the first-line agent, combining an antidegranulation effect through β-stimulation and a vasoconstrictive effect through α-stimulation. Dobutamine is a sympathomimetic agent with predominantly inotropic effects and would not correct the hypotension in anaphylactic shock. Norepinephrine and vasopressin are second-line agents that can be used in cases refractory to epinephrine and fluids. Steroids are used mostly to prevent late-phase reactions and have no immediate effects on hemodynamic abnormalities.

3. A patient is admitted to the intensive care unit with persistent hypotension and tachycardia in the context of anaphylactic shock, despite administration of multiple doses of epinephrine, fluids, and steroids. What are the potential second line agents? (Multiple responses are possible.)

a. Continuous epinephrine infusion
b. Norepinephrine
c. Vasopressin
d. Methylene blue
e. Glucagon
f. Esmolol

Answers: b, c, d, and e. This patient already received multiple doses of epinephrine and is quite tachycardic. Further stimulation of β-adrenergic receptors may increase tachycardia and is unlikely to have additional effects on degranulation. Norepinephrine, vasopressin, methylene blue, and glucagon can all be considered as second-line agents as an adjunct but not in replacement of first-line agents. Esmolol is contraindicated as β-blockers worsen the outcome of patients with anaphylactic shock.

29

Acute Coronary Syndromes and Acute Myocardial Infarction

STEVEN WERNS

CHAPTER OUTLINE

Definitions

ST-Segment Elevation Myocardial Infarction
- Clinical Manifestations
- Diagnostic Approach
- Approach to Management
- Management of Complications

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction
- Clinical Manifestations
- Diagnostic Approach
- Approach to Management

Definitions

Acute coronary syndrome (ACS) refers to "a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow."[1] Therefore the ACS spectrum encompasses unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). The presence or absence in the blood of either troponin or the MB (muscle-brain) fraction of creatine kinase (CK-MB) determines the distinction between a diagnosis of either UA or myocardial infarction (MI). (For convenience, these and other relevant abbreviations are listed in Table 29.1.) An expert consensus document titled the "Third Universal Definition of Myocardial Infarction" was published in 2012 by a joint task force of the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation.[2] The clinical diagnosis of an acute MI was defined as a rise or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]), development of pathologic Q waves in the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[2] Definitions also exist for the diagnosis of an acute MI in three other circumstances: sudden death, after percutaneous coronary intervention (PCI), and after coronary artery bypass graft (CABG) surgery.[2]

The increased sensitivity of troponin compared with CK-MB and the new criteria for the diagnosis of acute MI dictate that many patients who were classified as having UA by the old criteria are now given a diagnosis of acute MI. Among 1851 patients enrolled in a prospective study, 538 received a diagnosis of acute MI based on dynamic changes in troponin T, compared with only 427 patients when CK-MB was used to diagnose acute MI, representing a 41% increase.[3] A retrospective analysis of 2181 patients with suspected ACS and no ST-segment elevation found that the prevalence of acute MI ranged from 9.7% to 22% based on differing troponin-based definitions, compared with 7.8% based on CK-MB alone.[4] Meier and colleagues[5] studied 493 consecutive patients with suspected ACS. Of those, 224 patients had elevated CK-MB, and an additional 51 patients had normal CK-MB but elevated troponin I levels. The latter group was characterized by a greater incidence of comorbid conditions and higher 6-month mortality. Among 29,357 patients with non–ST-segment elevation ACS (NSTE-ACS) who were enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines? (CRUSADE) registry, 18% of patients were CK-MB negative and troponin positive.[6] The risk of in-hospital death was significantly increased among troponin-positive patients regardless of CK-MB status.

The Global Registry of Acute Coronary Events (GRACE) is a prospective observational registry of 26,267 patients with ACS who were admitted to 106 hospitals in 14 countries.[7] (A list of eponyms in use for various cardiac registries and drug trials is provided in Table 29.2.) Among the 10,719 patients (10.4%) with both CK-MB and troponin data, 1110 patients without elevation of CK-MB were diagnosed with acute MI by virtue of elevated troponin. Patients who were troponin negative had similar 6-month mortality regardless of CK-MB status, but patients who were CK-MB negative and troponin positive had a twofold greater hospital case-fatality rate.

The advent of highly sensitive troponin assays has contributed to further changes in the detection of acute MI in patients with myocardial ischemia.[8–10] Bonaca and colleagues[8] conducted a prospective study of the prognostic value of a sensitive assay for

TABLE 29.1 Cardiac Critical Care Abbreviations

Abbreviation	Definition	Abbreviation	Definition
ACC	American College of Cardiology	ICD	Implantable cardioverter-defibrillator
ACCF	American College of Cardiology Foundation	INR	International normalized ratio
ACE	Angiotensin-converting enzyme	IRA	Infarct-related artery
ACS	Acute coronary syndrome	LAD	Left anterior descending (artery)
ACT	Activated clotting time	LBBB	Left bundle branch block
AF	Atrial fibrillation	LDL	Low-density lipoprotein
AHA	American Heart Association	LMWH	Low-molecular-weight heparin
APSAC	Anisoylated plasminogen-streptokinase activator complex	LVEF	Left ventricular ejection fraction
aPTT	Activated partial thromboplastin time	MI	Myocardial infarction
ARB	Angiotensin receptor blocker	MR	Mitral regurgitation
AVB	Atrioventricular block	MRI	Magnetic resonance imaging
BMS	Bare metal stent	NNT	Number needed to treat
BNP	Brain natriuretic peptide	NO	Nitric oxide
CABG	Coronary artery bypass grafting	NSAIDs	Nonsteroidal antiinflammatory drugs
CAD	Coronary artery disease	NSTE-ACS	Non–ST-segment elevation acute coronary syndrome
HF	Congestive heart failure	NSTEMI	Non–ST-segment elevation myocardial infarction
CCTA	Coronary CT angiography	NTG	Nitroglycerin
CI	Confidence interval	PA	Pulmonary artery
CK-MB	Muscle-brain fraction of creatine kinase	PCI	Percutaneous coronary intervention
CT	Computed tomography	PCWP	Pulmonary capillary wedge pressure
DAPT	Dual antiplatelet therapy	RCA	Right coronary artery
DES	Drug-eluting stent	rPA	Reteplase
ECG	Electrocardiogram	RR	Relative risk
EF	Ejection fraction	RVMI	Right ventricular myocardial infarction
ESC	European Society of Cardiology	SK	Streptokinase
FDA	U.S. Food and Drug Administration	STEMI	ST-segment elevation myocardial infarction
GP	Glycoprotein	t-PA	Tissue plasminogen activator
HDL	High-density lipoprotein	UA	Unstable angina
HF	Heart failure	UFH	Unfractionated heparin
HIT	heparin-induced thrombocytopenia	VF	Ventricular fibrillation
IABP	Intraaortic balloon pump	VSR	Ventricular septal rupture
ICH	Intracranial hemorrhage	VT	Ventricular tachycardia
ICU	Intensive care unit		

cardiac troponin I in 4513 patients with NSTE-ACS enrolled in a randomized trial of ranolazine versus placebo. Patients with low-level increases of serum troponin I (0.04 μg/L to < 0.1 μg/L) had a significantly higher risk of death at 12 months (6.4% versus 2.4%, $P = 0.005$). Another study found that implementation of a sensitive assay for troponin I in patients with suspected ACS increased the detection of MI by 29%, identified patients who were at the highest risk of recurrent MI and death, and was associated with improved clinical management that resulted in fewer deaths and admissions with recurrent MI.[9] It is important to recognize that other conditions that occur frequently in patients with cardiovascular disease, such as heart failure (HF) and chronic kidney disease, may confound the diagnosis of ACS because they can be associated with elevated troponin levels.[10]

TABLE 29.2 Cardiac Drug Trial and Registry Eponyms

Eponym	Definition
4S	Scandinavian Simvastatin Survival Study
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
AIMI	AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction
AIRE	Acute Infarction Ramipril Efficacy
APEX-AMI	Assessment of Pexelizumab in Acute Myocardial Infarction
APRICOT	Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis
ASPECT-2	Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2
ASSENT	Assessment of Safety and Efficacy of a New Thrombolytic
AVOID	Air Versus Oxygen in myocarDial infarction study
BHAT	Beta-Blocker Heart Attack Trial
CADILLAC	Controlled Abciximab and Device Investigation to Lower Angioplasty Complications
CAPRICORN	Carvedilol Post-Infarct Survival Control in LV Dysfunction
CARE	Cholesterol and Recurrent Events Trial
CAST	Cardiac Arrhythmia Suppression Trial
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CRISP AMI	Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines
CT-STAT	Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
DANAMI	Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty for Acute Myocardial Infarction
DAPT	Dual Antiplatelet Therapy Study
DAVIT-II	Danish Verapamil Infarction Trial
DETO2X-AMI	The Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction
Early ACS	The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome
EARLY-BAMI	Early-Beta Blocker Administration Before Reperfusion Primary PCI in Patients with ST-elevation Myocardial Infarction
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EUROMAX	European Ambulance Acute Coronary Syndrome Angiography Trial
EXTRACT	Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment
FRISC	Fast Revascularization during Instability in Coronary Artery Disease
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
HINT	Holland Interuniversity Nifedipine/Metoprolol Trial
HORIZONS-AMI	Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction
IABP-SHOCK II	Investigators in the Intraaortic Balloon Pump in Cardiogenic Shock II
ICTUS	Invasive versus Conservative Treatment in Unstable Coronary Syndromes

TABLE 29.2 Cardiac Drug Trial and Registry Eponyms—cont'd

Eponym	Definition
ISIS	International Study of Infarct Survival
LATE	Late Assessment of Thrombolytic Efficacy
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease Trial
MDPIT	Multicenter Diltiazem Postinfarction Trial
MERLIN	Middlesbrough Early Revascularization to Limit Infarction
METOCARD-CNIC	Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction
MILIS	Multicenter Investigation of the Limitation of Infarct Size
MITI	Myocardial Infarction Triage and Intervention
NRMI	National Registry of MI
OASIS	Organization for the Assessment of Strategies for Ischemic Syndromes
OAT	Occluded Artery Trial
OPTIMAAL	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PAMI	Primary Angioplasty in Myocardial Infarction
PAMI-II	Second Primary Angioplasty in Myocardial Infarction
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54
PLATO	Study of Platelet Inhibition and Patient Outcomes
PROVE IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
REACT	Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
RITA-3	Randomized Intervention Trial of Unstable Angina
SAVE	Survival and Ventricular Enlargement
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?
SMILE	Survival of Myocardial Infarction Long-Term Evaluation
SWORD	Survival With Oral *d*-Sotalol
TACTICS	Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy
TAPAS	Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study
TASTE	Thrombus Aspiration During ST-Segment Elevation MI
TIMACS	Timing of Intervention in Acute Coronary Syndrome
TIMI	Thrombolysis in Myocardial Infarction
TOTAL	Trial of routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI
TRACE	Trandolapril Cardiac Evaluation
TRANSFER-AMI	Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction
TRILOGY-ACS	Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
TRITON-TIMI 38	Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38
VALIANT	Valsartan in Acute Myocardial Infarction
VANQWISH	Veterans Affairs Non-Q Wave Infarction Strategies in Hospital
WARIS II	Warfarin, Aspirin, Reinfarction Study

ST-Segment Elevation Myocardial Infarction

Clinical Manifestations

Clinical History

The initial differentiation of ACS from other causes of chest pain is based on the chest pain history, physical examination, presence of risk factors for coronary artery disease (CAD), and the ECG. Certain chest pain characteristics are associated with decreased or increased likelihoods of ACS.[11] The feature that was found to be associated with the highest risk of a diagnosis of ACS is radiation of pain to one or both shoulders or arms. A prospective study of patients who presented to an emergency department for evaluation of chest pain determined that pain relief by nitroglycerin is not a useful indicator of the presence or absence of ACS.[12] Nitroglycerin relieved chest pain in 35% of patients with active CAD, compared with 41% of patients without active CAD ($P > 0.2$).[12]

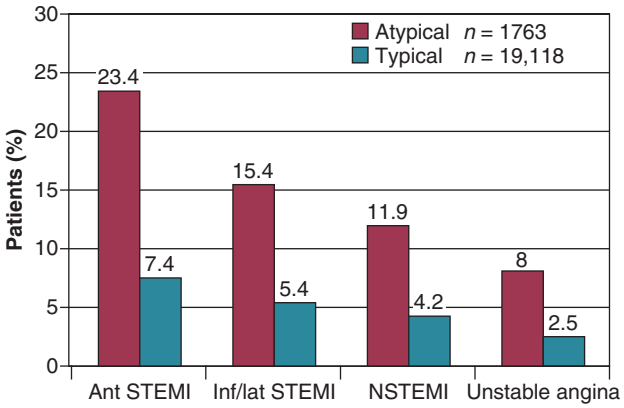
Another literature review included 15 studies published from 1989 to 2002 that identified symptoms of ACS.[13] Chest pain was the most common symptom among both men and women, but atypical symptoms were common, especially among women. Compared with men, women with ACS were significantly more likely to report back and jaw pain, nausea, vomiting, dyspnea, indigestion, and palpitations. A significant fraction of patients with acute MI do not complain of chest pain at the time of presentation.[14–16] A total of 1674 U.S. hospitals contributed patients to the National Registry of Myocardial Infarction (NRMI) 2.[14] Among 434,877 patients with confirmed MI who were enrolled in the NRMI 2 registry between June 1994 and March 1998, 142,445 (33%) did not have chest pain at the time of presentation to the hospital. There were several notable differences between the groups who presented with and without chest pain. Only 23% of patients without chest pain had ST-segment elevation on the initial ECG, compared with 47% of the patients with chest pain. The group of patients who presented without chest pain was older (74 years vs. 67 years) and had a higher proportion of women (49% vs. 38%). A subsequent analysis of 1,143,513 patients enrolled in the registry found that the proportion of patients who presented without chest pain was significantly higher for women than men (42% vs. 30.7%; $P < 0.001$).[16] The gender differences in clinical presentation without chest pain diminished with increasing age.[16]

The absence of chest pain has a major impact on hospital management and outcomes, even among patients who present with ST-segment elevation.[14–16] A report from the GRACE registry compared 6385 patients with STEMI and typical symptoms with 541 patients whose presenting symptoms did not include chest pain.[15] Patients without chest pain were significantly less likely to receive reperfusion therapy (i.e., fibrinolysis or primary PCI), β-blockers, and aspirin. Perhaps as a consequence of undertreatment, hospital mortality was significantly greater among patients with STEMI and no chest pain than among patients with chest pain (18.7% vs. 6.3%; $P < 0.001$) (Fig. 29.1).

There is a long-standing belief that diabetes is associated with silent myocardial ischemia and painless MI owing to autonomic neuropathy. Nevertheless, in the NRMI 2 registry, only 33% of the patients with painless MI had diabetes mellitus, and in the GRACE registry, only 32% of patients with painless ACS had diabetes.[14,15]

Physical Examination

The initial physical examination provides important prognostic information in patients with acute MI. Killip and Kimball published their classic study in 1967.[17] Among 250 patients with acute MI, 81 patients (33%) had no HF (Killip class I), 96 (38%) had mild HF (Killip class II), 26 (10%) had pulmonary edema (Killip class III), and 47 (19%) had cardiogenic shock (Killip class IV). Respective mortality rates were 6%, 17%, 38%, and 81%. Although the overall mortality for acute MI has decreased since 1967, the Killip class on admission remains a powerful predictor of outcome among patients treated with reperfusion therapy.[18,19] DeGeare and coworkers[19] performed an analysis of 2654 patients with acute MI who were enrolled in three primary angioplasty trials. Patients in Killip class IV were excluded. Increasing Killip class was associated with an increased need for intraaortic balloon counterpulsation and a greater incidence of renal failure, major arrhythmias, and major bleeding. After controlling for confounding variables, the Killip class on admission remained a multivariate predictor of both in-hospital and 6-month mortality.



• **Fig. 29.1** In-hospital mortality rate in subgroups with acute coronary syndrome (ACS) according to presenting symptoms. *Ant,* Anterior; *Inf/lat,* inferior or lateral; *NSTEMI,* non–-ST-segment elevation myocardial infarction; *STEMI,* ST-segment elevation myocardial infarction. (From Brieger D, Eagle KA, Goodman SG, et al. Acute coronary syndromes without chest pain, an underdiagnosed and underreated high-risk group: Insights from the Global Registry of Acute Coronary Events. *Chest.* 2004;126:461–469.)

The physical examination also may provide clues to the diagnosis of causes of chest pain other than ACS. A pericardial friction rub may be audible in patients with pericarditis. Aortic dissection may be associated with diminished or absent pulses. Both diagnoses are important to exclude because they are contraindications to fibrinolytic therapy.

Diagnostic Approach

The ACCF/AHA Task Force on Practice Guidelines and the ESC have published detailed recommendations for the diagnosis and management of patients with ACS.[1,20–24] Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective are categorized as class I[1,24] (not to be confused with Killip class I). Conditions for which there is conflicting evidence or divergence of opinion are categorized as class II. The weight of evidence or opinion is in favor of usefulness or efficacy for class IIa conditions, whereas usefulness or efficacy is less well established for class IIb conditions. Class III conditions are those for which there is evidence or general agreement that a procedure/treatment is not useful or effective and may be harmful in some cases.

Electrocardiogram

The 2004 iteration of the ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction include three class I indications for an ECG.[20] The first is that all patients with chest discomfort or other symptoms suggestive of STEMI should have a 12-lead ECG within 10 minutes of arrival in the emergency department (and it should be interpreted by an experienced physician). The second is that serial ECGs should be performed at intervals of 5 to 10 minutes in patients with a nondiagnostic initial ECG if the patient remains symptomatic and there is a high clinical suspicion of STEMI. The third is that right-sided ECG leads should be obtained to screen for right ventricular MI in patients with inferior STEMI. A fourth class I indication for a 12-lead ECG was included in the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction.[24] It recommended that a 12-lead ECG be performed by emergency medical services personnel at the site of first medical contact in patients with symptoms consistent with a STEMI.

The electrocardiographic diagnosis of acute MI in the presence of an LBBB is problematic.[25,26] Angiographic studies have demonstrated a low prevalence of acute MI among patients with a new LBBB.[27–30] Analysis of the Mayo Clinic's primary PCI database found that only 12 of 36 patients with a new LBBB and clinical symptoms suspicious for an MI met troponin criteria for an MI, resulting in emergency activation of the cardiac catheterization laboratory for a false-positive diagnosis of acute MI in two-thirds of patients with a new LBBB.[28]

Sgarbossa and associates[31] devised an algorithm for the diagnosis of acute MI in patients with LBBB that used three electrocardiographic criteria: ≥1-mm ST-segment elevation concordant with the QRS complex; ≥1-mm ST-segment depression in leads V_1, V_2, or V_3; and ≥5-mm ST-segment elevation discordant with the QRS complex. Several subsequent studies investigated the utility of the so-called Sgarbossa criteria.[26,29] A study that enrolled 83 patients with LBBB and symptoms suggestive of acute MI found that the ECG algorithm based on the Sgarbossa criteria had a sensitivity of only 10%.[26]

Patients with an acute MI who present with an LBBB that is new or of indeterminate age have a worse prognosis than patients without an LBBB. A bundle branch block was present on the admission ECG in 4% of the patients with a suspected acute MI who were included in a meta-analysis of nine trials that randomly assigned 58,600 patients to either a control group or fibrinolytic therapy.[32] Mortality at 35 days for patients who were randomly assigned to the control groups was greater among patients who presented with a bundle branch block (23.6%), compared with patients who had ST-segment elevation in the anterior leads (16.9%) or inferior leads (8.4%), or ST-segment depression (13.8%).[32] Fibrinolytic therapy was associated with a 25% reduction in mortality among patients who presented with a bundle branch block on ECG.[32] The publication did not provide information regarding the age of the bundle branch block or whether the meta-analysis was limited to patients with an LBBB or also included patients with a right bundle branch block.[32] Among 3053 patients with an acute MI who were enrolled in the Primary Angioplasty in Myocardial Infarction (PAMI) trials, an LBBB was an independent predictor of in-hospital death (odds ratio [OR] 5.53; 95% confidence interval [CI] 1.89–16.1; $P = 0.002$).[33]

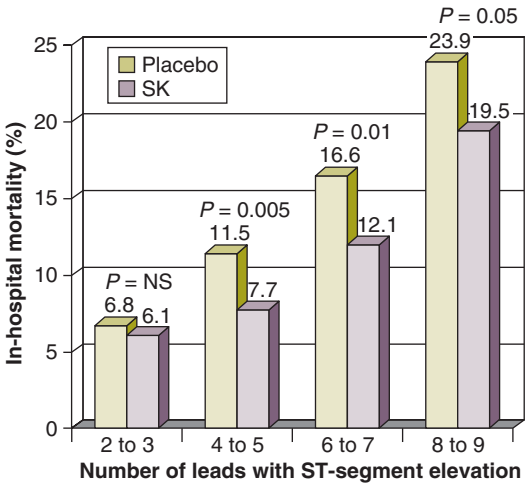
Patients with LBBB and acute MI frequently have no chest pain at the time of presentation. Chest pain was not reported by 47% of the 29,585 patients with LBBB and acute MI who were enrolled in the NRMI 2 registry.[34] Patients who presented without chest pain were less likely to receive aspirin or a β-blocker and four times less likely to receive reperfusion therapy (OR 0.25).[34] This may explain why patients with acute MI and LBBB who presented without chest pain had a 47% greater in-hospital mortality rate than patients who presented with chest pain (27% vs. 18%; $P < 0.001$).[34]

A new or presumably new LBBB in patients with symptom onset within the prior 12 hours was designated as a class I indication for either fibrinolytic therapy or PCI in the guidelines for the management of acute MI issued by the American College of Cardiology (ACC)/AHA Task Force on Practice Guidelines in 2004.[20] According to the most recent revision of the practice guidelines for ST-segment elevation MI, a new or presumably new LBBB "should not be considered diagnostic of acute MI in isolation."[24] The risks of fibrinolytic therapy may be increased in patients with LBBB owing to older age and a higher prevalence of hypertension. Therefore the most prudent strategy in patients with LBBB and a suspected acute MI may be immediate coronary angiography, both to diagnose an acute coronary artery occlusion and to eliminate the risk of fibrinolytic therapy in patients who cannot benefit from it (i.e., patients with a NSTEMI or a noncardiac condition). A more detailed discussion of the management of patients with LBBB and suspected MI can be found in an excellent review article published in 2012.[25]

The ECG provides additional important information in patients with acute MI. Patients with acute inferior STEMI who have ST-segment depression in the precordial leads have larger infarctions, more post-MI complications, and a higher mortality rate than patients without precordial ST-segment depression.[35] The presence of Q waves in the infarct territory on the initial ECG is an independent predictor of greater 30-day mortality irrespective of the infarct location or time between symptom onset and administration of fibrinolytic therapy.[36] Nevertheless, substantial myocardial salvage is possible despite Q waves on the initial ECG.[37]

The electrocardiographic leads with ST-segment elevation have been correlated with occlusions of the left anterior descending (LAD), left circumflex, or right coronary arteries.[38,39] The number of leads with ST-segment elevation before reperfusion therapy and the degree of resolution of ST-segment elevation after either fibrinolytic therapy or primary angioplasty confer useful prognostic information. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial investigators reported that in-hospital mortality was directly related to the number of leads with ST-segment elevation for both the patients treated with streptokinase and the control group.[40] Treatment with streptokinase significantly reduced in-hospital mortality among patients with ST-segment elevation in four or more leads, but not among patients with ST-segment elevation that was confined to two or three leads[40] (Fig. 29.2). Early ST-segment recovery is associated with improved infarct zone wall motion[41] and greater myocardial salvage as assessed by technetium-99m sestamibi scintigraphy.[42] Also, resolution of ST-segment elevation within 90 minutes after either primary angioplasty or fibrinolytic therapy identifies patients with lower mortality at 30 days and 1 year and 5 years after STEMI.[43–46] Continuous ECG monitoring is customary for the detection of arrhythmias and conduction abnormalities.

It is important to recognize that ST-segment elevation occurs in numerous conditions other than acute MI.[47] The list includes left ventricular hypertrophy, LBBB, acute pericarditis, hyperkalemia, Brugada syndrome, pulmonary embolism, and left ventricular apical ballooning syndrome (takotsubo cardiomyopathy)[47,48] (Fig. 29.3).



• **Fig. 29.2** In-hospital mortality among patients randomly assigned to the streptokinase *(SK)* and control groups in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-1) trial. Treatment with streptokinase significantly reduced in-hospital mortality among patients with ST-segment elevation in four or more leads, but not among patients with ST-segment elevation that was confined to two or three leads. *NS,* Not significant. (Data from Mauri F, Gasparini M, Barbonaglia L, et al. Prognostic significance of the extent of myocardial injury in acute myocardial infarction treated by streptokinase (the GISSI trial). *Am J Cardiol.* 1989;63:1291–1295.)

Cardiac Enzymes

Myocardial necrosis is accompanied by the release of several biochemical markers in circulating blood, including creatine kinase, myoglobin, troponins T and I, and lactate dehydrogenase. As noted previously, a typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB are required to diagnose an acute, evolving, or recent MI.[2] The ACC/AHA guidelines, however, stress that decisions such as initiation of reperfusion therapy for patients with ST-segment elevation and symptoms of STEMI should not be delayed until the results of serum cardiac biomarkers are available.[20]

Although troponin has become the preferred biomarker for myocardial necrosis, the serum troponin is frequently elevated in patients with HF[10] or chronic kidney disease.[49] Numerous other causes of an elevated troponin have been recognized, and several may be associated with chest pain or ST-segment elevation.[50] An elevated troponin in patients with pulmonary embolism is associated with right ventricular dysfunction and an increased risk of hypotension and death.[51–53] Elevated cardiac troponin also has been reported in patients with acute pericarditis, and patients with ST-segment elevation were more likely to have an elevated troponin.[54]

Echocardiography

Echocardiography may be a useful diagnostic tool under a variety of circumstances. A transesophageal echocardiogram may be useful to differentiate STEMI from aortic dissection. Both transthoracic and transesophageal echocardiography are useful in patients with HF or hypotension to evaluate left and right ventricular function, to rule out cardiac tamponade, and to diagnose ventricular septal rupture (VSR) or mitral regurgitation (MR). Mitral regurgitation is frequent among patients with uncomplicated MI. Color Doppler echocardiography was performed within 48 hours of admission in a series of 417 consecutive patients with acute MI.[55] Mild MR was present in 121 patients (29%), moderate MR in 21 (5%), and severe MR in 4 (1%).[55] Patients with any MR had higher 30-day and 1-year mortality rates, and MR was independently associated with increased 1-year mortality.[55] Echocardiography performed within 30 days after acute MI revealed MR in 50% of a cohort of 773 patients.[56] Cardiac auscultation did not detect a murmur in 54% of patients with mild and 31% of patients with moderate or severe MR.[56] Among 30-day survivors of an MI, during a mean follow-up period of 4.7 years moderate or severe MR detected by echocardiography within 30 days of MI was associated with a 55% increase in the relative risk (RR) of death independent of age, gender, left ventricular ejection fraction (LVEF), and Killip class.[56]

Hemodynamic Monitoring

The value of pulmonary artery (PA) catheterization in critically ill patients has been questioned.[57] The evidence base regarding the impact of PA catheters on outcome in patients with acute MI is limited to retrospective studies because PA catheterization in patients with acute MI has not been evaluated in a prospective, randomized, controlled trial.[58–60] Cohen and associates[60] performed a retrospective analysis of PA catheterization in patients with ACS who were enrolled in two large international randomized clinical trials, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IIb and GUSTO III. The study compared the outcomes in 735 patients who received PA catheters with those in 25,702 patients who did not. Except for patients with cardiogenic shock, mortality at 30 days was significantly greater among patients who received PA catheters, both before and after adjustment for baseline differences and subsequent events that may have prompted insertion of a PA catheter.

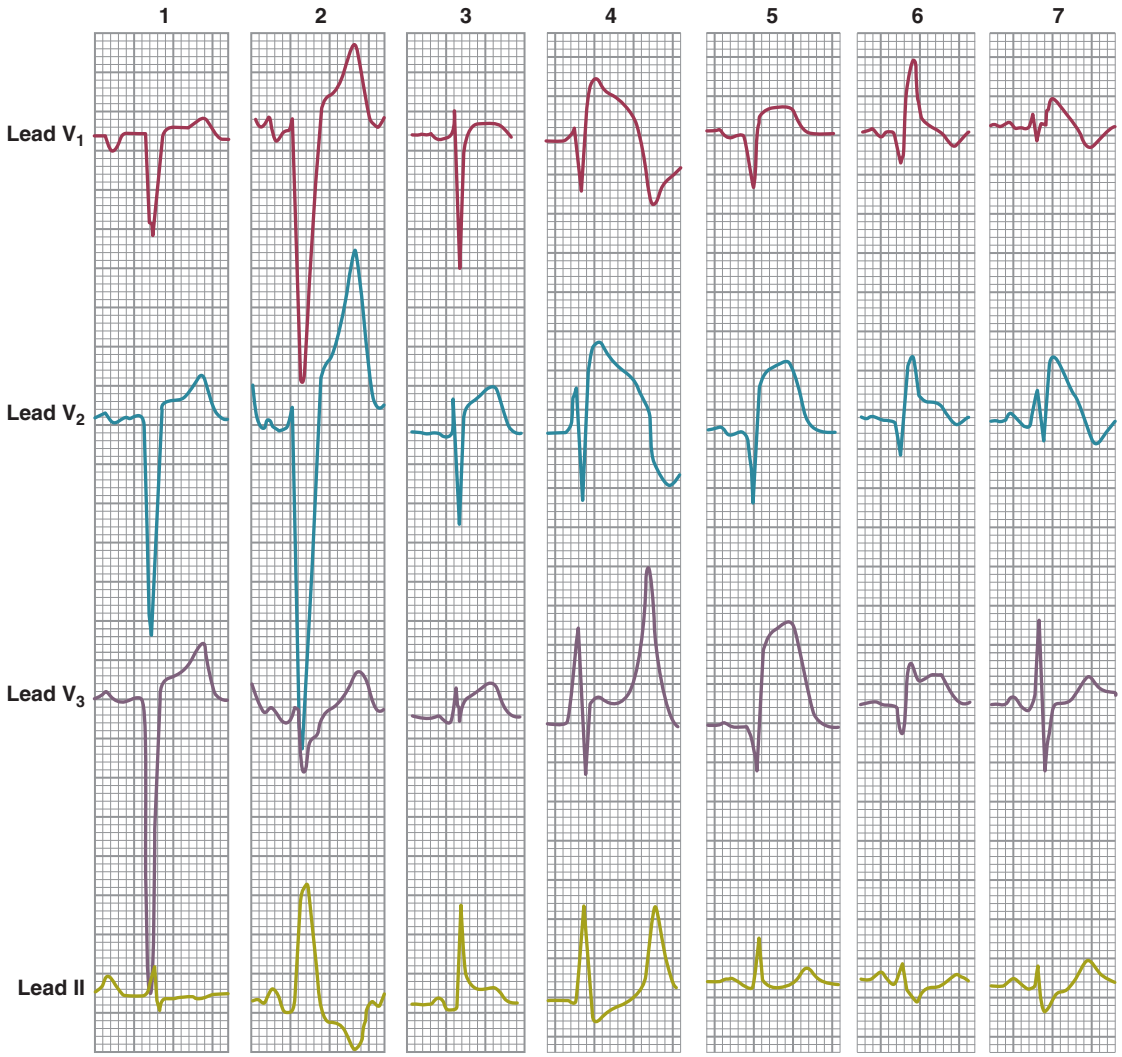
According to the ACC/AHA Guidelines, the class I indications for PA catheter monitoring are (1) progressive hypotension that either is unresponsive to fluid administration or is developing in a patient in whom fluid administration is contraindicated; and (2) a suspected mechanical complication, such as a VSR or papillary muscle rupture, if an echocardiogram has not been performed.[20] Intraarterial pressure monitoring is recommended for patients with systolic blood pressure less than 80 mm Hg, patients with cardiogenic shock, and patients receiving vasopressor and inotropic drugs.[20]

Access site bleeding is a major risk of central line insertion in patients who have received fibrinolytic drugs. The femoral route is preferred, and noncompressible sites, such as the subclavian vein, are relatively contraindicated.

Diagnostic Cardiac Catheterization and Coronary Angiography

Conditions other than STEMI can cause ST-segment elevation. Pericarditis, for example, is a relative contraindication to fibrinolytic therapy because of the risk of intrapericardial bleeding and tamponade. Therefore urgent coronary angiography and primary angioplasty if indicated would be preferable to intravenous fibrinolytic therapy if there is any suspicion of pericarditis. Similarly, diagnostic cardiac catheterization should be performed if clinical findings and noninvasive studies are unable to differentiate aortic dissection from acute MI.

Right heart catheterization and contrast ventriculography can provide useful diagnostic information in patients with suspected acute MI. Measurement of right heart pressures is useful in patients with suspected right ventricular MI and in patients with hypotension. Measurement of the oxygen content of blood in the right atrium and PA is useful in patients with a suspected VSR. A



• **Fig. 29.3** ST-segment elevation in various conditions. *Tracing 1,* Left ventricular hypertrophy. *Tracing 2,* Left bundle branch block. *Tracing 3,* Acute pericarditis. *Tracing 4,* Hyperkalemia. *Tracing 5,* Acute anteroseptal infarction. *Tracing 6,* Acute anteroseptal infarction and right bundle branch block. *Tracing 7,* Brugada syndrome. (From Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med.* 2003;349:2128–2135.)

contrast left ventriculogram provides an assessment of regional and global left ventricular function and the competence of the mitral valve. Left ventriculography was performed during the index cardiac catheterization in 1976 (95%) of 2082 patients with acute MI who were enrolled in the Controlled Abciximab and Device Investigation to Lower Angioplasty Complications (CADILLAC) trial.[61] Mild MR was present in 192 patients (9.7%), and moderate or severe MR was present in 58 patients (2.9%). Mitral regurgitation was not detected by physical examination in 50% of a cohort of 50 patients with acute MI and moderately severe or severe MR that was demonstrated by left ventriculography.[62]

Numerous studies have addressed the role of routine early angioplasty after fibrinolytic therapy.[63–68] A prospective cohort study of 21,912 patients with a first acute MI concluded that revascularization within 14 days of the acute MI was associated with a significant reduction in 1-year mortality (RR 0.47; 95% CI 0.37–0.60; $P < 0.001$).[63] Several randomized trials have shown beneficial effects of a routine invasive strategy immediately after fibrinolysis,[65] within 24 hours after fibrinolysis,[66] and 1 to 6 weeks after acute MI.[67] The most recent trials have provided support for the practice of routine early angioplasty after fibrinolytic therapy.[68–70] The Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) enrolled 1059 patients with a "high-risk" STEMI who received fibrinolytic therapy at centers that did not have the capability to perform PCI.[68] The patients were randomly assigned to either "standard" treatment (including rescue PCI or delayed angiography) or immediate transfer to another hospital for PCI within 6 hours after fibrinolysis. The primary endpoint—the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days—occurred in 11% of the patients who were assigned to routine early PCI, compared with 17.2% of the patients who were assigned to standard treatment (RR 0.64; 95% CI 0.47–0.87; $P = 0.004$). Borgia and colleagues[69] performed a meta-analysis of seven randomized, controlled trials that compared routine early PCI after successful fibrinolysis with PCI only for patients without evidence of reperfusion (rescue PCI). After a follow-up period of

• BOX 29.1 ACC/AHA Practice Guidelines for Coronary Angiography in Patients With S-T Segment Elevation Myocardial Infarction (STEMI) Who Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

Class I

Cardiac catheterization and coronary angiography with intent to perform revascularization should be performed after STEMI in patients with any of the following:

1. Cardiogenic shock or acute severe heart failure that develops after initial presentation
2. Intermediate- or high-risk findings on predischarge noninvasive ischemia testing
3. Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization

Class IIa

1. Coronary angiography with intent to perform revascularization is reasonable for patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy. Angiography can be performed as soon as logistically feasible.
2. Coronary angiography is reasonable before hospital discharge in stable patients with STEMI after successful fibrinolytic therapy. Angiography can be performed as soon as logistically feasible, and ideally within 24 h, but should not be performed within the first 2–3 h after administration of fibrinolytic therapy.

STEMI, *ST-segment elevation myocardial infarction.*

From O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2013;61:e78–e140.*

30 days routine early PCI after successful fibrinolysis reduced the rates of reinfarction (OR 0.55; 95% CI 0.36–0.82; $P = 0.003$), the combined end point of death and reinfarction (OR 0.65; 95% CI 0.49–0.88; $P = 0.004$), and recurrent ischemia (OR 0.25; 95% CI 0.13–0.49; $P < 0.001$). The benefits of early PCI persisted after 6 to 12 months of follow-up. D'Souza and associates[70] performed a meta-analysis of eight randomized trials that compared routine early PCI with ischemia-driven PCI after fibrinolysis in patients with STEMI. PCI within 24 hours after fibrinolytic therapy was associated with less reinfarction and recurrent ischemia.

The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction includes three class I recommendations and two class IIa recommendations for coronary angiography in patients who were managed initially with fibrinolytic therapy or who did not receive reperfusion therapy[24] (Box 29.1). Coronary angiography is recommended in survivors of STEMI who are candidates for revascularization therapy with spontaneous ischemia, intermediate-risk or high-risk findings on noninvasive testing, hemodynamic or electrical instability, mechanical defects, prior revascularization, or high-risk clinical features.

Approach to Management

Fig. 29.4 presents an algorithm for the treatment of acute STEMI.

General Considerations

Patients who present to the emergency department with an acute MI will usually be diagnosed and treated before admission to the intensive care unit (ICU). It is not unusual, however, for STEMI to occur in patients receiving ICU treatment for other conditions, such as gastrointestinal bleeding or respiratory failure, or those undergoing surgical procedures. As in the patients who present to an emergency department, prompt performance and interpretation of an ECG constitute a critical initial step in management. Continuous ECG monitoring for arrhythmias is routinely practiced. Patients usually are advanced from nothing-by-mouth status to clear liquids to a low-fat, low-cholesterol diet as tolerated. Stool softeners should be used to prevent the hemodynamic effects of constipation.

Oxygen

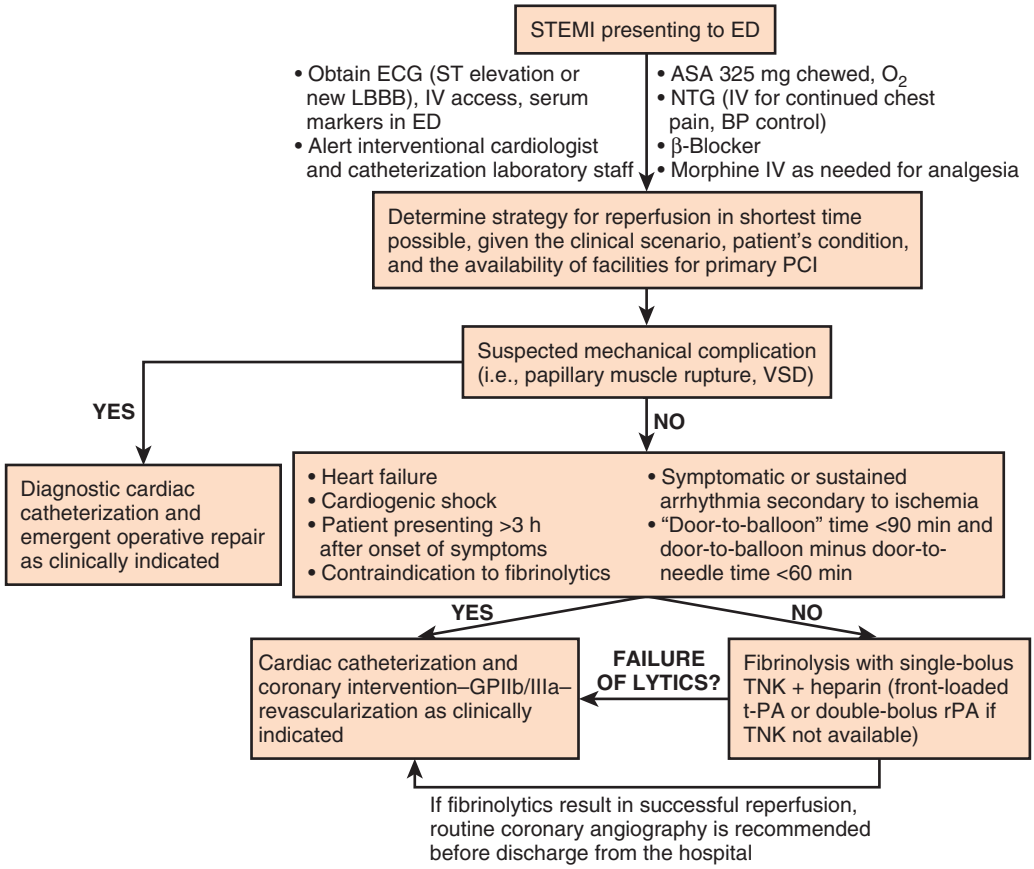
Despite both experimental and clinical studies of oxygen therapy, it remains unclear whether oxygen has beneficial, detrimental, or neutral effects in patients with acute MI. Clinical studies have shown that hyperoxia during inhalation of high concentrations of oxygen causes an increase in coronary vascular resistance and a decrease in coronary blood flow.[71] Nevertheless, in patients with an anterior STEMI who underwent PCI of the LAD, an intracoronary infusion of supersaturated oxygen for 90 minutes was associated with a significantly smaller infarct size measured by Tc^{99m}-sestamibi single-photon emission computed tomography (CT) 14 days after MI.[72] The Air Versus Oxygen in myocarDial infarction study (AVOID) randomly assigned 638 patients with a suspected STEMI to no supplemental oxygen or supplemental oxygen administered via face mask at 8 L/min by paramedics.[73] Oxygen therapy was started in the field and continued until the patient was transferred from the cardiac catheterization laboratory to the cardiac care ward. The data from 441 patients with a confirmed STEMI showed that the patients who received supplemental oxygen had greater rates of recurrent MI and cardiac arrhythmias, and a greater peak creatine kinase.[73] Among the subset of 139 patients who underwent cardiac magnetic resonance imaging (MRI) 6 months after MI, treatment with supplemental oxygen was associated with increased myocardial infarct size (2.3 vs. 13.1 g; $P = 0.04$).[73]

The DETermination of the role of OXygen in suspected Acute Myocardial Infarction (DETO2X-AMI) trial intends to randomly assign 6600 normoxemic patients with suspected acute MI to room air or supplemental oxygen at 6 L/min by mask for 6 to 12 hours.[74] The primary objective is to determine whether oxygen reduces 1-year all-cause mortality.[74]

The 2004 ACC/AHA STEMI guidelines included a class I indication for supplemental oxygen in patients with an arterial oxygen saturation less than 90%.[20] The 2004 guidelines also included a class IIa indication: "It is reasonable to administer supplemental oxygen to all patients with uncomplicated STEMI during the first 6 hours."[20] The 2013 ACCF/AHA STEMI Guidelines do not include any class I or II recommendations regarding supplemental oxygen, and state that "Oxygen therapy is appropriate for patients who are hypoxemic (oxygen saturation <90%)".[24]

Analgesia and Sedation

Relief of pain is an important goal in patients with acute MI. According to the 2013 ACCF/AHA STEMI Guideline, morphine sulfate is the drug of choice for pain relief in patients with STEMI.[24] There are no published randomized trials of morphine therapy in patients with acute MI. An analysis of the CRUSADE registry, however, revealed that use of morphine was associated with a 50% higher mortality in patients with NSTEMI even after risk adjustment.[75] In a study of 24 healthy subjects, 5 mg of intravenous morphine delayed the absorption of clopidogrel, decreased the



• **Fig. 29.4** Algorithm for the treatment of acute ST-segment elevation myocardial infarction *(STEMI). Note:* Nitroglycerin should be used with caution in patients with inferior wall myocardial infarction with possible right ventricular involvement. Nitroglycerin should be avoided altogether in hypotensive patients. *ASA,* Acetylsalicylic acid (aspirin); *BP,* blood pressure; *ECG,* electrocardiogram; *ED,* emergency department; *GP,* glycoprotein; *IV,* intravenous; *LBBB,* left bundle branch block; *NTG,* nitroglycerin; *PTCA,* percutaneous transluminal coronary angioplasty; *PCI,* percutaneous coronary intervention, *rPA,* recombinant plasminogen activator (reteplase); *TNK,* tenecteplase; *t-PA,* tissue plasminogen activator; *VSD,* ventricular septal defect.

plasma levels of the active metabolite of clopidogrel, and delayed and diminished the inhibition of platelet function.[76] Morphine has been shown to delay and attenuate the onset of platelet inhibition by either prasugrel or ticagrelor in patients with acute MI.[77–78] Therefore morphine may increase the risk of coronary reocclusion after fibrinolytic therapy and stent thrombosis after PCI. Until additional data become available, it may be prudent to limit the use of morphine to patients with persistent pain despite treatment with nitrates and a β-adrenergic antagonist.

The abundant evidence that nonsteroidal antiinflammatory drugs (NSAIDs) have adverse effects in patients with cardiovascular disease has been reviewed in great detail in multiple publications, including a scientific statement from the AHA and a meta-analysis of 31 trials that enrolled 116,429 patients.[79–81] Treatment with either a selective cyclooxygenase-2 inhibitor or a nonselective NSAID after discharge from the hospital significantly increases the risk of death and recurrent MI. A Danish study of 61,971 patients who were hospitalized for a first-time acute MI between 2002 and 2011 found that treatment with either a selective cyclooxygenase-2 inhibitor or a nonselective NSAID after discharge from the hospital significantly increased the risk of bleeding and thrombotic events, even after short-term treatment.[82] Also, the use of NSAIDs is associated with an increased risk of death or recurrent MI regardless of the time elapsed after an initial MI.[83] One possible explanation for the adverse cardiovascular effects of NSAIDs is inhibition of the clinical benefits of aspirin. An analysis of the Physicians' Health Study concluded that there was greater than a twofold increased risk of a first MI among healthy male U.S. physicians who were randomly assigned to receive aspirin and also took other NSAIDs on more than 60 days per year.[84] An important pharmacologic study demonstrated that inhibition of platelet aggregation by aspirin was blocked when ibuprofen was administered before aspirin.[85] On July 9, 2015, the U.S. Food and Drug Administration (FDA) issued a drug safety communication that announced strengthening of the existing label warning that NSAIDS increase the chance of a heart attack or stroke. According to the 2013 ACCF/AHA STEMI Guideline, NSAIDs, including cyclooxygenase-2 inhibitors, are contraindicated in patients with STEMI.[24]

Nitrates

The beneficial physiologic effects of nitrates include vasodilation of the coronary arteries, which may improve myocardial oxygen supply, especially in patients with a component of coronary spasm, and vasodilation of peripheral arteries and veins, causing reductions

in pulmonary capillary wedge pressure (PCWP), mean arterial pressure, and peripheral vascular resistance, thereby decreasing left ventricular preload and afterload and myocardial oxygen demand.[86] Severe hypotension and bradycardia have been observed after administration of either sublingual or intravenous nitroglycerin in patients with acute MI.[87] Patients with right ventricular MI may experience severe hypotension during administration of nitroglycerin because adequate right ventricular preload is required to maintain cardiac output. Nitroglycerin is contraindicated in patients who have taken phosphodiesterase inhibitors because they potentiate nitroglycerin-induced hypotension.[88]

The 2013 ACCF/AHA STEMI Guideline endorses sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses for relief of ischemic discomfort, and intravenous nitroglycerin for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion.[24] It has been proposed that intravenous nitroglycerin may limit myocardial infarct size and expansion.[89] Two large clinical trials, however, were unable to demonstrate significant improvements in mortality by the prolonged administration of nitroglycerin after acute MI.[90,91] The GISSI-3 trial enrolled 19,394 patients with acute MI.[90] Patients who were randomly assigned to treatment with nitroglycerin received intravenous nitroglycerin for 24 hours, followed by transdermal nitroglycerin for 6 weeks.[90] Nitroglycerin did not reduce the 6-week rate of death or clinical HF. The Fourth International Study of Infarct Survival (ISIS-4) enrolled 58,050 patients with suspected acute MI in a $2 \times 2 \times 2$ factorial study that included randomization to isosorbide mononitrate 60 mg daily or placebo for 28 days.[91] No significant effect of nitroglycerin on mortality was found after 5 weeks or 1 year.

Several studies have investigated the effect of another nitrate, nitroprusside, on hemodynamics and outcome in patients with acute MI.[92–95] Intravenous nitroprusside reduced PCWP and increased cardiac index in patients with acute MI.[92,93] A comparison of intravenous nitroprusside with intravenous nitroglycerin in 10 patients with acute anterior MI demonstrated that ST-segment elevation increased during infusion of nitroprusside, whereas it decreased during infusion of nitroglycerin.[92] Experimental data indicate that nitroprusside may exacerbate myocardial ischemia or injury by redistribution of myocardial blood flow from ischemic to nonischemic zones.[92] A Veterans Administration Cooperative Study enrolled 812 patients with acute MI and a PCWP greater than 12 mm Hg in a double-blind, randomized trial of nitroprusside infused for 48 hours.[95] Compared with the placebo group, mortality at 13 weeks was increased by nitroprusside in patients whose infusions started within 9 hours of the onset of pain. A smaller European trial randomly assigned 328 patients with acute MI to infusion of nitroprusside or 5% glucose.[94] The trial was terminated when 1-week mortality in the control group was significantly greater than in the nitroprusside group (10.9% vs. 3.1%; $P < 0.05$). The use of nitroprusside in patients with acute MI should probably be reserved for patients with severe hypertension that is unresponsive to treatment with intravenous nitroglycerin.

Aspirin

The Second International Study of Infarct Survival (ISIS-2) provided definitive evidence that aspirin reduces mortality in patients with acute MI.[96] The study used a 2×2 factorial design to randomly assigned 17,187 patients to four treatment groups: streptokinase, aspirin 160 mg daily for 1 month, both, or neither. Aspirin reduced the rate of in-hospital reinfarction both in the patients who received streptokinase and in the patients who did not receive fibrinolytic therapy. At 35 days, the vascular-cause mortality rate was 9.4% among the patients in the aspirin treatment group, compared with 11.8% among those in the placebo group, representing a 23% reduction ($P < 0.00001$). Aspirin also significantly reduced all-cause mortality. Also, the combination of aspirin and streptokinase reduced mortality more than did either agent alone. The effects of the initial dose of aspirin on short-term outcomes after fibrinolytic therapy were tested by analyzing the outcomes of 48,422 patients with STEMI who were enrolled in two large clinical trials, GUSTO I and GUSTO III.[97] Compared with an initial dose of 162 mg, an initial dose of 325 mg was associated with a significant increase in in-hospital moderate or severe bleeding, but the rates of reinfarction and death at 24 hours, 7 days, and 30 days were not significantly different.[97] The ACCF/AHA Guideline for the Management of STEMI includes a class I recommendation for a loading dose of aspirin of 162 to 325 mg before primary PCI and for patients who receive fibrinolytic therapy.[24] A second class I recommendation is for aspirin to be continued indefinitely.[24] Finally, there is a class IIa recommendation that it is reasonable to prescribe a maintenance aspirin dose of 81 mg/day in preference to higher doses after either fibrinolytic therapy or primary PCI.[24] Also, patients who are treated with ticagrelor should receive a maintenance aspirin dose of 81 mg/day because higher doses of aspirin were associated with reduced efficacy of ticagrelor.[98]

Reocclusion of a patent infarct artery after successful fibrinolytic therapy is associated with higher in-hospital mortality, reduced event-free survival after hospital discharge, and long-term impairment of regional and global left ventricular function.[99–102] There are conflicting opinions regarding aspirin's effect on reocclusion of an infarct artery.[103,104] The Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) study randomly assigned 300 patients with an open infarct artery within 48 hours after fibrinolysis to three treatment groups: aspirin 325 mg daily, warfarin, or placebo.[105] Cardiac catheterization was performed 3 months later in 248 patients. The reocclusion rates were not significantly different: 32% (24/74) with placebo, 30% (24/81) with warfarin, and 25% (23/93) with aspirin. A pooled analysis of published studies estimated that the incidence of reocclusion after streptokinase or tissue plasminogen activator (t-PA) is approximately 11% with aspirin, compared with 25% without aspirin.[103]

Inhibitors of the Platelet $P2Y_{12}$ Receptor

The combination of aspirin with inhibitors of the platelet $P2Y_{12}$ receptor has been shown to be superior to aspirin alone in patients with a STEMI.[106–108] The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study enrolled 3491 patients who received fibrinolytic therapy for STEMI and randomly assigned them to receive clopidogrel 75 mg daily or placebo in a double-blind fashion.[106] Coronary angiography performed at a median of 84 hours after randomization in each group demonstrated an occluded infarct-related artery (IRA) in 18.4% of the placebo group patients, compared with 11.7% of the clopidogrel group patients ($P < 0.001$). PCI was performed during the index hospitalization in 1863 (53.4%) of the patients who were enrolled in the CLARITY trial.[108] The combined incidence of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after randomization was significantly lower among patients who were treated with clopidogrel and aspirin compared with the patients who received aspirin alone (3.6% vs. 6.2%; adjusted OR 0.54; 95% CI 0.35–0.85; $P = 0.008$).[108] The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomly assigned 45,852 patients with suspected

acute MI to receive treatment with aspirin 162 mg daily plus clopidogrel 75 mg daily or placebo.[107] The in-hospital mortality rate was significantly lower for the clopidogrel group than for the placebo group (7.5% vs. 8.1%; $P = 0.03$). The CLARITY study used a clopidogrel loading dose of 300 mg; the COMMIT study did not use a loading dose.

A multivariate-weighted logistic regression analysis of the outcomes of 8429 STEMI patients who were enrolled in 26 randomized clinical trials concluded that pretreatment with a loading dose of clopidogrel before primary PCI was an independent predictor of coronary artery patency before PCI (OR 1.51; 95% CI 1.31–1.74; $P < 0.0001$) and decreased mortality after PCI (OR 0.57; 95% CI 0.38–0.85; $P = 0.0055$).[109] Among patients with STEMI who were enrolled in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial and underwent primary PCI, a clopidogrel loading dose of 600 mg ($n = 2158$), compared with 300 mg ($n = 1153$) was associated with significantly lower 30-day rates of mortality, reinfarction, and stent thrombosis and was an independent predictor of freedom from major adverse cardiac events at 30 days.[110]

Prasugrel, another inhibitor of the platelet $P2Y_{12}$ receptor, was studied in patients with ACS, including patients with STEMI, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38.[111,112] The trial randomly assigned 3534 patients with STEMI who were undergoing either primary PCI (PCI within 12 hours of symptom onset) or secondary PCI (PCI between 12 hours and 14 days after symptom onset) to either prasugrel (60-mg loading dose and 10-mg/day maintenance dose) or clopidogrel (300-mg loading dose and 75-mg maintenance dose) for 6 to 15 months.[112] The primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke, was significantly less frequent at both 30 days and 15 months among patients who were randomly assigned to prasugrel compared with patients who were assigned to clopidogrel.[112]

Ticagrelor, an inhibitor of the platelet $P2Y_{12}$ receptor, was studied in patients with ACS, including patients with STEMI, in the Study of Platelet Inhibition and Patient Outcomes (PLATO).[113,114] The trial randomly assigned 7544 patients with STEMI who were undergoing primary PCI to either ticagrelor (180-mg loading dose and 90-mg twice-daily maintenance dose) or clopidogrel (300-mg loading dose and 75-mg maintenance dose) for 6 to 12 months.[114] Compared with clopidogrel, treatment with ticagrelor reduced several secondary end points, including MI (hazard ratio [HR] 0.80; $P = 0.03$), total mortality (HR 0.82; $P = 0.05$), and definite stent thrombosis (HR 0.66; $P = 0.03$); major bleeding was not significantly different (HR 0.98; $P = 0.76$).[114]

The recommendations regarding adjunctive antiplatelet therapy for patients with STEMI that were endorsed by the 2013 ACCF/AHA STEMI Guideline are summarized in Box 29.2.[24] The U.S. FDA has issued several pronouncements regarding inhibitors of the platelet $P2Y_{12}$ receptor. Prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke and active pathologic bleeding. Also, prasugrel should not be administered to patients older than age 75 because of an increased risk of fatal and intracranial bleeding. Finally, the maintenance dose of prasugrel should be reduced to 5 mg daily in patients who weigh less than 60 kg. Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. The 2013 ACCF/AHA STEMI Guideline does not reflect a label revision for clopidogrel announced by the FDA on September 16, 2016. The revision restricts the use of clopidogrel in patients with STEMI to medically

• BOX 29.2 ACCF/AHA Guideline for Antiplatelet Therapy for Patients With STEMI

Antiplatelet Therapy in Patients Who Receive Fibrinolytic Therapy

Class I

1. Aspirin (162–325-mg loading dose) and clopidogrel (300-mg loading dose for patients ≤75 years of age, 75-mg dose for patients >75 years of age)
2. Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to 1 year

Class IIa

1. It is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses

Antiplatelet Therapy to Support Primary PCI in STEMI

Class I

1. Aspirin 162–325 mg should be given before primary PCI
2. After PCI aspirin should be continued indefinitely
3. A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI. Options include the following:
   a. Clopidogrel 600 mg
   b. Prasugrel 60 mg
   c. Ticagrelor 180 mg
4. $P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
   a. Clopidogrel 75 mg daily
   b. Prasugrel 10 mg daily
   c. Ticagrelor 90 mg twice a day

Class IIa

1. It is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses
2. It is reasonable to begin treatment with an intravenous GP IIb/IIIa receptor antagonist such as abciximab, high-bolus-dose tirofiban, or double-bolus eptifibatide at the time of primary PCI in selected patients with STEMI who are receiving unfractionated heparin

Class IIb

1. It may be reasonable to administer intravenous GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting to patients with STEMI for whom primary PCI is intended
2. It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI
3. Continuation of a $P2Y_{12}$ inhibitor beyond 1 year may be considered in patients undergoing DES placement

Class III

1. Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy in STEMI

Class I

1. Aspirin 162–325 mg should be given before primary PCI
2. After PCI aspirin 81–325 mg daily should be continued indefinitely
3. For patients who received a loading dose of clopidogrel with fibrinolytic therapy, continue clopidogrel 75 mg daily without an additional loading dose
4. For patients who have not received a loading dose of clopidogrel with fibrinolytic therapy, the loading dose of clopidogrel should be 300 mg within 24 hours and 600 mg more than 24 hours after receiving fibrinolytic therapy

BMS, *Bare metal stent;* DES, *drug-eluting stent;* GP, *glycoprotein;* PCI, *percutaneous coronary intervention;* STEMI, *ST-segment elevation myocardial infarction.*

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2013;61:e78–e140.*

managed patients only (see http://www.fda.gov/Drugs/DrugSafety/ucm423079.htm and http://www.fda.gov/Drugs/DrugSafety/ucm471286.htm).

Anticoagulant Therapy

The rationale for anticoagulant therapy in patients with STEMI includes promotion of infarct artery patency, and prevention of deep vein thrombosis, pulmonary embolism, left ventricular mural thrombus, and cerebral embolism. Left ventricular mural thrombus formation after acute MI occurs more commonly after anterior than nonanterior wall MI and is associated with an increased risk of systemic embolization.[115,116] Data differ regarding the incidence of left ventricular thrombus in patients who receive reperfusion therapy. The GISSI-2 study, in which all patients received fibrinolytic therapy, observed left ventricular thrombi in 51 of 180 consecutive patients with a first anterior acute MI who underwent serial echocardiography within 48 hours after the onset of symptoms and before hospital discharge.[117] Another study, however, detected left ventricular thrombi in only 6.4% of patients with acute anterior MI who underwent echocardiography on days 1, 14, and 90 after MI.[118] A double-blind, randomized trial compared a 10-day course of high-dose subcutaneous unfractionated heparin (UFH) (12,500 units every 12 hours) with low-dose subcutaneous UFH (5,000 units every 12 hours) in the prevention of left ventricular thrombus in 221 patients with acute anterior MI who did not receive fibrinolytic therapy.[119] Echocardiography 10 days after MI demonstrated left ventricular thrombi in 10 of 95 patients (11%) in the high-dose group and in 28 of 88 patients (32%) in the low-dose group ($P = 0.0004$). A meta-analysis of seven studies that enrolled 270 patients suggests that systemic anticoagulation in patients with mural thrombi reduces embolic complications.[115]

Clinical trials have evaluated both subcutaneous and intravenous UFH in patients with acute MI who were treated with various fibrinolytic agents. Randomized, controlled clinical trials have shown that adjunctive therapy with intravenous UFH increases the patency of the IRA after administration of t-PA.[120,121] A meta-analysis that included 68,000 patients enrolled in randomized trials that compared UFH plus aspirin with aspirin alone showed that only 5 lives were saved per 1000 patients who received UFH in addition to streptokinase.[122] The meta-analysis was heavily influenced by two studies, GISSI-2[123] and ISIS-3,[124,125] that enrolled 62,067 patients randomly assigned to receive fibrinolytic therapy plus either aspirin alone or aspirin plus subcutaneous UFH. Another meta-analysis was limited to six randomized controlled trials that enrolled 1735 patients who received either intravenous UFH or no heparin after fibrinolytic therapy.[126] The analysis found that the addition of intravenous UFH to t-PA or streptokinase had insignificant effects on mortality and reinfarction, but the risk of bleeding was significantly increased.[126]

Several randomized clinical trials[127–131] and meta-analyses[132,133] have been performed to compare low-molecular-weight heparin (LMWH) with placebo or UFH as adjuncts to fibrinolytic therapy in patients with STEMI. A meta-analysis of 16,943 patients enrolled in four randomized trials revealed that the endpoints of death or reinfarction at 7 days and at 30 days were significantly reduced by LMWH compared with placebo.[133] A meta-analysis of 7098 patients enrolled in six randomized trials revealed that LMWH, compared with UFH, reduced the rates of reinfarction during hospitalization and at 30 days, but the rates of death were not significantly different.[133] Neither meta-analysis included a subsequent trial, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI 25, that compared enoxaparin, an LMWH, with UFH in patients with STEMI who received fibrinolytic therapy.[129,130] The study was a double-blind, randomized comparison of enoxaparin given subcutaneously twice daily until hospital discharge versus intravenous UFH for 48 hours in 20,506 patients with STEMI. A fibrinolytic agent was received by 99.7% of the patients: 55% received alteplase, 20% received streptokinase, 19% received tenecteplase (TNK), and 5.5% received reteplase (rPA). The primary endpoint, death or nonfatal recurrent MI through 30 days, occurred in 12% of patients in the UFH group and in 9.9% of patients in the enoxaparin group ($P < 0.001$). The rates of major bleeding at 30 days were 1.4% in the UFH group and 2.1% in the enoxaparin group ($P < 0.001$), but the rates of intracranial hemorrhage were not significantly different (UFH 0.7%, enoxaparin 0.8%; $P = 0.14$). The enoxaparin strategy significantly reduced the risk of nonfatal MI at 1 year (5.7% vs. 6.8%; HR 0.82; 95% CI 0.73–0.92; $P < 0.001$).[130] One of the mechanisms underlying the benefit of LMWH compared with UFH may be improved patency of the infarct artery after fibrinolytic therapy.[131]

Fondaparinux, a synthetic pentasaccharide, is a factor Xa inhibitor that binds antithrombin and inhibits factor Xa. The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) conducted two trials to evaluate fondaparinux in patients with ACS[134] and STEMI.[135,136] The OASIS-6 trial was a randomized, double-blind comparison of fondaparinux 2.5 mg daily or control from days 3 through 9 in 12,092 patients with STEMI.[135] Forty-five percent of the patients received fibrinolytic therapy (streptokinase in 73%), 28.9% underwent primary PCI, and 23.7% did not receive any reperfusion therapy. The primary efficacy outcome—death or reinfarction at 30 days—was significantly lower in the fondaparinux group than in the control group (9.7% vs. 11.2%; HR 0.86; 95% CI 0.77–0.96; $P = 0.008$). Fondaparinux also significantly reduced the rates of death at day 9, day 30, and the end of the study (3–6 months). Significant heterogeneity in the effect of fondaparinux was observed in relation to the reperfusion strategy, with benefit observed in patients who received no reperfusion therapy or a fibrinolytic agent, but not in patients who underwent primary PCI. The rate of severe bleeding was not increased by fondaparinux.

A subgroup analysis of the OASIS-6 results was performed to compare the effects of fondaparinux with usual care (i.e., UFH or placebo) in patients with STEMI who did not receive any reperfusion therapy.[136] Fondaparinux significantly reduced the composite endpoint of death or recurrent MI, without an increase in severe bleeding or stroke, compared with UFH or placebo.[136]

The dose of fondaparinux must be adjusted in patients with renal insufficiency, but adjustment for body weight is not necessary. The anticoagulant effect of the drug cannot be monitored by conventional clotting tests, such as the activated clotting time or partial thromboplastin time. Also, the relatively long half-life of fondaparinux, 17 to 21 hours, conceivably may be viewed as an impediment to early sheath removal and ambulation after cardiac catheterization. Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant during PCI, and an additional anticoagulant with antifactor IIa activity should be administered.[24]

Multiple randomized trials have compared bivalirudin, a direct thrombin inhibitor, with UFH in patients with STEMI.[137–142] Bivalirudin was compared with UFH plus glycoprotein (GP) IIb/IIIa inhibitors in 3602 patients with STEMI undergoing primary PCI in the HORIZONS-AMI trial.[137–139] Compared with UFH plus GP IIb/IIIa inhibitors, anticoagulation with bivalirudin was

associated with a reduced rate of net adverse clinical events and major bleeding at 30 days and 1 year.[137,138] Also, treatment with bivalirudin was associated with both cardiac and all-cause mortality rates that were significantly lower after 30 days and 1 year.[137,138] Among the 477 patients who were classified as high risk, the mortality rates at 1 year were 8.4% among patients treated with bivalirudin, compared with 15.9% among patients treated with UFH plus a glycoprotein IIb/IIIa inhibitor ($P = 0.01$).[139] A patient-level, pooled analysis of two of the randomized trials, HORIZONS-AMI and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial), examined the 30-day outcomes in 4935 patients with STEMI who underwent primary PCI with stent implantation and were randomly assigned to receive either bivalirudin or heparin with or without a GP IIb/IIIa inhibitor.[143] Although acute stent thrombosis (within 24 hours of PCI) was more frequent in patients treated with bivalirudin (2.5% vs. 1.6%, $P = 0.04$), the 30-day mortality attributable to early stent thrombosis occurred in 4 of 2479 (0.2%) bivalirudin-treated patients versus 16 of 2456 (0.7%) patients treated with heparin with or without GP IIb/IIIa inhibitor ($P = 0.007$).[143]

According to the 2013 ACCF/AHA STEMI Guideline,[24] "patients with STEMI undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of the index hospitalization, up to 8 days or until revascularization if performed." Enoxaparin is preferred over UFH if anticoagulant therapy is given for more than 48 hours because of the risk of heparin-induced thrombocytopenia (HIT) with prolonged UFH treatment. The 2013 ACCF/AHA Guideline for the Management of STEMI recommends adjustment of the dose of UFH to maintain an activated partial thromboplastic time of 1.5 to 2.0 times control.[24] Also, the platelet count should be monitored daily during treatment with UFH because there is a 3% incidence of HIT.[144] The guideline noted that bivalirudin can be used after treatment with a fibrinolytic agent in patients who develop HIT and require continued anticoagulation.[24]

For patients with STEMI who undergo primary PCI, the 2013 ACCF/AHA STEMI Guideline recommends (class I) either UFH or bivalirudin. Also, it includes a class IIa recommendation that "in patients who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist."[24] As noted above, a class III recommendation states that "Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis."[24] Box 29.3 lists recommendations regarding the doses of UFH, enoxaparin, fondaparinux, and bivalirudin.

The 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction included a class IIa recommendation that "it is reasonable for patients with STEMI who do not undergo reperfusion therapy to be treated with anticoagulant therapy (non-UFH regimen) for the duration of the index hospitalization, up to 8 days," but the 2013 ACCF/AHA STEMI Guideline does not include a recommendation for anticoagulation in patients who do not undergo reperfusion therapy.[21,24]

• BOX 29.3 Dosing of Anticoagulant Drugs for Patients With STEMI

Anticoagulation to Support Primary PCI in STEMI

Class I

UFH

1. With glycoprotein IIb/IIIa receptor antagonist planned: 50–70 U/kg IV bolus to achieve ACT 200–250 s
2. With no GP IIb/IIIa receptor antagonist planned: 70–100 U/kg IV bolus to achieve ACT 250–300 s

Bivalirudin

1. 0.75 mg/kg IV bolus, then 1.75 mg/kg per hour infusion with or without prior treatment with UFH. Reduce infusion to 1 mg/kg per hour with estimated creatinine clearance <30 mL/min

Class IIa

1. Bivalirudin preferred over UFH with GP IIb/IIIA antagonist in patients at high risk of bleeding

Class III

1. Fondaparinux: not recommended as sole anticoagulant for primary PCI

Anticoagulation in Patients Who Receive Fibrinolytic Therapy

Class I

Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 h and preferably for the duration of the index hospitalization, up to 8 days or until revascularization if performed (regimens other than UFH are recommended if anticoagulant therapy is given for more than 48 h because of the risk of heparin-induced thrombocytopenia with prolonged UFH treatment). Recommended regimens include the following:

a. UFH: initial intravenous bolus 60 U/kg (maximum 4000 U) followed by an intravenous infusion of 12 U/kg per hour (maximum 1000 U/h) initially, adjusted to maintain the activated partial thromboplastin time at 1.5 to 2 times control (approximately 50–70 s) for 48 h or until revascularization

b. Enoxaparin (provided the serum creatinine is <2.5 mg/dL in men and 2 mg/dL in women): The dose for patients younger than 75 years of age is an initial 30-mg intravenous bolus, followed 15 minutes later by subcutaneous injections of 1 mg/kg every 12 hours. For patients at least 75 years of age, the initial bolus is eliminated and the subcutaneous dose is reduced to 0.75 mg/kg every 12 hours. Regardless of age, if the creatinine clearance (using the Cockcroft-Gault formula) during the course of treatment is estimated to be <30 mL/min, the subcutaneous regimen is 1 mg/kg every 24 hours. Treatment should be continued for up to 8 days or until revascularization.

c. Fondaparinux (contraindicated if CrCl < 30 mL/min): initial dose 2.5 mg intravenously; subsequent subcutaneous injections of 2.5 mg daily starting the following day and continued for up to 8 days or until revascularization.

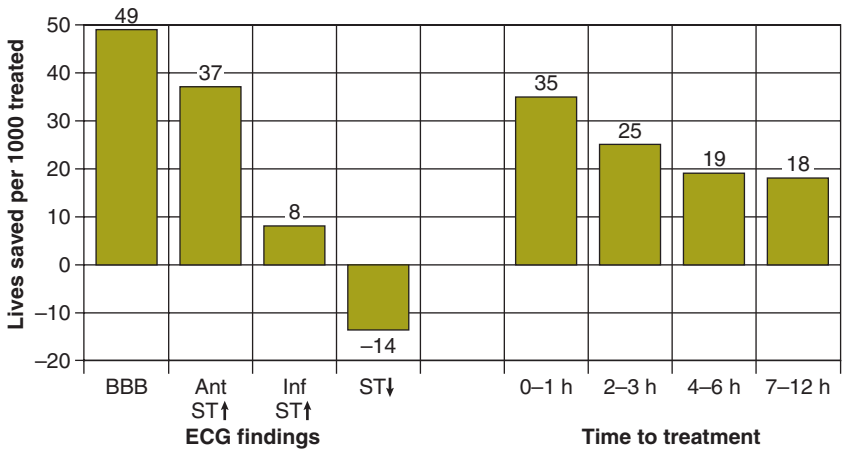
ACT, *Activated clotting time;* CrCl, *creatinine clearance;* GP, *glycoprotein;* IV, *intravenous;* PCI, *percutaneous coronary intervention;* STEMI, *ST-segment elevation myocardial infarction;* UFH, *unfractionated heparin.*

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2013;61:e78–e140.*

Fibrinolytic Therapy

Effect of Fibrinolysis on Survival

The landmark angiographic study performed by DeWood and coworkers[145] confirmed the presence of coronary artery thrombi in patients with STEMI. Four well-designed, multicenter randomized trials established that three fibrinolytic agents—streptokinase,[96,146,147] anisoylated plasminogen-streptokinase activator complex (i.e., anistreplase),[148] and t-PA[149]—each reduced short-term and long-term mortality in patients with acute MI. In the GISSI trial the survival benefit observed in the patients treated with streptokinase remained significant at 10 years, with an absolute benefit of 19 (95% CI 1–17) lives saved per 1000 patients treated.[147] The Fibrinolytic Therapy Trialists' Collaborative Group analyzed nine trials that randomly



• **Fig. 29.5** The impact of the presenting electrocardiogram *(ECG)* and the time to treatment on the 35-day mortality of 58,600 patients enrolled in nine randomized trials comparing streptokinase, anisoylated plasminogen-streptokinase activator complex (anistreplase), urokinase, or tissue plasminogen activator with placebo or control, expressed as the number of lives saved per 1000 patients who received fibrinolytic therapy. *Ant ST* anterior ST-segment elevation; *BBB* bundle branch block; *Inf ST* inferior ST-segment elevation. (From Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' [FTT] Collaborative Group. *Lancet.* 1994;343:311–322.)

assigned a total of 58,600 patients with suspected acute MI to a fibrinolytic therapy group or a control group.[150] The absolute risk of death increased with age, but absolute reductions in mortality were comparable among younger and older patients up to 75 years of age. Several trials had upper age limits for enrollment. The remaining trials enrolled 5788 patients 75 years or older and found no significant effect of fibrinolytic therapy on mortality at 35 days (25.3% for the control patients vs. 24.3% for patients who received fibrinolytic therapy).[150]

The baseline ECG findings and the elapsed time between the onset of symptoms and the initiation of treatment were significant determinants of the impact of fibrinolytic therapy on mortality at 35 days[150] (Fig. 29.5). The greatest reduction in mortality was observed in patients who presented with either bundle branch block (BBB) (control 23.6% vs. fibrinolytic 18.7%) or ST-segment elevation in the anterior leads (control 16.9% vs. fibrinolytic 13.2%).[150] Fibrinolytic therapy increased mortality among patients with ST-segment depression on the baseline ECG.

A linear relationship between the absolute reduction in mortality and the delay from symptom onset to randomization was found among the 45,000 patients who presented with ST elevation or BBB on the ECG.[150] Fibrinolytic therapy significantly reduced mortality even among patients who received treatment 7 to 12 hours after the onset of symptoms, but patients who received treatment within the first hour after the onset of their symptoms received the greatest benefit. Patients who receive fibrinolytic therapy within the first hour after symptom onset have the greatest proportional mortality reduction,[151] as well as the highest incidence of so-called aborted MI, defined as maximal creatine kinase level up to twice the upper limit of normal and typical evolution of ECG changes.[152,153] A multicenter trial of fibrinolytic therapy reported that the baseline-adjusted mortality was significantly lower among the 13.3% of patients who had an aborted MI than among those who did not.[152]

Persistent occlusion of the IRA after acute MI is associated with left ventricular remodeling, resulting in increased left ventricular end-systolic volume, a major predictor of survival after acute MI.[154,155] Some evidence suggests that reperfusion later than 6 hours after the onset of symptoms has a favorable effect on ventricular remodeling, with less ventricular dilation observed after successful reperfusion than after no reperfusion therapy.[156,157] Several clinical trials have investigated the effects of fibrinolytic therapy on clinical events in patients who received treatment more than 6 hours after the onset of symptoms. A South American multicenter trial randomly assigned 2080 patients within 7 to 12 hours after the onset of symptoms to receive streptokinase or placebo and found no significant difference in mortality rates in the hospital, after 35 days, and after 1 year.[158] The Late Assessment of Thrombolytic Efficacy (LATE) study randomly assigned 5711 patients who presented with suspected acute MI between 6 and 24 hours after the onset of symptoms to receive t-PA or placebo.[159] Treatment with t-PA significantly reduced mortality among patients who received treatment within 12 hours of symptom onset; the 35-day mortality rate was 8.9% for the t-PA group versus 11.97% for placebo, representing a relative reduction of 25.6% (95% CI 6.3%–45%; $P = 0.0229$). Mortality at 35 days was not significantly reduced by the administration of t-PA to patients who received treatment 12 to 24 hours after symptom onset.

The major causes of delayed fibrinolytic therapy for acute MI are failure of patients to seek medical care[160,161] and delays in administration of fibrinolytic therapy.[162,163] A retrospective review of data for 2409 patients hospitalized with acute MI in Minnesota in 1992 and 1993 reported that 40% of the patients delayed presentation to the hospital more than 6 hours after the onset of symptoms.[160] The ACC/AHA Practice Guidelines set a goal of initiating fibrinolytic therapy within 30 minutes of contact with the medical system.[20] A study of 3219 patients with STEMI who received fibrinolytic therapy in 178 hospitals between 2007 and 2008 found that the "door-to-needle" time was 30 minutes or less in only 44.5% of patients.[163] Female gender and age older than 75 years were associated with longer door-to-needle times.[163] A total of 5296 patients who received fibrinolytic therapy before

transfer from hospitals without PCI capability to PCI-capable hospitals were enrolled in a registry of 22,481 STEMI patients between July 1, 2008, and March 31, 2012.[164] Only 43.8% of the patients achieved a door-to-needle time within 30 minutes.[164]

Prehospital administration of fibrinolytic therapy has been investigated as one approach to reducing the delay between symptom onset and reperfusion.[165–167] A meta-analysis of six randomized trials that compared prehospital with in-hospital fibrinolytic therapy for acute MI found that the time to fibrinolytic therapy and all-cause in-hospital mortality were significantly reduced by the prehospital administration of fibrinolytic drugs.[165] An international study randomly assigned 1892 patients with STEMI who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour to either prehospital fibrinolytic therapy with bolus TNK or primary PCI.[167] All patients were transferred to a PCI-capable hospital. Emergency coronary angiography was required in 36.3% of the patients in the fibrinolysis group, and coronary angiography was performed at a median of 17 hours after randomization in the remainder of the prehospital fibrinolysis group.[167] The primary endpoint—a composite of death, shock, HF, or reinfarction within 30 days—occurred in 116 of 939 patients (12.4%) in the fibrinolysis group compared with 135 of 943 patients (14.3%) in the primary PCI group (RR 0.86; 95% CI 0.68–1.09; $P = 0.21$).[167] For the entire study group the rate of intracranial hemorrhage was greater in the fibrinolysis group than in the primary PCI group (1.0% vs. 0.2%; $P = 0.04$).[167] However, after the dose of TNK was reduced by 50% in patients 75 years of age or older, there were no additional cases of intracranial hemorrhage in that age group, and the rates of intracranial hemorrhage after the protocol amendment were 0.5% for the fibrinolysis group compared with 0.3% for the primary PCI group ($P = 0.45$).[167]

Coronary Artery Patency After Fibrinolytic Therapy

Early angiographic studies investigated the rates of coronary reperfusion after intracoronary[168–170] or intravenous administration of fibrinolytic agents.[171] The Thrombolysis in Myocardial Infarction (TIMI) Study Group devised a grading system of coronary patency that has been adopted widely[171] (Box 29.4). Fibrinolysis was judged to be successful if an IRA that was occluded (TIMI grade 0 or 1) before treatment improved to either partial perfusion (TIMI grade 2) or complete perfusion (TIMI grade 3) 90 minutes after the fibrinolytic therapy began.[171] The first TIMI trial revealed that only 31% of occluded arteries were patent (TIMI grade 2 or 3) 90 minutes after intravenous streptokinase, compared with a 62% patency rate after a 3-hour intravenous infusion of t-PA ($P < 0.001$).[172] Subsequent studies that examined the relationship between the TIMI grade flow and clinical outcome concluded that TIMI grade 3 flow, but not TIMI grade 2 flow, improves both in-hospital and long-term mortality after acute MI.[173,174] Therefore the criteria for evaluating fibrinolytic therapy were revised, and TIMI grade 2 flow is no longer considered a successful outcome.[175]

• BOX 29.4 Definitions of Perfusion in the TIMI Trial

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than the rate of entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction).

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

TIMI, *Thrombolysis in Myocardial Infarction.*

From TIMI Study Group. Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med. *1985;312:932–936.*

The GUSTO-I trial randomly assigned 41,021 patients to four fibrinolytic strategies: streptokinase plus subcutaneous UFH, streptokinase plus intravenous UFH, accelerated t-PA plus intravenous UFH, or a combination of streptokinase and t-PA plus intravenous UFH.[176] Thirty-day mortality was lowest for the accelerated t-PA–UFH regimen, 6.3%. A substudy of GUSTO-I included 2431 patients who underwent coronary angiography to assess patency of the IRA.[177,178] TIMI grade 3 flow was achieved 90 minutes after initiation of fibrinolytic therapy in 54% (157/292) of patients in the accelerated t-PA–UFH group, compared with 31% of patients who received streptokinase plus UFH (176/576). Analysis of the relationship between patency at 90 minutes and mortality at 30 days regardless of treatment assignment revealed a significant difference between the mortality rate associated with grade 3 flow and the mortality associated with grade 0 or 1 flow (4.4% vs. 8.9%; $P = 0.009$).

The relationship between time to treatment and the mortality reduction by fibrinolytic therapy may be a reflection of several factors. One is that earlier reperfusion achieves greater myocardial salvage.[179] Another factor is that time to treatment may influence the patency rate 90 minutes after administration of certain fibrinolytic drugs.[180] Patency of the IRA 90 minutes after administration of a nonfibrin-specific fibrinolytic drug, such as streptokinase, anistreplase, or urokinase, is lower when patients are first treated beyond 3 hours after the onset of symptoms than when the drugs are administered within 3 hours after onset.[172,180–182] After treatment with t-PA or rPA, fibrin-specific fibrinolytic agents, the rates of TIMI grade 3 flow are similar for patients who received treatment within 3 hours or at 3 hours or later after the onset of symptoms.[172,181,182] The time-dependent reperfusion efficacy is reflected by the rates of in-hospital mortality. A retrospective analysis of six angiographic trials that included 1174 patients found that in-hospital mortality among patients who received nonfibrin-specific drugs was twofold greater for patients treated more than 3 hours after symptom onset compared with patients treated within 3 hours.[182] Among patients who received t-PA or rPA, in-hospital mortality did not differ for patients treated within 3 hours of symptom onset or later than 3 hours after symptom onset.

More sophisticated methodologies for assessing myocardial reperfusion have been devised, such as the TIMI frame count and TIMI myocardial perfusion grade.[183–185] Application of these methods demonstrated that even among patients with TIMI grade 3 flow after fibrinolytic therapy, clinical outcomes and survival are related to the speed of epicardial flow and the state of myocardial perfusion.[183,184] Therefore a major goal of research has been to determine whether combinations of fibrinolytic and antiplatelet drugs might enhance myocardial reperfusion and achieve further reductions in mortality. Compared with full-dose t-PA or rPA, a combination of a reduced dose of either t-PA or rPA plus abciximab,

a platelet GP IIb/IIIa inhibitor, was found to increase the rates of TIMI 3 flow at 60 and 90 minutes after administration.[186,187] Unfortunately, a difference in 30-day mortality between standard-dose rPA and half-dose rPA plus full-dose abciximab was not demonstrated by a large clinical trial, GUSTO-V, that enrolled 16,588 patients with evolving STEMI.[188]

Complications of Fibrinolytic Therapy

Intracranial hemorrhage and other hemorrhagic complications are the major risks associated with the administration of fibrinolytic therapy.[189,190] The NRMI 2 database accrued 71,073 patients who received t-PA for acute MI from June 1, 1994, to September 30, 1996. Intracranial hemorrhage was confirmed by CT or MRI in 625 patients (0.88%).[190] In-hospital mortality was 53%, and 25.3% of patients with intracranial hemorrhage who survived to hospital discharge had neurologic deficits. A multivariate analysis identified several risk factors that were significantly associated with an increased risk of intracranial hemorrhage: older age, female gender, systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 100 mm Hg, and history of stroke. An activated partial thromboplastin time longer than 70 seconds was associated with an increased risk of hemorrhagic stroke in the GUSTO-I trial.[122] Bolus administration of fibrinolytic agents may be associated with an increased risk of intracranial hemorrhage compared with infusion.[191,192] Although phase II trials indicated a statistically nonsignificant reduction in the risk of intracranial hemorrhage, meta-analysis of phase III trials revealed a statistically significant 25% increase in the risk of intracranial hemorrhage with bolus fibrinolytic therapy.[192] According to the ACC/AHA guidelines, "The occurrence of a change in neurological status during or after reperfusion therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to intracranial hemorrhage until proven otherwise."[20] When intracranial hemorrhage is suspected, an emergency CT scan should be performed, and fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until the diagnosis is ruled out. Cryoprecipitate or fresh frozen plasma should be given to replenish coagulation factors.[20] Protamine should be administered to patients who are receiving UFH. Neurosurgery to evacuate parenchymal hemorrhages or subdural hematomas may improve outcome.[193]

Among 40,903 patients enrolled in the GUSTO-I trial, 1.2% had severe bleeding, defined as bleeding that caused hemodynamic compromise that required treatment, and 11.4% experienced moderate hemorrhage, defined as bleeding that required transfusion but did not lead to hemodynamic compromise requiring intervention.[189] The most common sources of moderate and severe bleeding were procedure related. The rate of moderate or severe bleeding was 6% among patients who underwent no procedures, compared with 17% among patients who underwent coronary angiography, 43% among patients who received a PA catheter, and 50% among patients who received an intraaortic balloon pump (IABP) or underwent coronary artery bypass surgery. Older age, lower body weight, and female sex were the three strongest independent predictors of hemorrhage. The risk of noncerebral bleeding was greater after streptokinase than after t-PA, but the risk of intracranial hemorrhage was greater after t-PA.

Patient Selection

The 2013 ACCF/AHA Guideline for STEMI includes one class I indication for fibrinolytic therapy: in the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of the first medical contact.[24] The 2013 STEMI Guideline also includes one class IIa recommendation for fibrinolytic therapy: in the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability.[24] There is a long list of absolute and relative contraindications to fibrinolytic therapy (Box 29.5). Special attention should be paid to factors that may increase the risk of intracranial hemorrhage, such as a history of such hemorrhage, recent closed head or facial trauma, uncontrolled hypertension, or ischemic stroke within the previous 3 months. PCI is preferable to fibrinolytic therapy in patients with an increased risk of intracranial hemorrhage. Active menstrual bleeding should not be considered a contraindication to fibrinolytic therapy.[194,195] The GUSTO-I trial included 12 menstruating women who received fibrinolytic therapy, 2 of whom required a transfusion for moderate vaginal bleeding.[195] Nontraumatic cardiopulmonary resuscitation also should not be considered a contraindication to fibrinolytic therapy.[194,196]

Increasing age is a risk factor for death and other adverse events after either primary PCI or fibrinolytic therapy for STEMI.[197] The risk of intracranial hemorrhage after fibrinolytic therapy also increases with advancing age.[190,198] Data are conflicting regarding

• BOX 29.5 Contraindications and Cautions for Fibrinolysis in ST-Segment Elevation Myocardial Infarction

Absolute Contraindications

Any prior intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months; *exception:* acute ischemic stroke within 4.5 h
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed head or facial trauma within 3 months
Intracranial or intraspinal surgery within 2 months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, prior treatment within the previous 6 months

Relative Contraindications

1. History of chronic, severe, poorly controlled hypertension
2. Severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
3. History of prior ischemic stroke more than 3 months earlier, dementia, or known intracranial pathology not covered in absolute contraindications
4. Traumatic or prolonged (beyond 10 min) CPR or major surgery (within 3 weeks)
5. Recent (within 2–4 weeks) internal bleeding
6. Noncompressible vascular punctures
7. For streptokinase/anistreplase: prior exposure (>5 days earlier) or prior allergic reaction to these agents
8. Pregnancy
9. Active peptic ulcer
10. Oral anticoagulant therapy

CPR, *Cardiopulmonary resuscitation.*
From O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2013;61:e78–e140.*

the benefit or lack of benefit of fibrinolytic therapy in patients with STEMI who are older than 75. One analysis of a Medicare database that included 2673 patients aged 76 to 86 found that fibrinolytic therapy conferred a survival disadvantage, with an HR of 1.38 for 30-day mortality.[199] Fibrinolytic therapy was associated with a 13% reduction in the composite of 1-year mortality and cerebral bleeding in a cohort of 6891 patients 75 years and older with a first STEMI who were enrolled in a Swedish registry.[200] A study performed in the Netherlands randomly assigned 87 patients with acute MI who were older than 75 to primary PCI or streptokinase.[201] The primary composite endpoint of death, reinfarction, or stroke at 30 days occurred in 4 (9%) patients in the PCI group, compared with 12 (29%) in the streptokinase group (RR 4.3, 95% CI 1.2 to 20; $P = 0.01$). After 1 year, mortality was significantly greater for the streptokinase group than for the PCI group (29% vs. 11%; RR 3.4, 95% CI 1.0 to 13.5; $P = 0.03$). One caveat regarding the study is that the mean time from hospital admission to first balloon inflation was 59 ± 19 minutes (range 33–120 minutes)—considerably shorter than door-to-balloon times in the United States.

Many patients with acute MI have contraindications to fibrinolytic therapy or do not meet eligibility criteria for fibrinolytic therapy.[202,203] Contraindications, such as recent surgery, trauma, or gastrointestinal bleeding, would be relatively frequent in patients who develop an acute MI while already hospitalized for another illness. Analysis of patients with STEMI who were enrolled in the NRMI 2, 3, and 4 databases suggested that immediate mechanical reperfusion using either PCI or coronary artery bypass surgery reduced the risk of in-hospital death among patients with contraindications to fibrinolytic therapy.[204]

Percutaneous Coronary Intervention

Numerous randomized trials and observational studies have been performed to investigate PCI in patients with acute MI. Primary PCI is defined as PCI without previous or concomitant fibrinolytic therapy After successful fibrinolysis, PCI may be performed immediately, on a routine, deferred basis, or in a selective fashion (e.g., to treat inducible ischemia). Rescue PCI refers to PCI that is performed after unsuccessful fibrinolytic therapy.

Primary Percutaneous Intervention

Dr. Andreas Gruentzig performed the first balloon angioplasty of a coronary artery in 1977.[205] Dr. K. Peter Rentrop reported his initial experience with PCI for acute MI in 1979.[206,207] O'Neill and colleagues[208] published a randomized trial of PCI compared with intracoronary streptokinase for acute MI in 1986. A meta-analysis identified 32 observational studies that included 185,900 patients with STEMI, and 23 trials that randomly assigned a total of 8140 patients with STEMI to undergo primary PCI or receive intravenous fibrinolytic therapy.[209]

Myocardial salvage and long-term mortality are correlated with both the TIMI grade flow and the myocardial blush grade achieved after primary PCI for STEMI.[210–213] TIMI grade 3 flow is achieved in a high percentage of patients who undergo primary PCI for STEMI. The largest clinical trial of PCI compared with fibrinolytic therapy for acute MI was the Danish Multicenter Randomized Study on Fibrinolytic Therapy versus the Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) study.[214–216] Immediate angiography was performed in 777 of the 790 (98%) patients who were randomly assigned to undergo PCI. The initial angiogram showed TIMI grade 0 or 1 flow in 68% of patients, and grade 3 flow in 18%. PCI was attempted in 706 patients, resulting in postprocedural flow of TIMI grade 3 in 82%, grade 2 in 16%, and grade 0 or 1 in 2%. The Zwolle Myocardial Infarction Study Group reported the outcome of 1702 patients who underwent PCI for STEMI.[217] Successful PCI, defined as TIMI grade 3 flow and a residual lumen diameter less than 50%, was achieved more often during routine hours (8 a.m. to 6 p.m.) than during off-hours (6 p.m. to 8 a.m.) (96.2% vs. 93.1%; $P < 0.01$).

Despite the presence of TIMI grade 3 flow, the myocardial blush grade, an indicator of myocardial perfusion, is abnormal in a majority of patients who undergo primary PCI for STEMI.[211,212] Among a cohort of 777 patients who underwent primary PCI for STEMI, normal myocardial blush (grade 3) was achieved in only 148 patients (19%), whereas 236 patients (30%) had blush grade 0 or 1.[211] Multivariate analysis showed that myocardial blush grade was an independent predictor of long-term mortality, with mortality after follow-up for 1.9 ± 1.7 years of 3% for grade 3, 6% for grade 2, and 23% for grade 0 or 1 myocardial blush ($P < 0.0001$).[211]

Distal Protection and Thrombectomy Devices

Distal embolization of thrombus[218] and microvascular "no reflow"[219] are two of the mechanisms of impaired myocardial perfusion after primary PCI. Distal embolization was observed in 27 of 178 patients (15%) who underwent primary PCI for STEMI.[218] Patients with distal embolization had lower LVEFs at discharge from the hospital and higher long-term mortality. Microvascular obstruction detected by MRI is a prognostic marker for cardiovascular events after acute MI, even after controlling for infarct size.[219] Numerous clinical trials have been performed to investigate various mechanical methods of protecting the coronary microcirculation during PCI for ACS or acute STEMI.[220–231] Two different distal embolic protection devices, one that consists of a distal balloon occlusion and aspiration system and another that uses a filter, failed to improve myocardial reperfusion, reduce infarct size, or improve event-free survival in patients with acute MI.[224–226] A meta-analysis of 12 clinical studies concluded that the distal embolic protection devices had no significant effect on mortality.[229]

Use of the X-Sizer thrombectomy catheter (ev3, Inc., Plymouth, MN) before coronary angioplasty or stenting appears to reduce distal embolization and improve epicardial flow, myocardial blush, and resolution of ST-segment elevation, especially in patients with angiographic evidence of intraluminal thrombus.[220–222] The AngioJet Rheolytic Thrombectomy catheter (Possis Medical, Inc., Minneapolis, MN) was evaluated in a multicenter, randomized study called the AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AIMI) study.[223] The AIMI trial randomly assigned 480 patients within 12 hours of symptom onset of STEMI to PCI alone or PCI with adjunctive rheolytic thrombectomy. No significant differences were observed in myocardial perfusion blush or resolution of ST-segment elevation. Infarct size measured by myocardial perfusion imaging was greater in the thrombectomy group, and major adverse cardiac events were more frequent in the thrombectomy group (6.7% vs. 1.7%; $P = 0.01$).[223] A meta-analysis of five randomized trials concluded that adjunctive mechanical thrombectomy with either the AngioJet catheter or the X-Sizer catheter was associated with increased mortality compared with PCI alone (5.3% vs. 2.8%; $P = 0.05$) in patients with acute MI.[229]

At least 19 clinical trials have been performed to test the effect of aspiration thrombectomy on clinical outcomes in patients with STEMI. The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) was an open trial with a blinded evaluation of endpoints that randomly

assigned 1071 patients to either conventional PCI or thrombus aspiration using a 6F aspiration catheter during PCI.[227,228] Thrombus aspiration resulted in improved myocardial blush grade, resolution of ST-segment elevation, and lower 1-year mortality.[227,228]

Subsequently, two large trials, TASTE[230] (Thrombus Aspiration During ST-Segment Elevation MI), which enrolled 7244 patients, and TOTAL[231] (Trial of routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI), which enrolled 10,732 patients, were unable to show a beneficial effect of aspiration thrombectomy in patients with STEMI. The TASTE[230] and TOTAL[231] trials were included in a meta-analysis of 17 trials that found no significant reduction in death, reinfarction, or stent thrombosis in patients with STEMI who underwent routine aspiration thrombectomy.[232] Also, aspiration thrombectomy was associated with a small but nonsignificant increase in the risk of stroke.[232] Therefore the 2015 ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) Focused Update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction cited the TASTE[230] and TOTAL[231] trials and the updated meta-analysis[232] as the basis for a class III (no benefit) recommendation that "Routine aspiration thrombectomy before primary PCI is not useful."[23] Also, the 2015 Update on primary PCI included a class IIb recommendation that "The usefulness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI is not well established."[23] Subsequently, the investigators who conducted the TAPAS, TASTE, and TOTAL trials analyzed the pooled individual patient data from these three trials that compared aspiration thrombectomy and PCI alone in patients with STEMI.[233] Although routine thrombus aspiration did not improve clinical outcomes, there were trends toward reduced cardiovascular death and increased stroke or transient ischemic attack in the subgroup of patients with a high thrombus burden, defined as TIMI thrombus grade 3 or higher.[233]

Culprit Artery–Only Versus Multivessel PCI

Multivessel CAD is common among patients with STEMI. Among the 2081 patients who underwent primary PCI for acute MI in the CADILLAC trial, only 51.2% had single-vessel CAD, whereas 33.2% had two-vessel CAD and 15.6% had three-vessel CAD, based on a definition of 70% or more occlusion of a noninfarct artery.[234] Similarly, a pooled analysis of 8 STEMI clinical trials found that 18.8% of patients had three-vessel CAD and 29.6% had two-vessel CAD, defined as a 50% or more diameter stenosis of a noninfarct artery.[235] Both studies found that multivessel disease was associated with an adverse prognosis after MI. The treatment of multivessel CAD in patients with STEMI is an area of active investigation and was addressed in the 2015 ACC/AHA/SCAI Focused Update on Primary PCI for Patients with STEMI.[23] Based on safety concerns, the 2013 ACCF/AHA STEMI Guideline recommended against PCI of nonculprit arteries at the time of primary PCI in patients who are hemodynamically stable.[24] The results of four recent randomized clinical trials served as the basis for upgrading the previous class III recommendation regarding multivessel primary PCI in hemodynamically stable patients to a class IIb recommendation for either staged multivessel PCI or multivessel PCI at the time of primary PCI.[23]

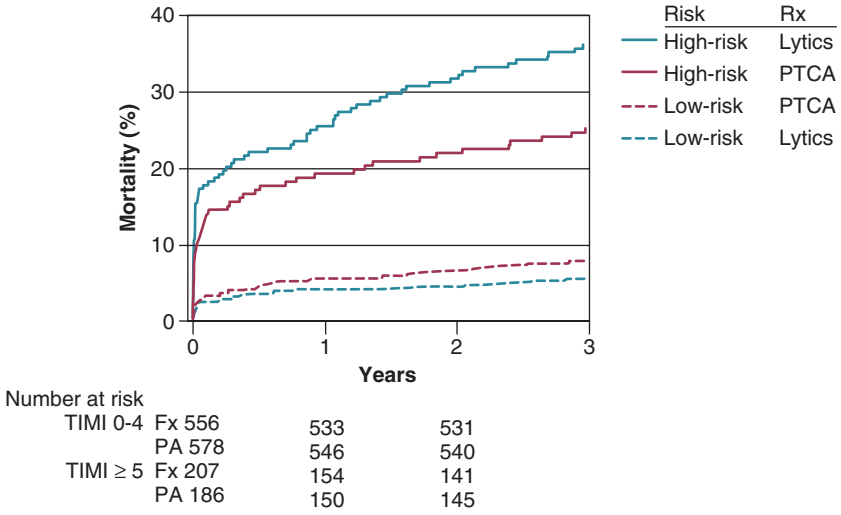
The PCI options for patients with STEMI and multivessel CAD are multivessel PCI at the time of primary PCI, culprit-only primary PCI followed by staged PCI of nonculprit arteries, or culprit-only primary PCI with PCI of nonculprit arteries only for either spontaneous ischemia or intermediate-risk or high-risk findings on predischarge noninvasive testing. Bates et al.[236] published a state-of-the-art review of the numerous randomized trials and observational studies of PCI strategies in patients with STEMI and multivessel CAD, and multiple meta-analyses have been published.[237–239] Although the studies concluded that complete revascularization is associated with improved outcomes, the data were considered insufficient to formulate a recommendation regarding the optimal timing of nonculprit artery PCI.

Primary Percutaneous Intervention Versus Fibrinoltyic Therapy

The evidence base supporting primary PCI for STEMI includes single-center series, multicenter randomized trials, large registries, and several meta-analyses. The Myocardial Infarction Triage and Intervention (MITI) Project Registry described a cohort of patients with acute MI who either underwent primary angioplasty (1050 patients) or received fibrinolytic therapy (2095 patients) at 19 hospitals in Seattle, Washington, between 1988 and 1994.[240] No significant difference in mortality was observed during hospitalization or long-term follow-up between the two groups. The MITI Registry included patients who received streptokinase, whereas a subsequent NRMI 2 report limited to patients who received t-PA also found that in-hospital outcomes were similar for both methods of reperfusion.[241] Another cohort study of 20,683 Medicare beneficiaries with acute MI concluded that 30-day and 1-year mortality rates were lower among patients who underwent primary angioplasty than among patients who received fibrinolytic therapy.[242]

The Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) trial did not show a significant difference between PCI and fibrinolytic therapy in the rates of death or stroke at 30 days, but the rate of reinfarction at 30 days was significantly lower: 1.6% for the PCI group compared with 6.3% for the fibrinolysis group ($P < 0.001$).[214] Among 1527 patients who were enrolled in the DANAMI-2 trial, no difference in mortality was observed between low-risk patients (TIMI score 0–4) who underwent primary PCI and those who received fibrinolytic therapy (8% vs. 5.6%; $P = 0.11$) (Fig. 29.6).[215] The 3-year mortality rate was significantly lower in high-risk patients who underwent PCI than in patients who received fibrinolytic therapy (25.3% vs. 36.2%; $P = 0.02$) (see Fig. 29.6).[215]

Published meta-analyses of PCI versus fibrinolytic therapy included DANAMI-2 and 22 other randomized trials.[209,243] The trials were rather heterogeneous in design: stents were used in 12 trials, GP IIb/IIIa inhibitors were used in 8 trials, and 5 trials compared fibrinolytic therapy with PCI performed after transfer from a referral hospital to a hospital that provides invasive cardiac services. The meta-analysis by Keeley et al.[243] concluded that, compared with fibrinolytic therapy, primary PTCA was associated with lower rates of death during both short-term (7% [$n = 270$] vs. 9% [$n = 360$]; $P = 0.0002$) and long-term follow-up, and lower rates of nonfatal reinfarction (3% [$n = 80$] vs. 7% [$n = 222$]; $P < 0.0001$), and stroke (1% [$n = 30$] vs. 2% [$n = 64$]; $P = 0.0004$). Subsequently, Huynh et al.[209] published meta-analyses of the 23 randomized clinical trials and 32 observational studies. Primary PCI was associated with 34% (OR 0.66; 95% CI 0.51–0.82) lower short-term (≤6-week) mortality in randomized trials, and 23% (OR, 0.77; 95% CI 0.62–0.95) lower short-term mortality in observational studies.[209] Also, primary PCI was associated with a 63% reduction in stroke in the randomized trials and a 61% reduction in the observational studies.[209] Another analysis pooled the individual patient 6-month follow-up data from 11 randomized trials of PCI versus fibrinolytic therapy for acute MI.[244] At 6 months, the mortality rates were 6.2% for PCI and 8.2% for fibrinolysis



• **Fig. 29.6** Mortality rates for low-risk patients *(dashed lines)* and high-risk patients *(solid lines)* who were randomly assigned to receive fibrinolysis *(Fx) (blue lines)* or primary angioplasty *(PA) (red lines)* in the DANAMI-2 trial. Among 1134 patients who were classified as low risk by virtue of a TIMI risk score of 0 to 4, mortality after fibrinolysis and primary angioplasty was not significantly different. Among 393 patients with a TIMI risk score of 5 or higher, mortality was significantly lower after primary angioplasty compared with fibrinolysis. *DANAMI,* Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction; *Fx,* fibrinolytic therapy; *PA,* primary angioplasty; *PTCA,* percutaneous transluminal coronary angioplasty; *Rx,* treatment; *TIMI,* Thrombolysis in Myocardial Infarction study. (From Thune JJ, Hoefsten DE, Lindholm MG, et al. Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. *Circulation.* 2005;112:2017–2021.)

(RR 0.73; CI 0.55–0.98; $P = 0.04$). A meta-analysis of 11 randomized trials that enrolled 4320 patients with STEMI found that long-term mortality (≥1 year) was 24% lower among patients treated with primary PCI compared with patients treated with fibrinolytic therapy.[209]

Analysis of patients enrolled in NRMI 2 showed that the in-hospital mortality was 28% lower among patients who underwent primary PCI at hospitals with the highest volume than among those who had PCI at hospitals with the lowest volume (adjusted RR 0.72; 95% CI 0.60–0.87; $P < 0.001$).[245] Among 463 hospitals that performed primary PCI for STEMI and participated in NRMI 4, the hospitals with the greatest relative utilization of primary PCI, versus fibrinolytic therapy, for reperfusion had shorter door-to-balloon times and lower in-hospital mortality rates.[246] These data may have provided some of the rationale for the ACC/AHA Practice Guidelines regarding the performance of PCI for STEMI.[20] PCI should be performed in a cardiac catheterization laboratory that performs more than 200 PCI procedures per year, including at least 36 cases of primary PCI for STEMI. The operator should perform more than 75 PCI procedures per year.

Door-to-Balloon Time. Both the extent of myocardial salvage[179,247] and the mortality benefit[150,248,249] of fibrinolytic therapy and primary PCI are inversely related to the time elapsed between symptom onset and treatment. Among a cohort of 1791 patients with STEMI treated with primary PCI, the RR of death at 1 year increased by 7.5% for each 30-minute delay.[250] Several studies have analyzed the relationship between mortality and the so-called door-to-balloon time, defined as the duration of time between arrival at the hospital and the first balloon inflation.[249,251–253] Although some studies found that in-hospital mortality was not related to the door-to-balloon time,[251] most studies have shown that both in-hospital and late mortality are higher when door-to-balloon time is longer.[249,252,253] Among 2082 patients with acute MI who were enrolled in the CADILLAC trial, door-to-balloon time was an independent predictor of 1-year mortality in patients who presented within 2 hours after the onset of symptoms (n = 965; HR 1.24; 95% CI 1.05–1.46; $P = 0.013$), but not in patients who presented later than 2 hours (n = 944; HR 0.88; 95% CI 0.67–1.15; $P = 0.33$).[254]

The ACC/AHA Practice Guidelines set a goal of balloon inflation within 90 minutes of presentation, and recent observational studies indicate that this goal is frequently achieved.[255] Among 96,738 patients with STEMI who underwent primary PCI between July 2005 and June 2009 at 515 hospitals that participated in the ACC's CathPCI Registry, the percentage of patients for whom the door-to-balloon time was 90 minutes or less increased from 59.7% in the first year to 83.1% in the last year ($P < 0.001$).[255] Krumholz and colleagues[256] analyzed the door-to-balloon times reported by hospitals to the Centers for Medicare & Medicaid Services from January 1, 2005 through September 30, 2010. Door-to-balloon time decreased from a median of 96 minutes in 2005 to a median of 64 minutes during the first three quarters of 2010.[256] The percentage of patients who had door-to-balloon times less than 90 minutes increased from 44.2% to 91.4%.[256]

The time of day and day of week had significant effects on door-to-balloon times among 33,647 patients with STEMI who underwent primary PCI between 1999 and 2002 and were enrolled in the NRMI 3 and NRMI 4 registries.[257] Fifty-four percent of patients who underwent primary PCI were treated during off-hours (weekdays 5 p.m.–7 a.m. and weekends). Door-to-balloon times exceeded 90 minutes in 74% of patients who underwent PCI during off-hours, compared with 53% of patients treated during regular hours (weekdays 7 a.m.–5 p.m.) ($P < 0.001$). Treatment delays are far greater among patients who are transferred to another hospital to undergo primary PCI.[255] Among 17,052 patients with STEMI who underwent interhospital transfer for primary PCI

between July 2008 and December 2012, the median door-to-balloon time was 118 minutes, and only 20% of patients had a first door-to-balloon time of 90 minutes or less.[258] Analysis of 23 randomized trials that compared primary PCI with fibrinolytic therapy for STEMI indicated that PCI affords a mortality advantage only if the door-to-balloon time exceeds the door-to-needle time by less than 1 hour.[259]

Several approaches have been suggested to reduce the delay between symptom onset and reperfusion in patients treated by primary PCI. One approach that has been tested is the performance of primary PCI at hospitals that have cardiac catheterization laboratories but lack on-site cardiac surgery.[260] One trial randomly assigned patients with STEMI to undergo primary PCI ($n = 225$) or receive accelerated t-PA ($n = 226$) at 11 community hospitals without on-site cardiac surgery.[260] The composite endpoint of death, recurrent MI, and stroke was significantly lower among patients treated with primary PCI than among those who received t-PA, both 6 weeks after MI (10.7% vs. 17.7%; $P = 0.03$) and 6 months after MI (12.4% vs. 19.9%; $P = 0.03$). A subsequent study by the NRMI investigators compared the outcomes of 58,821 patients with STEMI who presented to 214 hospitals with on-site cardiac surgery with the outcomes of patients who presented to 52 hospitals without on-site cardiac surgery.[261] The patients who presented to hospitals without on-site cardiac surgery were less likely to receive guideline-recommended medications within 24 hours and less likely to undergo acute reperfusion therapy, but there was no difference in mortality among patients who underwent primary PCI.[261] A meta-analysis of 11 studies that included 124,074 patients who underwent primary PCI for STEMI found that the in-hospital mortality for patients at hospitals without on-site cardiac surgery was not different from hospitals having on-site surgery (OR 0.96; 95% CI 0.88–1.05).[262] Another proposed strategy to reduce the delay between symptom onset and reperfusion is the diversion of patients with acute MI to a primary PCI hospital, instead of the current practice of transporting patients to the nearest emergency department. A survey of 365 hospitals identified six strategies that were significantly associated with a faster door-to-balloon time.[263] The use of prehospital ECGs to diagnose and triage patients with a suspected STEMI is associated with a greater use of reperfusion therapy and shorter door-to-needle and door-to-balloon times.[264]

Coronary Stents

Late reocclusion after successful primary angioplasty is associated with decreased long-term survival.[265] The CADILLAC trial randomly assigned 2082 patients with acute MI to undergo percutaneous transluminal coronary angioplasty (PTCA) or stenting.[266] Although stenting did not improve the myocardial blush score,[267] the angiographic rate of reocclusion of the IRA at 7 months was 5.7% after coronary stenting, compared with 11.3% after PTCA.[266]

At least 22 randomized clinical trials and at least 5 observational studies, plus numerous meta-analyses of those studies, have been performed to compare drug-eluting stents (DESs) with bare metal stents (BMSs) in patients with STEMI. A meta-analysis of five observational studies found that STEMI patients treated with first-generation DESs (paclitaxel-eluting or sirolimus-eluting stents) had a significantly lower mortality compared with patients who received BMS (OR 0.65; 95% CI 0.53–0.80; $P < 0.001$).[268] A meta-analysis of 15 randomized, controlled trials that enrolled a total of 7867 STEMI patients concluded that compared with a BMS, first-generation DES are associated with a reduction in target vessel revascularization and stent thrombosis during the first year after stent implantation, but an increased risk of very late stent thrombosis (>1 year after PCI).[269] The apparent increased risk of very late stent thrombosis is consistent with both postmortem and in vivo evidence of higher rates of incomplete stent apposition and uncovered stent struts among STEMI patients treated with DESs compared with BMSs.[270,271]

A network meta-analysis of 22 controlled trials that randomly assigned a total of 12,453 patients with STEMI concluded that second-generation cobalt-chromium everolimus-eluting stents were associated with significantly lower risk of 1-year cardiac death/MI, MI, and stent thrombosis compared with BMS, and significantly lower 1-year rates of stent thrombosis than paclitaxel-eluting stents.[272] A trial that randomly assigned 1498 patients with STEMI to PCI with either BMSs or everolimus-eluting stents provided encouraging results after follow-up for 5 years.[273] All-cause mortality was significantly lower for the group treated with drug-eluting stents (9% vs. 12%; HR 0.72; CI 0.52–0.10; $P = 0.047$).[273] The 2014 ESC/EACTS Guidelines on myocardial revascularization include a class I recommendation that new-generation DESs are recommended over BMSs in STEMI patients who undergo primary PCI.[274]

Rescue Percutaneous Coronary Intervention

Compared with TIMI grade 3 flow, TIMI grade 0 or 1 flow at 90 minutes after fibrinolytic therapy is associated with worse left ventricular function and increased mortality rates.[177,178] Compared with complete resolution of ST-segment elevation, incomplete resolution of ST-segment elevation after fibrinolytic therapy is associated with larger infarct size and greater short-term and long-term mortality.[42,44,275] Therefore various angiographic or electrocardiographic criteria have been used to define unsuccessful fibrinolysis and rescue PCI. A report from the TIMI 10B and TIMI 14 trials of fibrinolytic therapy defined rescue PCI as PCI performed between 90 and 150 minutes after the start of therapy for patients with TIMI 0 or 1 flow 90 minutes after the start of therapy.[276] The Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial defined failed fibrinolytic therapy as failure of the ST-segment elevation in the worst lead to have resolved by 50% 60 minutes after the onset of fibrinolytic therapy.[277] The Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial's definition of rescue PCI was PCI performed within 12 hours after failed fibrinolytic therapy, defined as an ECG obtained 90 minutes after the start of fibrinolytic therapy that showed less than 50% resolution of the ST-segment in the lead showing the greatest ST-segment elevation.[278] Thus many of the patients who underwent PCI in the REACT trial would meet the TIMI group's definition of either adjunctive PCI (defined as PCI for patients with TIMI grade 2 or 3 flow) or delayed PCI (defined as PCI longer than 150 minutes after fibrinolytic therapy), rather than rescue PCI as defined by the TIMI group and other investigators.[276] Among patients enrolled in the TIMI 10B and 14 trials, the rate of TIMI grade 3 flow was significantly greater after adjunctive PCI than after rescue PCI (89% vs. 78%; $P = 0.001$),[276] which might account for the REACT trial's 98% (106 of 108 patients) success rate for rescue PCI.[278]

There is conflicting information regarding the impact of rescue PCI on mortality. Among 150 patients who were enrolled in the TIMI 10B trial and had TIMI 0 or 1 flow 90 minutes after fibrinolytic therapy, 2-year mortality was significantly lower among the patients who underwent rescue PCI ($n = 120$) than among those who did not ($n = 30$) ($P = 0.03$).[279] The randomized trials that compared rescue PCI with conservative therapy were insufficiently powered to detect an effect on mortality. Although

differences in trial design and the definition of rescue PCI make it somewhat difficult to compare the results of various trials, at least two meta-analyses of the randomized trials have been published.[280,281] A pooled analysis of the short-term mortality (in-hospital or 30-day) among 942 patients who were enrolled in five randomized trials revealed that the risk of death was 36% lower among patients who were randomly assigned to PCI (RR 0.64; 95% CI 0.41–1.00; $P = 0.048$).[280] Another meta-analysis included six trials that randomly assigned 908 patients to rescue PCI or conservative therapy.[281] Rescue PCI was not associated with a reduction in all-cause mortality at 6 months (RR 0.69; 95% CI 0.46–01.05), but it was associated with significant reductions in the risk of HF and reinfarction and an increased risk of stroke and minor bleeding.[281]

The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction included three indications for transfer for angiography after fibrinolytic therapy: class I—immediate transfer for cardiogenic shock or severe acute HF; class IIa—urgent transfer for failed reperfusion or reocclusion; and class IIa—as part of an invasive strategy in stable patients with PCI between 3 and 24 hours after successful fibrinolysis.[24]

Selection of Reperfusion Strategy

According to the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, there are three class I indications for primary PCI in patients with STEMI who present initially to a PCI-capable hospital:

1. Patients with ischemic symptoms of less than 12 hours' duration
2. Patients with ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from first medical contact
3. Patients with cardiogenic shock or acute severe HF, irrespective of time delay from MI onset[24]

Patients who are candidates for reperfusion therapy and present initially to a non–PCI-capable facility may be treated with fibrinolytic therapy or transferred to a PCI-capable facility for primary PCI.[24] Fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact.[24]

There are two class IIa indications for reperfusion therapy in patients with STEMI who present 12 or more hours after symptom onset. First: "Primary PCI is reasonable in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset."[24] Second: "In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability."[24]

The Occluded Artery Trial (OAT) randomly assigned 2166 stable patients with one- or two-vessel CAD and a total occlusion of the IRA 3 to 28 days after MI to medical therapy or PCI with stenting.[282] PCI did not reduce the occurrence of death, reinfarction, or HF. Consequently, the following class III recommendation was included in the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: "PCI of a totally occluded infarct artery greater than 24 hours after STEMI should not be performed in asymptomatic patients with one- or two-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia."[24]

Acute MI in patients who have undergone previous CABG surgery frequently is due to thrombotic occlusion of saphenous vein bypass grafts, rather than occlusion of native coronary arteries.[283,284] Among 1784 patient with previous CABG surgery who were enrolled in the GUSTO-1 trial, angiography after fibrinolytic therapy showed that 61.9% of the infarct vessels were native coronary arteries and 38.1% were occluded bypass grafts.[283] Among the patients with previous CABG surgery, angiography showed more infarct-related vessels with TIMI 0 or 1 flow (50%) and fewer infarct-related vessels with TIMI 3 flow (32%) compared with patients without previous CABG (29% and 49%, respectively).[283] Also, in patients with previous CABG surgery, native arteries and bypass grafts had nearly identical rates of TIMI 0 or 1 flow and TIMI 3 flow.[283] The APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) study, a randomized trial of pexelizumab in STEMI patients undergoing primary PCI, enrolled 128 patients (2.2%) with previous CABG surgery.[284] The infarct-related vessel was a native coronary artery in 55 patients and a bypass graft in 63 patients.[284] Among the patients with previous CABG surgery who underwent PCI, post-PCI TIMI flow grade 3 was achieved in only 66.7% of bypass graft infarct-related vessels, compared with 88.0% of native artery infarct-related vessels.[284] The 90-day death rates were 19% for patients with a bypass graft infarct-related vessel, compared with 5.7% for patients with previous CABG surgery and a native artery infarct-related vessel, and 4.6% for patients without previous CABG surgery.[284]

According to an analysis of the National Cardiovascular Data Registry, the percentage of patients with STEMI who were eligible for reperfusion therapy and underwent reperfusion therapy increased from 78% in 2007 to 89% in 2013.[285] There is evidence, however, that reperfusion therapy may be underused in two high-risk groups: elderly patients and patients with chronic kidney disease. Although the utilization rate of PCI to treat STEMI patients aged 65 years and older old increased during the decade 2001–2010, among STEMI patients older than 80 years of age with similar number of comorbidities the utilization of PCI was lower.[286] Analysis of a cohort of 26,620 patients with end-stage renal disease and STEMI showed that only 30.4% underwent PCI, with an increase in the use of PCI for patients with end-stage renal disease and STEMI from 18.6% in 2003 to 37.8% in 2011.[287] The report did not state whether any patients with end-stage renal disease and STEMI were treated with fibrinolytic therapy.

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Numerous clinical trials have investigated the role of platelet GP IIb/IIIa inhibitors in patients with acute STEMI, either in conjunction with fibrinolytic agents or primary PCI.[288,289] One rationale of including a GP IIb/IIIa inhibitor in either pharmacologic or mechanical reperfusion strategies is that platelet inhibition may improve myocardial perfusion and enhance salvage of ischemic muscle by reducing distal embolization of platelet aggregates. Another proposed rationale is to achieve coronary artery patency using lower doses of fibrinolytic drugs. Although the addition of abciximab to either t-PA[290] or rPA[187] has been shown to improve angiographic indices of myocardial reperfusion, combination therapy with abciximab and a fibrinolytic drug has not been shown to reduce mortality compared with fibrinolytic therapy alone. A trial that randomly assigned 16,588 patients with acute STEMI to treatment with either standard-dose rPA or half-dose rPA plus full-dose abciximab showed no differences in either 30-day or 1-year mortality.[291] A meta-analysis of three fibrinolytic trials that included 23,166 patients who were randomized to receive either abciximab plus half-dose rPA or TNK versus full-dose rPA or TNK found that abciximab was associated with a significant reduction

in the 30-day rate of reinfarction (2.3% vs. 3.6%; $P < 0.001$), but 30-day mortality was 5.8% for both groups.[288] Therefore there are no class I or II indications for a combination of fibrinolytic agents with GP IIb/IIIa inhibitors in the ACC/AHA Practice Guidelines.[24]

Although at least 18 randomized trials have been performed to evaluate GP IIb/IIIa inhibitors in patients with acute STEMI who undergo primary PCI, it has been difficult to draw definitive conclusions for several reasons.[289] First, three different GP IIb/IIIa inhibitors have been studied, abciximab and the so-called small-molecule inhibitors eptifibatide and tirofiban. Second, the agents have been studied in conjunction with various other antiplatelet, anticoagulant, and fibrinolytic regimens, and periprocedural administration of a platelet $P2Y_{12}$ inhibitor was not mandated in many of the trials. Third, the timing of drug administration has varied from prehospital therapy to periprocedural treatment. Fourth, the trials have been underpowered to evaluate the effects on mortality.

The largest trial, HORIZONS-AMI, compared the combination of UFH and a GP IIb/IIIa inhibitor, either abciximab or eptifibatide, with bivalirudin in 3602 patients with STEMI who were treated with primary PCI.[137–139] Compared with UFH plus a GP IIb/IIIa inhibitor, treatment with bivalirudin was associated with a reduced rate of major bleeding and, among patients who were classified as high risk, a lower 1-year mortality rate.[138,139] A meta-analysis of 16 trials that enrolled a total of 10,085 patients with STEMI who underwent primary PCI concluded that GP IIb/IIIa inhibitors did not reduce the rates of mortality or reinfarction at 30 days.[289] A meta-analysis of five randomized trials ($n = 2138$ patients) that compared abciximab with the small-molecule GP IIb/IIIa inhibitors in STEMI patients undergoing primary PCI found no differences in outcome.[292]

A meta-analysis that included 1662 patients who were enrolled in 11 randomized trials that compared early versus late administration of GP IIb/IIIa inhibitors before primary PCI concluded that early administration of abciximab improved postprocedural TIMI 3 flow, myocardial blush grade, and survival compared with late administration.[293] A registry that enrolled 1086 patients who received abciximab also found that early administration of abciximab before transfer for PCI, compared with late administration, was associated with lower 1-year mortality among patients with a TIMI risk score of 3 or higher.[294] The 2013 ACCF/AHA Guideline for the Management of STEMI includes a class IIb recommendation that "It may be reasonable to administer intravenous GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended."[24]

Numerous trials have investigated the utility of intracoronary administration of GP IIb/IIIa inhibitors during primary PCI for STEMI. A study that used MRI to measure infarct size in 795 patients with STEMI who underwent primary PCI found that there was no difference between intracoronary and intravenous administration of abciximab.[295] A meta-analysis of the individual data of 3158 patients who were enrolled in five randomized trials comparing intracoronary versus intravenous abciximab in STEMI patients undergoing primary PCI found no differences in the risk of death, reinfarction, or stent thrombosis at 30 days.[296] The 2013 ACCF/AHA Guideline for the Management of STEMI includes a class IIb recommendation that "It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI."[24] The use of intravenous GP IIb/IIIa inhibitors as an adjunctive or "bailout" therapy in selected patients who are receiving UFH and undergo primary PCI received a class IIa recommendation in the ACCF/AHA Practice Guidelines for STEMI. There are no class I indications for GP IIb/IIIa inhibitors in patients with STEMI who are treated with either fibrinolytic therapy or primary PCI.

β-Blockers

β-Adrenergic blockers exert both antiarrhythmic and antiischemic effects. Numerous studies have investigated the effects of intravenous and/or oral β-blockers on arrhythmias, infarct size, and clinical outcomes in the acute and convalescent phases of MI. Randomized clinical trials have demonstrated that early administration of intravenous followed by oral metoprolol reduces the incidence of ventricular fibrillation (VF) in patients with acute STEMI.[297,298] Experimental studies have shown that β-blockers can limit the extent of MI during coronary occlusion because they reduce heart rate, systemic arterial pressure, and myocardial contractility, thereby decreasing myocardial oxygen demand. Clinical data are conflicting, however, regarding the effects of β-blockers on infarct size in patients. In the "prereperfusion era," several studies concluded that administration of intravenous timolol followed by oral timolol reduced the size of infarction measured by release of creatinine kinase and electrocardiographic assessment.[299,300]

More recent studies in patients with STEMI who were treated with intravenous metoprolol before primary PCI used cardiac MRI to assess infarct size and produced conflicting results.[301,302] The METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial randomly assigned 270 patients with an anterior STEMI who were Killip class I or II to receiving intravenous metoprolol before primary PCI or no metoprolol before PCI.[301] All patients without contraindications received oral metoprolol within 24 hours.[301] The mean infarct size measured by MRI 5 to 7 days after STEMI was smaller in the group treated with intravenous metoprolol compared with the control group (21.2% of the left ventricle vs. 25.1% of the left ventricle; $P = 0.029$).[301] The EARLY-BAMI (Early-Beta Blocker Administration Before Reperfusion Primary PCI in Patients with ST-elevation Myocardial Infarction) trial was a larger, double-blind study that randomly assigned 683 Killip class I and II patients with either anterior or nonanterior STEMI to intravenous metoprolol or placebo before primary PCI.[302] The incidence of malignant ventricular arrhythmias in the acute phase was 3.6% in the metoprolol group versus 6.9% in the placebo group ($P = 0.05$).[302] Infarct size assessed by MRI 30 days after MI was 15.3% of the left ventricle for the metoprolol group compared with 14.9% for the placebo group ($P = 0.616$).[302]

Trials have been performed to examine the effects of early or delayed β-blockade on short-term and long-term clinical outcomes in patients with acute MI. Both atenolol[303] and metoprolol[304] administered by intravenous infusion followed by oral administration reduced mortality in patients who did not receive fibrinolytic therapy. A pooled analysis of 27 randomized trials indicated that early β-blockade reduced mortality by 13% in the first week, and the mortality reduction benefit was greatest in the first 2 days.[305]

Subsequent trials examined the impact of early intravenous β-blockade on the outcome of patients treated with fibrinolytic agents for acute STEMI.[306,307] In the TIMI II-B study, 1434 patients who received intravenous t-PA for acute STEMI were randomly assigned to receive immediate or deferred β-blockade.[306] The deferred blockade group received oral metoprolol beginning on day 6, whereas the immediate blockade group received intravenous metoprolol within 2 hours of initiation of t-PA, followed by oral

metoprolol. The incidence of reinfarction (2.7% vs. 5.1%, $P = 0.02$) and recurrent chest pain (18.8% vs. 24.1%, $P < 0.02$) at 6 days was lower in the immediate group. The GUSTO-I trial protocol recommended that patients without hypotension, bradycardia, or HF receive intravenous atenolol as soon as possible after enrollment, followed by oral atenolol daily.[307] Although adjusted 30-day mortality was significantly lower in patients who received atenolol, intravenous atenolol was associated with greater mortality compared with oral treatment alone (OR 1.3; 95% CI 1.0–1.5; $P = 0.02$). Also, administration of intravenous atenolol was associated with increased risks of HF, shock, recurrent ischemia, and need for a pacemaker. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomly assigned patients with suspected acute MI to treatment with metoprolol (up to 15 mg intravenously, followed by 200 mg/day orally; $n = 22{,}929$) or placebo ($n = 22{,}923$).[298] Treatment was discontinued either at discharge from the hospital or on day 28 of the hospital stay; 93% of the patients had STEMI, and approximately 54% of the patients received a fibrinolytic agent. The risk of reinfarction during treatment was 18% lower among patients who received metoprolol (2% vs. 2.5%; $P = 0.001$). The overall in-hospital mortality rates were 7.7% in the metoprolol treatment group and 7.8% in the placebo group (OR 0.99; 95% CI 0.92–1.05; $P = 0.69$). Allocation to metoprolol was associated with a significant 22% reduction in death attributed to arrhythmia (1.7% vs. 2.2%; $P = 0.0002$), but there was a 29% increase in death attributed to cardiogenic shock among the metoprolol treatment group (2.2% vs. 1.7%; $P = 0.0002$).

At least 32 randomized trials including nearly 27,000 patients have been conducted to determine the effect of β-blockade on long-term survival after acute MI, and several meta-analyses have been published.[305,308] The Norwegian Multicenter Study Group randomly assigned 1884 patients to receive double-blind treatment with either oral timolol or placebo beginning 7 to 28 days after acute MI.[309] The cumulative mortality rate at 33 months was 39% lower in the timolol group than in the placebo group (10.6% vs. 17.5%; $P = 0.0005$), and the sudden-death rate at 33 months was reduced by 45% (7.7% vs. 13.9%; $P = 0.0001$). After continued follow-up for up to 6 years, a significant difference in mortality was maintained.[310] The Beta-Blocker Heart Attack Trial (BHAT) demonstrated that treatment with propranolol beginning 5 to 21 days after acute MI also reduced mortality during an average follow-up period of 25 months.[311] A pooled analysis of 31 long-term trials found that β-blocker therapy was associated with a 23% reduction in the odds of death (95% CI 15–31).[308] According to that analysis, the calculated number of patients needed to treat for 2 years with a β-blocker to avoid one death is 42, which is less than the calculated number needed to treat for antiplatelet therapy, which is 153.[308]

The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study is an important trial that was not available for inclusion in the pooled analyses discussed earlier.[312] The CAPRICORN study randomly assigned 1959 patients with an LVEF 40% or lower to carvedilol or placebo beginning 3 to 21 days after acute MI. Forty-six percent of the patients had received reperfusion therapy, and 97% had received an angiotensin-converting enzyme (ACE) inhibitor for at least 48 hours before randomization. After an average follow-up period of 1.3 years, a 23% reduction was found for all-cause mortality (12% vs. 15%; HR 0.77; 95% CI 0.60–0.98; $P = 0.031$), identical to that reported in a meta-analysis of previous randomized trials.[308] The CAPRICORN trial supports the conclusion that β-blockade reduces mortality after acute MI even among patients who receive reperfusion therapy and ACE inhibitors for left ventricular dysfunction.

The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction contains three class I recommendations for beta blockers in patients with STEMI.[24] The three class I recommendations regarding oral β-blocker therapy are as follows:

1. Oral β-blocker therapy should be initiated in the first 24 hours for patients who do not have any of the following: (a) signs of HF, (b) evidence of a low output state, (c) increased risk for cardiogenic shock (age > 70 years, systolic blood pressure < 120 mm Hg, sinus tachycardia > 110 beats/min or heart rate < 60 beats/min, and increased time since onset of symptoms of STEMI), or (d) other relative contraindications to β-blockade (PR interval > 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease).
2. β-Blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.
3. Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility.

There is one class IIa recommendation regarding intravenous β-blockade in patients with STEMI: "It is reasonable to administer intravenous beta blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia."[24]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Acute MI triggers neurohormonal activation that is characterized by elevated plasma renin activity and aldosterone, and plasma renin activity was found to be an independent predictor of cardiovascular mortality among patients who were enrolled in the Survival and Ventricular Enlargement (SAVE) trial.[313] ACE inhibitors have been shown to attenuate left ventricular enlargement after acute MI.[314] Multiple clinical trials have demonstrated that ACE inhibitors reduce mortality after acute MI. The GISSI-3 trial randomly assigned 19,394 patients with acute MI, with or without ST-segment elevation, to an oral lisinopril treatment group or an open control group within 24 hours of symptom onset.[90] Seventy-one percent of the patients received fibrinolytic therapy. Six-week mortality was 11% lower among patients in the lisinopril treatment group than it was for those in the control group (6.3% vs. 7.1%; OR 0.88; 95% CI 0.79–0.99). The ISIS-4 trial randomly assigned 58,050 patients with acute MI to receive oral captopril or placebo within 24 hours of symptom onset.[91] Seventy-nine percent of the patients had ST-segment elevation on the initial ECG, and 70% of eligible patients received fibrinolytic therapy, predominantly with streptokinase. Five-week mortality was 7% lower among patients who received captopril than among those in the control group (7.19% vs. 7.69%; 95% CI 1–13; $P = 0.02$). The individual patient data from ISIS-4 and GISSI-3 were combined with the data from two other large trials, creating a database of 98,496 patients, who were randomly assigned to ACE inhibitor treatment or control groups during the acute phase (0–36 hours) of acute MI.[315] Thirty-day mortality was 7% lower among patients who received an ACE inhibitor (7.1% vs. 7.6%; 95% CI 2–11; $P = 0.004$). The absolute benefit of ACE inhibitor therapy was greater in patients with anterior MI.

Three additional trials have investigated the efficacy of ACE inhibitors in patients with acute MI and left ventricular dysfunction

or HF: the SAVE study,[316] the Acute Infarction Ramipril Efficacy (AIRE) study,[317] and the Trandolapril Cardiac Evaluation (TRACE) study.[318] The SAVE study enrolled 2231 patients with an acute MI, no overt HF, and an LVEF 40% or lower as measured by radionuclide ventriculography.[316] The patients were randomly assigned to double-blind treatment with captopril or placebo 3 to 16 days after acute MI. After an average follow-up period of 42 months, all-cause mortality was reduced by 19% (20% vs. 25%; 95% CI 3–32; $P = 0.019$). The risk reduction was 22% among patients treated with fibrinolytic therapy (33% of the patients) compared with 17% among patients who were not. Captopril reduced the risk of recurrent MI by 25% (95% CI 5–40; $P = 0.015$).[319] The AIRE study enrolled 2006 patients with an acute MI and clinical or radiologic evidence of HF.[317] The patients were randomly assigned to double-blind treatment with ramipril or placebo beginning 3 to 10 days after acute MI. After average follow-ups of 15 months, all-cause mortality was reduced by 27% (17% vs. 23%; 95% CI 11–40; $P = 0.002$). The TRACE study enrolled 1749 patients with an acute MI and LVEF 35% or lower as demonstrated by echocardiography.[318] The patients were randomly assigned to double-blind treatment with trandolapril or placebo beginning 3 to 7 days after acute MI. The RR of death from any cause in the trandolapril group, as compared with the control group, was 0.78 (95% CI 0.67–0.91; $P = 0.001$). After follow-up for a minimum of 6 years, the life expectancy of patients was 4.6 years for those who received placebo versus 6.2 years for those who were treated with trandolapril, a median increase of 15.3 months.[320] A pooled analysis of the data from individual patients enrolled in the SAVE, AIRE, and TRACE trials concluded that the mortality rate after a median treatment duration of 31 months was reduced from 29.1% in control patients to 23.4% in the ACE inhibitor group (OR 0.74; 95% CI 0.66–0.83; $P < 0.0001$).[321]

The Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) enrolled 105,225 patients with acute MI who were not treated with ACE inhibitors on admission.[322] The association between treatment with an ACE inhibitor at discharge from the hospital and the outcome at 1 year was evaluated using Cox regression analyses adjusted for medications at discharge and the propensity score. Among the entire cohort, treatment with an ACE inhibitor was associated with a 24% reduction in mortality (RR 0.76; 95% CI 0.73–0.80), but among patients without HF, a significant benefit was observed only in patients with renal dysfunction.

Two randomized clinical trials compared captopril with an angiotensin receptor blocker (ARB) in high-risk acute MI patients: the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)[323] and the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[324] The OPTIMAAL trial enrolled 5477 patients with acute STEMI who met any of the following entry criteria: symptoms or signs of HF, LVEF less than 35%, or new anterior Q waves. Fifty-four percent of the patients received fibrinolytic agents. The patients were randomly assigned to double-blind treatment with either losartan, titrated to a target dose of 50 mg daily, or captopril, titrated to a target dose of 50 mg three times daily, within 10 days of symptom onset. After an average follow-up period of 2.7 years, no significant difference in all-cause mortality was found between the losartan and the captopril treatment groups (18% vs. 16%; RR 1.13; 95% CI 0.99–1.28; $P = 0.07$). The prespecified criterion for noninferiority was not satisfied. The VALIANT trial enrolled 14,703 patients with acute MI complicated by clinical or radiographic signs of HF or reduced LVEF (≤35% by echocardiography or contrast ventriculography or ≤40% by radionuclide ventriculography), or both. Approximately 50% of the patients underwent reperfusion therapy; 35%, fibrinolytic therapy; and 15%, primary PCI. Within 10 days after the acute MI, the patients were randomly assigned to three treatment groups: valsartan monotherapy, captopril monotherapy, or the combination of valsartan and captopril. After an average follow-up period of 24.7 months, all-cause mortality was not significantly different for the three groups: valsartan 19.9%, captopril 19.5%, and the combination 19.3%. The investigators concluded that valsartan is at least as effective as captopril, because the criterion for noninferiority of valsartan relative to captopril was met.

Both aldosterone and angiotensin II, a potent stimulus of adrenal aldosterone production, are increased in patients with HF despite chronic treatment with an ACE inhibitor. Aldosterone exerts numerous adverse cardiovascular effects, including increased myocardial collagen deposition and fibrosis and cardiomyocyte apoptosis.[325] Eplerenone, a selective aldosterone blocker, was studied in a multicenter, international, randomized, double-blind, placebo-controlled trial called the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[326,327] The EPHESUS investigators enrolled 6632 patients with acute MI complicated by left ventricular dysfunction (ejection fraction <40%) plus either HF or diabetes.[326,327] The patients were randomly assigned to double-blind treatment with eplerenone or placebo beginning 3 to 14 days after acute MI. At the time of enrollment, 86% of the patients were taking an ACE inhibitor or ARB, and 75% were taking a β-blocker. During a mean follow-up period of 16 months, significantly fewer deaths occurred in the eplerenone group (478/3319 patients) than in the placebo group (554/3313 patients) (14.4% vs. 16.7%; RR 0.85; 95% CI 0.75–0.96; $P = 0.008$). A reduction in the rate of sudden death from cardiac causes (RR 0.79; 95% CI 0.64–0.97; $P = 0.03$) also was observed. Serious hyperkalemia, defined as a serum potassium of 6 mmol/L or more, occurred in 5.5% of patients in the eplerenone group versus 3.9% of those in the placebo group ($P = 0.002$).

The ACCF/AHA Practice Guidelines include three class I recommendations regarding inhibitors of the renin-angiotensin-aldosterone system. (1) An ACE inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or EF of 0.40 or below, unless contraindicated. (2) An ARB should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors. (3) An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an ejection fraction of 0.40 or lower and either symptomatic HF or diabetes mellitus.[24] There is one class IIa recommendation regarding ACE inhibitors in patients with STEMI: "ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use."[24]

Antiarrhythmic Drugs

Both atrial and ventricular arrhythmias are common in patients with acute MI. The incidence of atrial fibrillation (AF) was 10.4% among 40,891 patients who were enrolled in the GUSTO-I trial.[328] Patients in whom AF developed after admission were more likely to have a stroke or die within 30 days after acute MI. New-onset AF developed during hospitalization in 6.3% of the 5466 patients with STEMI who underwent primary PCI and were enrolled in the APEX-AMI trial.[329] New-onset AF was independently associated with 90-day mortality (HR 1.81; 95% CI 1.06–3.09; $P = 0.029$.[329] Intravenous β-adrenergic blockade is the preferred therapy for patients with sustained AF or atrial flutter that is not associated

with hemodynamic compromise, whereas sustained AF or flutter that is associated with hemodynamic compromise is an indication for synchronized cardioversion. Intravenous amiodarone is indicated for treatment of AF that does not respond to electrical cardioversion or recurs after cardioversion. Sustained AF should be treated with anticoagulants.

Primary VF, defined as VF occurring within 48 hours of the onset of symptoms in patients stable Killip class I, is an independent predictor of in-hospital mortality whether it occurs early (up to 4 hours) or late (after 4 to 48 hours) after the onset of acute MI.[330] Among 9720 patients with a first STEMI who were enrolled in the GISSI-2 fibrinolytic trial, 356 of the 7755 patients who were in Killip class I at entry developed primary VF.[330] Early primary VF occurred in 302 patients (3.7%) and late primary VF occurred in 54 patients (0.6%); 226 patients had VF within 1 hour of the onset of acute MI symptoms. In-hospital mortality rates were 13% among patients with late primary VF (RR 3.80; 95% CI 1.80–8.02) and 7% among patients with early primary VF (RR 2.00; 95% CI 1.29–3.12), compared with 4% among patients in Killip class I on admission in whom VF did not develop.

Among 11,712 patients enrolled in the GISSI–1 study, secondary VF, defined as VF in patients with acute MI complicated by HF or shock, occurred in 311 patients (2.7%).[331] The incidence of secondary VF within 24 hours of acute MI was similar among the patients treated with streptokinase and the control group, whereas streptokinase halved the frequency of secondary VF later than 24 hours after admission (27/5860 vs. 60/5852; RR 0.45; 95% CI 0.29–0.70). The protective effect of streptokinase was even greater among patients who were treated within 3 hours of symptom onset (9/3016 vs. 39/3078; RR 0.23; 95% CI 0.12–0.45). In-hospital mortality was higher among patients with secondary VF: 27.1% versus 17.3% for patients in Killip class II (RR 1.77; 95% CI 1.28–2.45) and 48.1% versus 35.3% for patients in Killip class III (RR 1.70; 95% CI 0.95 to 3.02). Secondary VF did not affect in-hospital mortality among the patients in Killip class IV (67.9% with secondary VF vs. 71.9% without secondary VF; RR 0.83; 95% CI 0.44–1.55).

Although primary and secondary VF are associated with an increased risk of in-hospital death, patients who survive to be discharged from the hospital after experiencing either type have a good prognosis. Among the patients who were enrolled in the GISSI-1 and GISSI-2 trials and had nonfatal primary VF, 6-month mortality after hospital discharge among patients with the primary type was not significantly different from that in patients who did not have this arrhythmia.[330,332] In GISSI-2, patients who survived the hospital phase of an acute MI complicated by secondary VF had a 1-year mortality of 10.4%, compared with 13.9% among patients who did not have secondary VF (20/193 vs. 322/2319; RR 0.72; 95% CI 0.44–1.15).[331]

The incidence of primary VF in the GISSI-1 trial was not significantly different in the streptokinase and control groups (2.73% vs. 2.93%; RR 0.93; 95% CI 0.75–1.15).[333] A meta-analysis of 15 randomized trials of fibrinolytic therapy for acute MI confirmed that the likelihood of this arrhythmia is not altered by fibrinolytic therapy, with an incidence of VF during the first hospital day of 2.99% for both the fibrinolytic treatment and placebo groups.[334] There is evidence, however, that fibrinolytic therapy exerts a protective effect against secondary VF.[331,334] Thus the meta-analysis of 15 fibrinolytic trials found that the OR for the development of VF at any time during hospitalization in the fibrinolytic treatment group was 0.83 (95% CI 0.76–0.90; $P < 0.0001$).[334]

Ventricular tachycardia (VT) or VF occurred in 329 of the 5745 patients (5.7%) with STEMI who underwent primary PCI in the APEX AMI trial.[335] Sixty-four percent of the arrhythmic events occurred before the end of the cardiac catheterization and 90% occurred within 48 hours of presentation to the hospital.[335] Ninety-day mortality was 17.2% (adjusted HR 2.34; 95% CI 1.44–3.80) among patients with early VT or VF—that is, during the cardiac catheterization—and 33.3% (adjusted HR 5.59; 95% CI 3.71–8.43) among patients who had late VT or VF—that is, after the catheterization, compared with 3.6% for patients without VT or VF.[335]

As discussed earlier, randomized clinical trials have demonstrated that early administration of intravenous followed by oral metoprolol reduces the incidence of VF in patients with acute STEMI.[297,298] The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomly assigned patients with suspected acute MI to treatment with metoprolol (up to 15 mg intravenously, followed by 200 mg/day orally; $n = 22{,}929$) or placebo ($n = 22{,}923$).[298] Ninety-three percent of the patients had STEMI, and approximately 54% of the patients received a fibrinolytic agent. Allocation to metoprolol was associated with a significant 22% reduction in death attributed to arrhythmia (1.7% vs. 2.2%; $P = 0.0002$), but there was a 29% increase in death attributed to cardiogenic shock among the metoprolol treatment group (2.2% vs. 1.7%; $P = 0.0002$). The EARLY-BAMI investigators reported that the incidence of malignant ventricular arrhythmias during the acute phase was 3.6% among the patients who received intravenous metoprolol compared with 6.9% in the placebo group ($P = 0.05$).[302]

Although a small, double-blind, randomized study supported the routine prophylactic administration of lidocaine to all patient with acute MI to prevent primary VF,[336] subsequent studies of prophylactic lidocaine in acute MI, including more than 20 randomized trials and at least 4 meta-analyses, concluded that lidocaine reduces the incidence of VF but increases mortality.[337] Therefore according to the ACC/AHA Practice Guidelines published in 2004, prophylactic antiarrhythmic therapy is not recommended with use of fibrinolytic agents.[20] Also, the routine use of lidocaine is not indicated for suppression of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT. The guidelines favor intravenous amiodarone for treatment of sustained monomorphic VT.

Although ventricular ectopy is a marker of an increased risk of sudden death in survivors of acute MI, trials of chronic, oral antiarrhythmic drugs have not shown beneficial effects. The Cardiac Arrhythmia Suppression Trial (CAST) I and CAST II found that treatment with the class IC drugs encainide and flecainide, or the class IA drug moricizine, increased mortality in survivors of acute MI.[338,339] *d*-Sotalol, a potassium channel blocker, also increased mortality among survivors of MI in the Survival with Oral *d*-Sotalol (SWORD) randomized trial.[340] Clinical trials of amiodarone, a class III antiarrhythmic drug, suggested that it may reduce the incidence of VF or arrhythmic death among survivors of acute MI.[341,342]

The implantable cardioverter-defibrillator (ICD) has become the standard of care for the prevention of sudden death in survivors of acute MI.[343] There is a class I indication for insertion of an ICD before discharge in patients who develop sustained VT/VF more than 48 hours after STEMI, provided the arrhythmia is not due to transient reversible ischemia, reinfarction, or metabolic abnormalities.[24] The indication for an ICD 40 days after STEMI are determined by the LVEF and New York Heart Association class of HF.[24] Implantation of an ICD is recommended for patients with an LVEF of 35% or less and class II or III HF symptoms, and patients with an LVEF of 30% or less regardless of HF symptoms.[24]

Calcium Antagonists

There are no class I or II indications for calcium channel blockers in patients with acute MI because neither individual clinical trials nor analyses of the pooled results of multiple trials showed a reduction in mortality after acute MI.[344,345] A randomized study that compared diltiazem with placebo starting 3 to 15 days after acute MI found that diltiazem therapy was associated with an increased risk of cardiac events in patients with radiographic evidence of pulmonary congestion.[346] The same trial concluded that diltiazem increases the risk of late-onset HF in patients with an LVEF less than 40%.[347] Nifedipine (immediate-release form) is contraindicated in the treatment of STEMI because of the reflex sympathetic activation, tachycardia, and hypotension associated with its use.[24]

Lipid-Lowering Agents

Numerous trials have evaluated the effects of statins on coronary events in patients with acute and chronic CAD, but none of the trials restricted enrollment to patients with STEMI or provided subgroup analyses of the outcomes among patients with STEMI before enrollment. The Scandinavian Simvastatin Survival Study (4S) was the first clinical trial to demonstrate significant reductions in total mortality and coronary heart disease mortality by treatment with lipid-lowering therapy.[348] Seventy-nine percent of the patients had a history of MI. After a median follow-up period of 5.4 years, total mortality was 12% in the placebo group versus 8% in the patients who were randomly assigned to receive simvastatin (RR 0.70; 95% CI 0.58–0.85; $P = 0.0003$). Also, there was a 37% reduction in the risk of undergoing a myocardial revascularization procedure. The beneficial effects of statin therapy in patients with a history of MI were confirmed by two studies that randomly assigned patients to receive pravastatin 40 mg daily or placebo: the Cholesterol and Recurrent Events (CARE) trial[349] and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.[350] All patients who were enrolled in the CARE trial had a history of MI between 3 and 20 months before enrollment, and 64% of the patients enrolled in the LIPID trial had a history of MI between 3 and 36 months before enrollment.

There is a class I indication for high-intensity statin therapy in all patients with STEMI and no contraindications.[24] A diagnosis of hyperlipidemia cannot be excluded during the first week after an acute MI because both total cholesterol and low-density lipoprotein (LDL) cholesterol decrease significantly during the first week after an acute MI.[351] There is a class IIa indication to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.[24]

Intraaortic Balloon Counterpulsation

Two very small randomized trials and one large randomized trial evaluated the use of an IABP in patients with acute MI complicated by cardiogenic shock.[352] The IABP-SHOCK II (Investigators in the Intraaortic Balloon Pump in Cardiogenic Shock II) trial randomly assigned 600 patients with cardiogenic shock complicating acute MI to intraaortic balloon counterpulsation or no IABP.[353,354] Primary PCI was performed in 95% of the IABP patients and 96% of the control patients ($P = 0.55$).[353,354] Use of an IABP did not reduce all-cause mortality at either 30 days or 12 months.[353,354]

The Second Primary Angioplasty in Myocardial Infarction (PAMI-II) investigators randomly assigned 436 patients with a high-risk acute MI to insertion of an IABP or no IABP after primary PCI.[355] The rates of reocclusion of the IRA, reinfarction, and mortality were not significantly different, and there was a higher incidence of stroke among patients who received an IABP (2.4% vs. 0%; $P = 0.03$). Also, there was no enhancement of myocardial recovery at the time of hospital discharge or 6 weeks after discharge. The Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) trial was a randomized trial to determine whether insertion of an IABP before primary PCI reduces infarct size in patients with an acute anterior STEMI without cardiogenic shock.[356] The mean infarct size, measured by cardiac MRI 3 to 5 days after PCI, was 42.1% of the left ventricle in the IABP group compared with 37.5% of the left ventricle in the control group ($P = 0.06$). Thus the IABP has not been shown to be beneficial in patients with high-risk or anterior acute MI who undergo primary PCI.

A meta-analysis by Ahmad et al.[352] identified 12 randomized, controlled trials comparing an IABP with a control group in patients with acute MI, 3 trials in patients with cardiogenic shock, and 9 in patients without shock. Fifteen observational studies were also analyzed separately.[352] The observational studies showed contradictory associations between IABP therapy and mortality that were mostly due to differences between studies in the balance of risk factors between the IABP and control groups.[352] There was no significant heterogeneity among the randomized trials, and analysis of the randomized trials did not show a statistically significant effect of IABP use on mortality (OR 0.96; 95% CI 0.74–1.24).[352] The use of the IABP in patients with cardiogenic shock is discussed in a subsequent section of this chapter and in the chapter on cardiogenic shock.

Coronary Artery Bypass Graft Surgery

Randomized trials have not been performed to compare surgical reperfusion for acute MI with either conservative medical therapy or reperfusion by means of fibrinolytic therapy or PCI. A nonrandomized study compared the outcomes in 200 patients managed conservatively with those in 187 patients who underwent surgical reperfusion between 1972 and 1976.[357] In-hospital mortality was 5.8% among patients who underwent CABG surgery, compared with 11.5% among patients who did not undergo myocardial reperfusion ($P < 0.08$). Among the patients who underwent coronary bypass grafting within 6 hours from the onset of symptoms of acute MI, in-hospital mortality was only 2% (2/100), compared with 10.3% (9/87) among the patients who underwent surgery more than 6 hours after the onset of symptoms.

Although registry data indicate that CABG surgery within 24 hours of an acute STEMI is associated with a marked increase of in-hospital mortality,[358] emergency surgical revascularization should be considered in certain subsets of patients. Emergency CABG surgery is a reasonable option in patients with cardiogenic shock and coronary anatomy poorly suited for PCI (e.g., severe stenosis of the left main coronary artery). Among patients enrolled in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial, survival rates were similar for CABG surgery and for PCI.[359]

The 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft (CABG) Surgery includes four class I, two class IIa, and two class III recommendations regarding CABG in patients with acute MI[360] (Box 29.6). The 2013 ACCF/AHA Guideline for the Management of STEMI, includes two class I indications for CABG: (1) urgent CABG is indicated in patients with STEM and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features; (2) CABG is recommended in patients with STEMI at time of operative repair of mechanical defects.[24]

• BOX 29.6 CABG in Patients With Acute MI

Class I

1. Emergency CABG is recommended in patients with acute MI in whom (1) primary PCI has failed or cannot be performed, (2) coronary anatomy is suitable for CABG, and (3) persistent ischemia of a significant area of myocardium at rest or hemodynamic instability refractory to nonsurgical therapy is present.
2. Emergency CABG is recommended in patients undergoing surgical repair of a postinfarction mechanical complication of MI, such as ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction or rupture, or free wall rupture.
3. Emergency CABG is recommended in patients with cardiogenic shock and who are suitable for CABG irrespective of the time interval from MI to onset of shock and time from MI to CABG.
4. Emergency CABG is recommended in patients with life-threatening ventricular arrhythmias (believed ischemic in origin) in the presence of left main stenosis greater than or equal to 50% or three-vessel CAD.

Class IIa

1. The use of CABG is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy.
2. Early revascularization with PCI or CABG is reasonable for selected patients older than 75 years of age with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock.

Class III

1. Emergency CABG should not be performed in patients with persistent angina and a small area of viable myocardium who are stable hemodynamically.
2. Emergency CABG should not be performed in patients with no reflow (successful epicardial reperfusion with unsuccessful microvascular reperfusion).

CABG, *Coronary artery bypass graft;* CAD, *coronary artery disease;* MI, *myocardial infarction;* PCI, *percutaneous coronary intervention;* STEMI, *ST-segment elevation myocardial infarction.*
From Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2011;58:e123–e210.*

The timing of surgery in stable patients may influence the risk of bleeding in patients who have received a $P2Y_{12}$ inhibitor. Red blood cell transfusion of 4 units or more after CABG was an independent predictor of 1-year mortality among 1491 patients with ACS who underwent CABG.[361] There are conflicting data regarding the impact of $P2Y_{12}$ inhibitors on the risk of bleeding and transfusion after CABG. One retrospective analysis of 596 patients with ACS who underwent CABG found that exposure to clopidogrel within 5 days of surgery increased the risk of major bleeding and reoperation.[362] Among 1539 patients with ACS who were enrolled in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial and underwent CABG before discharge, CABG within 5 days of the last clopidogrel dose was not associated with higher rates of transfusion or major bleeding compared with the rates among patients who did not receive any clopidogrel before CABG.[363] Administration of clopidogrel within 5 days before CABG was associated with a modestly increased risk of red blood cell transfusion but was not significantly associated with reoperation for bleeding among 332 patients who were enrolled in the Duke Databank between January 1999 and December 2003.[364]

According to the 2011 ACCF/AHA Guideline for CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days to limit blood transfusions, whereas clopidogrel and ticagrelor should be discontinued for at least 24 hours in patients referred for urgent CABG.[360] The 2013 ACCF/AHA Guideline for the Management of STEMI includes four class I recommendations for the timing of urgent CABG in patients with STEMI in relation to antiplatelet agents:

1. Aspirin should not be withheld before urgent CABG.
2. Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent on-pump CABG, if possible.
3. Short-acting intravenous GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2 to 4 hours before urgent CABG.
4. Abciximab should be discontinued at least 12 hours before urgent CABG.[24]

Management of Complications

Pericarditis and Pericardial Tamponade

Pericarditis, defined as the detection of a pericardial friction rub, was diagnosed in 20% (141/703) of patients who were enrolled in the Multicenter Investigation of the Limitation of Infarct Size (MILIS).[365] The frequency of pericarditis was higher in patients with Q-wave MI than in those with non–Q-wave MI (25% vs. 9%; $P < 0.001$). Pericarditis was associated with a lower admission LVEF (42% vs. 48%; $P < 0.001$) and a higher incidence of HF (47% vs. 26%; $P < 0.001$). Pericarditis was accompanied by pleuritic or positional chest pain in 70% of patients. Diagnostic electrocardiographic changes usually are absent in patients with infarction-associated pericarditis.[366] A prospective study of 423 patients with acute MI found that only 1 of the 31 patients with pericardial friction rubs had diagnostic ST-segment changes.[366]

There is evidence that reperfusion therapy reduces the risk of pericarditis after STEMI.[367,368] The GISSI investigators reported the frequency of pericardial involvement in patients who were enrolled in the GISSI-1 ($n = 11,806$) and GISSI-2 ($n = 12,381$) trials.[367] The incidence of pericardial involvement was lower among patients who received fibrinolytic therapy than among patients in the control groups (6.7% vs. 12%).[367] Earlier treatment with fibrinolytic therapy was associated with a lower risk of pericardial involvement. Although pericardial involvement was associated with a higher long-term mortality, it was not an independent prognostic factor because it was strongly associated with the extent of infarction as determined by ECG, peak creatine kinase, and echocardiography.[367] A relationship between the duration of symptoms before reperfusion and the incidence of post-MI pericarditis also was observed in a cohort of 743 consecutive patients with STEMI who were treated with primary PCI.[368] Early post-MI pericarditis was diagnosed in 31 patients (4.2%).[368] The prevalence was 1.7% among patients who underwent primary PCI less than 3 hours after the onset of symptoms, compared with 5.4% for presentation delays of 3 to 6 hours, and 13.6% for delays more than 6 hours.[368] Although early post-MI pericarditis was associated with larger infarct sizes, in-hospital and 1-year mortality were similar in the patients with and without pericarditis.[368]

The ACC/AHA Practice Guidelines recommend aspirin for treatment of pericarditis after STEMI.[24] Colchicine or acetaminophen is recommended for patients who do not respond to aspirin. Corticosteroids and NSAIDs are regarded as class III harmful therapies because of an increased risk of scar thinning and infarct

expansion. Finally, anticoagulation should be discontinued if a pericardial effusion is detected.

Although reperfusion therapy has decreased the occurrence of pericarditis in patients with STEMI, pericardial effusion remains relatively frequent. Among a total of 780 patients with STEMI who underwent primary PCI within 12 hours after symptom onset, a moderate to large pericardial effusion was detected by MRI in 183 patients (24%).[369] The incidence of a moderate to severe pericardial effusion was investigated in 4361 patients with STEMI who underwent an echocardiogram within 12 hours after hospitalization.[370] It varied from 12.0% in patients who did not receive reperfusion therapy, to 5.7% in patients who were treated with fibrinolytics, to 4.3% in patients who underwent primary PCI.[370] Among 228 patients with an echocardiographic pericardial effusion classified as moderate to severe, mortality was fivefold greater than those with a small or no pericardial effusion, and 80% of deaths were attributable to free wall rupture.[371]

Free wall rupture and hemorrhagic pericarditis are two potential mechanisms of cardiac tamponade after acute MI. Among 102,060 patients with STEMI who were enrolled in seven randomized clinical trials and received fibrinolytic therapy, cardiac tamponade developed in 1018 patients (1%).[372] Among the patients with tamponade, 153 also had a VSR or acute MR, and 865 had isolated cardiac tamponade. The adjusted 30-day mortality among 7-day survivors with tamponade was significantly increased (HR 7.9; 95% CI 4.7–13.5; $P < 0.0001$). Pericardial tamponade accounted for 1.4% of patients with cardiogenic shock among 1422 patients with acute MI who were enrolled in either the SHOCK registry or the randomized trial.[373]

Recurrent Ischemia or Infarction

Recurrent infarction (reinfarction) after an initial STEMI is relatively uncommon, but it often is an endpoint for clinical trials, because reinfarction is associated with increased morbidity and mortality.[374,375] Symptomatic recurrent MI during the index hospitalization occurred in 4.2% (836/20,101) of patients who were enrolled in four clinical trials of various fibrinolytic agents.[375] Recurrent MI occurred a median of 2.2 days after the initial MI and was associated with increased mortality rates at both 30 days (16.4% vs. 6.2%; $P < 0.001$) and 2 years (HR 2.11, $P < 0.001$). In-hospital reinfarction occurred in 4.3% of patients (2258/55,911) a median of 3.8 days after fibrinolytic therapy in the GUSTO I and GUSTO III trials.[374] The rates of reinfarction were 4.3% for alteplase, 4.5% for rPA, and 4.1% for streptokinase ($P = 0.55$). Patients with in-hospital reinfarction had higher mortality at 30 days (11.3% vs. 3.5%; OR 3.5; $P < 0.001$) and from 30 days to 1 year (4.7% vs. 3.2%; HR 1.5; $P < 0.001$).[374] Compared with patients who did not have reinfarction, patients with reinfarction had higher rates of HF (31.9% vs. 13.9%) and cardiogenic shock (15.9% vs. 2.4%).

The frequency of recurrent ischemia or reinfarction after an initial STEMI depends on the modality of reperfusion and the adjunctive therapy used. One of the purported advantages of primary PCI over fibrinolytic therapy is a decreased rate of reinfarction. The 30-day rates of reinfarction in the DANAMI-2 trial were 6.3% (49/782) among patients who were randomly assigned to fibrinolytic therapy compared with 1.6% (13/790) among patients who were assigned to the angioplasty group ($P < 0.001$).[214] In a meta-analysis of 13 randomized trials of primary angioplasty versus fibrin-specific agents, the frequency of nonfatal reinfarction was 3% (74/2753) among patients randomly assigned to angioplasty, compared with 6% (172/2757) among patients assigned to fibrinolytic therapy (OR 0.42; 95% CI 0.31–0.55).[209]

There is evidence that coronary revascularization reduces the risk of reinfarction after fibrinolytic therapy. Among patients who were enrolled in four clinical trials of various fibrinolytic drugs, PCI, or CABG surgery was performed during the index hospitalization in 26.1% (5238/20,039) of the patients and was associated with lower rates of both in-hospital recurrent MI (1.4% vs. 4.7%, $P < 0.001$) and 2-year mortality.[375]

A variety of antithrombotic and antiplatelet therapies have been shown to reduce the risk of reinfarction after STEMI. In a trial that randomly assigned 20,506 patients with STEMI to either enoxaparin or UFH as adjunctive treatment after fibrinolytic therapy, the rates of reinfarction at 30 days were 3% for the enoxaparin group (309/10,256) compared with 4.5% for the UFH group (458/10,223) (RR 0.67; 95% CI 0.58–0.77; $P < 0.001$).[131] A meta-analysis of 11 clinical trials found that administration of abciximab was associated with a reduction in the 30-day reinfarction rates among patients who underwent primary angioplasty (1% vs. 1.9%; OR 0.56; 95% CI 0.33–0.94; $P = 0.03$) and among patients who received fibrinolytic therapy (2.3% vs. 3.6%; OR 0.64; 95% CI 0.54–0.75; $P < 0.001$).[288]

Numerous clinical trials have investigated the effect of warfarin alone or in combination with aspirin on the risk of reinfarction and other events in patients with ACS, but most of the studies were not restricted to patients with STEMI, the target international normalized ratio (INR) has varied, and conflicting results have emerged.[376,377] The Warfarin Re-Infarction Study randomly assigned 1214 patients to receive placebo or warfarin (target INR 2.8–4.8) after an average interval between the index MI and enrollment of 27 days.[378] Approximately 70% of patients had Q waves on the baseline ECG, most patients did not receive reperfusion therapy, and all patients were advised not to take aspirin or other antiplatelet drugs. During an average treatment period of 37 months, the rate of reinfarction was significantly reduced by warfarin compared with placebo (82/607 vs. 124/607; RR 34%; 95% CI 19%–54%; $P = 0.0007$).

The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) study randomly assigned 999 patients to receive one of three antithrombotic regimens: aspirin 80 mg daily, warfarin (target INR 3.0–4.0), or the combination of aspirin 80 mg daily and warfarin (target INR 2.0–2.5).[379] Patients were enrolled within 8 weeks of hospitalization for either UA (13%) or Q-wave or non–Q-wave MI. During a median follow-up period of 12 months, the primary composite endpoint of MI, stroke, or death was significantly less frequent for the two groups that received warfarin, but warfarin did not reduce the risk of MI, and it increased the risk of both major and minor bleeding.

The APRICOT-2 trial randomly assigned 308 patients with a patent IRA within 48 hours after fibrinolytic therapy to receive either aspirin alone (80 mg daily) or aspirin plus warfarin for 3 months (target INR 2.0–3.0).[380] The rate of reinfarction during 3 months of follow-up was 2% (3/135) for combination therapy, compared with 8% (11/139) for aspirin alone ($P < 0.05$). The Warfarin, Aspirin, Reinfarction Study (WARIS II) randomly assigned 3630 patients who were hospitalized for an acute MI to one of three treatment groups: warfarin alone (with a target INR of 2.8–4.2), aspirin alone (160 mg daily), or the combination of aspirin 75 mg daily and warfarin (target INR 2.0–2.5).[381] Fibrinolytic drugs were administered to 53% to 55% of the patients in each group. During a mean observation period of 4 years, the rates of reinfarction were significantly less in both groups of patients who received warfarin: 9.7% (117/1206) for aspirin alone, 7.4% (90/1216) for warfarin alone (RR 0.74; 95% CI 0.55–0.998; P

= 0.03), and 5.7% (69/1208) for aspirin plus warfarin (RR 0.56; 95% CI 0.41–0.78; $P < 0.001$). Another study that used a target INR of 1.5 to 2.5 found that the addition of warfarin to aspirin 81 mg daily did not reduce the rate of reinfarction compared with aspirin monotherapy (162 mg daily).[382] The combination of aspirin 80 mg daily with low, fixed-dose warfarin (1 mg or 3 mg) was not superior to aspirin 160 mg daily in patients with a recent STEMI or NSTEMI.[383] Thus the clinical trials suggest that warfarin is superior to placebo, that the combination of aspirin and warfarin is superior to aspirin alone if the target INR is sufficiently high, and that the risk of major bleeding is increased by adding warfarin to aspirin. Also, the published data should not be extrapolated to patients who receive dual antiplatelet therapy (aspirin plus a thienopyridine) after either fibrinolytic therapy or coronary artery stenting, because most of the patients who were enrolled in the warfarin trials did not receive reperfusion therapy or a thienopyridine.

In the ISIS-2 trial, aspirin reduced the rate of in-hospital reinfarction both in the patients who received streptokinase and in those who did not receive fibrinolytic therapy. In the CLARITY study, higher platelet counts were associated with an increased risk of reinfarction among patients with STEMI for whom treatment consisted of aspirin plus a fibrinolytic drug.[384] The addition of clopidogrel to aspirin abolishes the increased risk of reinfarction as the platelet count increases.[384] In the CLARITY study, the rate of recurrent MI after fibrinolytic therapy was 4.1% among patients treated with clopidogrel and aspirin, compared with 5.9% among patients who received placebo and aspirin (representing a 31% reduction in odds).[106]

Clinical trials have demonstrated that β-blockers, ACE inhibitors, and statins also reduce the risk of reinfarction after acute MI, although most of the trials enrolled patients with both STEMI and NSTEMI, and subgroup analyses of outcomes in patients with STEMI were not published. Compared with metoprolol started 6 days after t-PA for acute STEMI, metoprolol started within 2 hours of t-PA was associated with lower rates of reinfarction (5.1% vs. 2.7%; $P = 0.02$) and recurrent chest pain (24.1% vs. 18.8%; $P < 0.02$) at 6 days.[306] The Norwegian Multicenter Study Group randomly assigned 1884 patients to double-blind treatment groups, to receive either oral timolol or placebo, beginning 7 to 28 days after acute MI.[309] The cumulative reinfarction rate at 33 months was 28% lower in the timolol group than in the placebo group (14.4% vs. 20.1%; $P = 0.0006$). The CAPRICORN study randomly assigned 1959 patients with a LVEF of 40% or less to receive carvedilol or placebo beginning 3 to 21 days after acute MI.[312] Forty-six percent of the patients had received reperfusion therapy, and 97% had received an ACE inhibitor for at least 48 hours before beginning the study treatment.[312] After an average follow-up period of 1.3 years, the rate of nonfatal MI was significantly lower in the carvedilol group than in the placebo group (3% vs. 6%; HR 0.59; 95% CI 0.39–0.90; $P = 0.014$).[312]

The GISSI 3 trial did not show an effect of lisinopril on the rate of reinfarction after 6 weeks.[90] Although the AIRE[317] and TRACE[318] trials failed to show a significant effect of ramipril or trandolapril on the long-term risk of reinfarction, the SAVE study[316,319] did observe a significant decrease in the reinfarction rate among patients who were randomly selected to receive captopril 3 to 16 days after acute MI. After an average follow-up period of 42 months, captopril reduced the risk of recurrent MI by 25% (95% CI 5–40; $P = 0.015$).[319] Thus ACE inhibitors may not reduce the short-term risk of reinfarction after acute MI, but they may decrease the long-term risk of reinfarction.

Among a cohort of 2301 patients in whom reinfarction occurred after administration of fibrinolytic therapy in the GUSTO I and Assessment of Safety and Efficacy of a New Thrombolytic 2 (ASSENT 2) clinical trials, reinfarction was treated with repeat fibrinolysis ($n = 864$), with revascularization ($n = 525$), or conservatively ($n = 835$).[385] After adjustment for baseline characteristics, the 30-day mortality was significantly greater in the conservative group, 28%, compared with the repeat fibrinolysis group, 11% (OR 2.2; 95% CI 1.5–3.1; $P < 0.001$) or the revascularization group, 11% (OR 2.2; 95% CI 1.4–3.3; $P < 0.0001$). No significant difference was observed between the revascularization and repeat fibrinolysis groups.

One of the causes of reinfarction in patients with STEMI is stent thrombosis after primary PCI. A network meta-analysis of 22 controlled trials that randomly assigned a total of 12,453 patients with STEMI concluded that second-generation cobalt-chromium everolimus-eluting stents were associated with significantly lower risk of 1-year cardiac death/MI, MI, and stent thrombosis compared with BMS, and significantly lower 1-year rates of stent thrombosis than paclitaxel-eluting stents.[272] The 2014 ESC/EACTS Guidelines on myocardial revascularization include a class I recommendation that new-generation DESs are recommended over BMSs in STEMI patients who undergo primary PCI.[274]

The 2004 version of the ACC/AHA Guidelines for the Management of Patients with STEMI provided recommendations regarding the management of recurrent ischemia and reinfarction that were not included in the 2013 version of the guideline.[20,24] The 2004 version recommended escalation of medical therapy with nitrates, β-blockers, and intravenous anticoagulation, and consideration of an IABP in patients with hemodynamic instability, poor left ventricular function, or a large area of myocardium at risk. Coronary angiography and PCI or CABG surgery were recommended for patients who are considered candidates for revascularization and have recurrent ischemic-type chest discomfort. Also, there was a class IIa recommendation for readministration of fibrinolytic therapy to patients with ischemic-type chest discomfort and recurrent ST-segment elevation who are not considered candidates for revascularization or for whom coronary angiography and PCI cannot be implemented within 60 minutes of the onset of recurrent ischemia. A class III recommendation regarding streptokinase stated that it should not be readministered to patients who received a nonfibrin-specific fibrinolytic agent more than 5 days previously.

Congestive Heart Failure

An analysis of 2654 patients with acute MI who were enrolled in three primary angioplasty trials found that the Killip class on admission was a multivariate predictor of both in-hospital and 6-month mortality.[19] Hasdai and associates[386] combined the data from four large randomized trials of fibrinolytic therapy for STEMI to describe the incidence, timing, and consequences of mild to moderate HF in patients with STEMI. Excluding patients with cardiogenic shock, 17,949 of 61,041 (29.4%) patients had mild to moderate HF. Among the cohort with mild to moderate HF, 8.7% had HF only at baseline, 57.6% had HF only after admission, and 33.7% had HF at baseline and after admission. The incidence of death was similar for patients without HF and patients with HF at baseline that resolved after admission. Patients with HF that persisted from baseline or developed after admission had a four times greater risk of death at 30 days (8% vs. 2%).

There is evidence that patients with STEMI complicated by HF benefit from early revascularization. Analysis of an Israeli database compared the outcomes of 629 patients with STEMI who presented

in Killip class II or III HF.[387] Mortality at 6 months was lower among patients who underwent PTCA or CABG surgery within 30 days compared with patients who were managed noninvasively (11.6% vs. 27.4%; OR 0.40; 95% CI 0.24–0.64; $P < 0.0001$). According to the 2013 ACCF/AHA STEMI Guideline for the Management of STEMI, "the development of HF after STEMI is an indication for angiography with intent to proceed with revascularization if not previously performed."[24]

It is important to recognize that HF also is an important prognostic factor in patients with UA or NSTEMI.[388] Among a cohort of 13,707 patients with a confirmed diagnosis of ACS without prior HF or cardiogenic shock at the time of presentation to the hospital, HF (Killip class II or III) was present at hospital admission in 1778 patients (13%), and HF developed later during hospitalization in an additional 869 patients (6.3%).[388] The incidence of HF was similar in patients with STEMI (15.6%) or NSTEMI (15.7%) but less frequent in patients with UA (8.2%). HF at the time of admission was associated with a fourfold increase in crude in-hospital mortality rates across all three ACS subsets. The cumulative 6-month mortality rate was greater among patients in whom HF developed during hospitalization (25.3%) than among patients who had HF at admission (20.7%) or patients who did not have HF (5.9%).

ACE inhibitors, eplerenone, and β-adrenergic antagonists are believed to improve the long-term survival of patients with MI complicated by HF.[389] BHAT, a study that randomly assigned patients to receive propranolol or placebo 5 to 21 days after acute MI, included 710 patients who had a history of HF before enrollment.[390] After an average follow-up period of 25 months, propranolol reduced total mortality by 27% and sudden death by 47%. A retrospective analysis of the AIRE study was performed to determine the effects of β-blockade on the outcomes for patients with acute MI complicated by HF.[391] β-Blocker treatment was an independent predictor of reduced risk of total mortality (HR 0.66; 95% CI 0.48–0.90). The CAPRICORN study showed that carvedilol, started 3 to 21 days after MI, reduced all-cause mortality by 33% in patients with an LVEF of 40% or less.[312] Unfortunately, patients with acute MI complicated by HF are less likely to receive a β–blocker than are patients without HF.[392]

The AIRE study showed that ramipril, initiated 3 to 10 days after acute MI, reduced all-cause mortality by 27% in patients with either STEMI or NSTEMI and clinical or radiologic evidence of HF.[317] The EPHESUS study randomly assigned patients with either STEMI or NSTEMI and LVEF less than 40%, to eplerenone or placebo beginning 3 to 14 days after the acute MI.[326,327] Ninety percent of the patients had HF, documented by the presence of pulmonary rales, a third heart sound, or evidence of pulmonary venous congestion on the chest radiograph. Concomitant medications included β-blockers in 75% of patients and an ACE inhibitor or angiotensin receptor blocker in 86%. At 30 days after randomization, eplerenone reduced the risk of all-cause mortality by 31% (3.2% vs. 4.6%; RR 0.69; 95% CI 0.54–0.89; $P = 0.004$).[327] During a mean follow-up period of 16 months, the all-cause mortality rate was 14.4% in the eplerenone group and 16.7% in the placebo group (RR 0.85; 95% CI 0.75–0.96; $P = 0.008$).[326]

Although the 2013 ACCF/AHA Guideline for the Management of STEMI did not include specific recommendation for the treatment of patients with STEMI complicated by pulmonary congestion, on the basis of the foregoing evidence, the 2004 version of the STEMI guideline included eight class I recommendations for patients with STEMI complicated by pulmonary congestion[20]:

1. An arterial oxygen saturation greater than 90% should be maintained using supplemental oxygen.
2. Morphine sulfate should be given.
3. Patients with a systolic blood pressure 100 mm Hg or higher should receive an ACE inhibitor, beginning with titration of a low dose of a short-acting drug such as captopril.
4. Patients with a systolic blood pressure of 100 mm Hg or higher should receive nitrates.
5. A loop diuretic should be administered to patients with volume overload.
6. Although β-blockade should be initiated before hospital discharge, β-blockers should not be administered acutely to patients with "frank cardiac failure evidenced by pulmonary congestion or signs of a low-output state."
7. Patients already receiving an ACE inhibitor who have an LVEF less than 40% and either symptomatic HF or diabetes should receive long-term aldosterone blockade unless hyperkalemia (serum potassium >5 mEq/L) or significant renal dysfunction (serum creatinine >2.5 mg/dL in men or >2 mg/dL in women) is present.
8. Echocardiography should be performed urgently to evaluate left and right ventricular function and to exclude a mechanical complication.

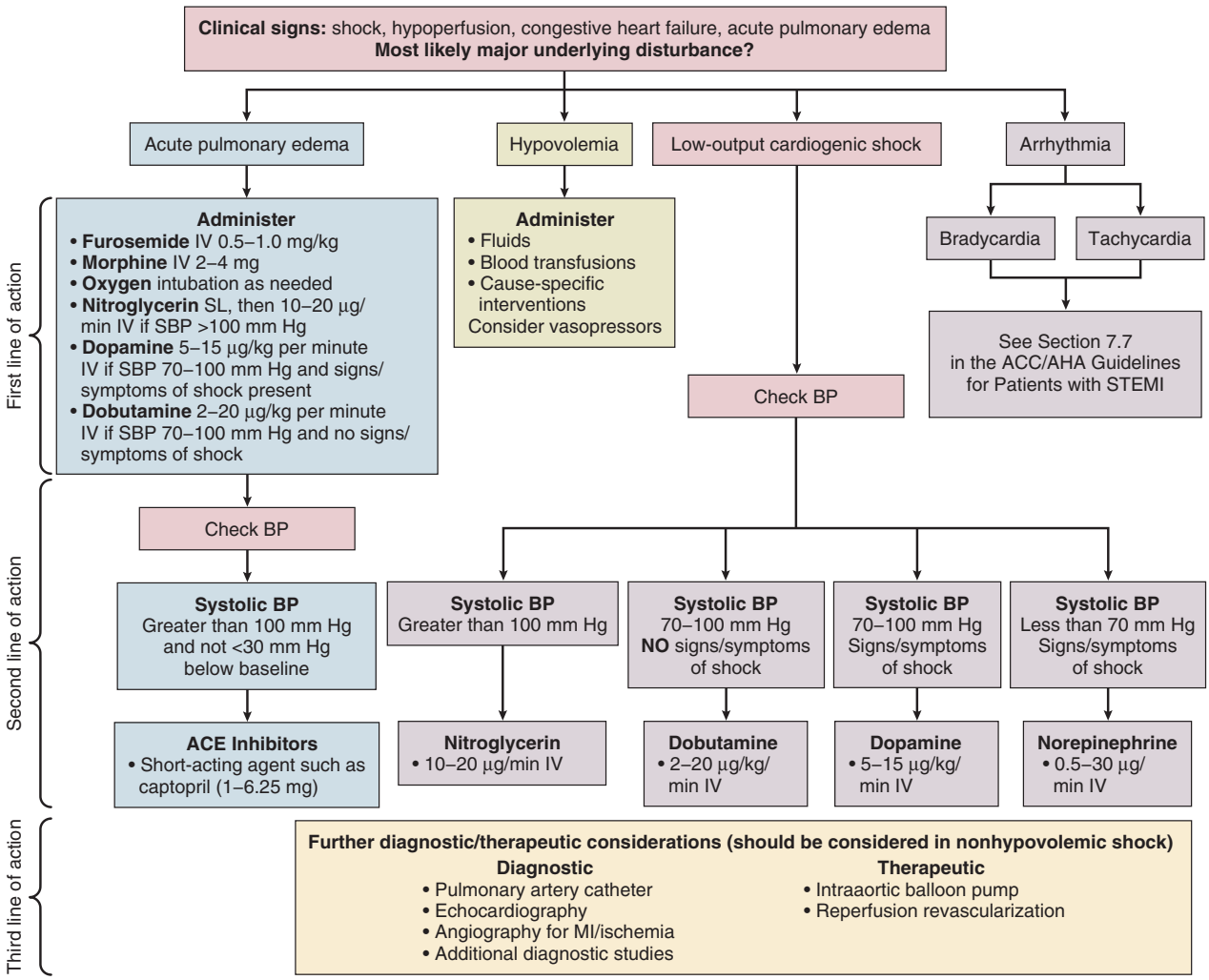
In view of the fact that the relevant clinical trials included patients with both STEMI and NSTEMI, it is logical that treatment of NSTEMI patients with HF should conform to the practice guidelines as discussed for STEMI patients with HF. Fig. 29.7 presents an algorithm for the emergency management of MI complicated by HF or hypotension.

Right Ventricular Dysfunction and Infarction

Among 416 patients with acute MI who were enrolled in an echocardiographic substudy of the SAVE trial, right ventricular function was an independent predictor of mortality and the development of HF.[393] The odds of cardiovascular mortality increased 16% for each 5% decrease in the percentage change in right ventricular cavity area from end diastole to end systole.

Occlusion of the right coronary artery (RCA) proximal to the acute marginal branches is the most frequent cause of right ventricular infarction, but occlusion of the LAD or a dominant left circumflex coronary artery also may result in right ventricular MI. Although autopsy studies have shown that anterior MI may be associated with a right ventricular infarction, right ventricular MI associated with hemodynamic compromise most commonly occurs in patients with an inferior MI because perfusion of the right ventricle occurs predominantly via the right ventricular branches of the RCA.[394,395] In a series of 125 patients with acute inferior MI who underwent emergency coronary angiography, echocardiography performed before coronary reperfusion demonstrated ischemic dysfunction of the right ventricle in 53 (42%) patients.[396] The RCA was the IRA in all patients with right ventricular MI, and depressed flow in the right ventricular branches was evident in each case. Right ventricular branch flow was preserved in patients without right ventricular MI.

Patients with inferior MI complicated by right ventricular infarction have an increased risk of major complications, including death, cardiogenic shock, and ventricular arrhythmias.[397] Cardiogenic shock during hospitalization occurred in 6.9% of a series of 491 patients with inferior MI complicated by right ventricular MI.[397] Patients with right ventricular infarction complicated by cardiogenic shock do not have a better prognosis than patients with cardiogenic shock associated with left ventricular failure.[398] Among a cohort of 1129 patients with acute inferior MI, there was no difference in left ventricular infarct size or function between patients with



• **Fig. 29.7** Algorithm for emergency management of complicated myocardial infarction *(MI). ACE,* Angiotensin-converting enzyme; *BP,* blood pressure; *IV,* intravenous; *SBP,* systolic BP; *SL,* sublingual; *STEMI,* ST-segment elevation myocardial infarction. (Data from Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 7, the era of reperfusion: section 1, acute coronary syndromes (acute myocardial infarction). The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation.* 2000;102(suppl I):I172–I1203.)

(n = 491) and patients without (n = 638) right ventricular MI, indicating that the increased risk of right ventricular MI is due to right ventricular dysfunction rather than greater left ventricular injury.[397] The impact of right ventricular MI on prognosis may depend on the patient's age.[399] Among a series of 798 consecutive patients with acute inferior MI, 296 (37%) satisfied electrocardiographic or echocardiographic criteria for right ventricular infarction.[399] Major complications (45% vs. 19%; $P < 0.0001$) and in-hospital death (22% vs. 6%; $P < 0.0001$) occurred more often in patients with than in those without right ventricular MI. The diagnosis of right ventricular MI increased the mortality risk in patients aged 65 or greater, but not among younger patients.

Although numerous electrocardiographic signs of right ventricular MI have been described, ST-segment elevation in lead V_4R is the most reliable electrocardiographic indicator of this form of MI.[400] Zehender and associates[401] studied the diagnostic and prognostic value of ST-segment elevation in V_4R in a series of 200 consecutive patients with acute inferior MI. ST-segment elevation in lead V_4R was present on the initial ECG in 107 patients (54%). Based on the results of autopsy, coronary angiography, right ventriculography, nuclear scan, or invasive hemodynamic data, ST-segment elevation in V_4R had 88% sensitivity, 78% specificity, and 83% diagnostic accuracy for right ventricular MI. ST-segment elevation in V_4R was associated with an in-hospital mortality of 31%, compared with 6% among patients without ST-segment elevation in V_4R ($P < 0.001$). Multivariate analysis of clinical data confirmed that 0.1 mV or greater of ST-segment elevation in V_4R was a strong independent predictor of in-hospital death (RR 7.7; 95% CI 2.6–23) and major complications (RR 4.7; 95% CI 2.4–9).

The triad of hypotension, clear lung fields, and elevated jugular venous pressure should raise suspicion of right ventricular MI in patients with inferior STEMI, but the triad has a sensitivity of less than 25%.[402] The hemodynamic criteria that have been used to diagnose right ventricular MI are right atrial pressure greater than 10 mm Hg and equal or nearly equal to the PCWP, or a noncompliant pattern in the right atrium.[403] Inferior STEMI with hemodynamic compromise is a class I indication for recording lead V_4R and an echocardiogram to screen for right ventricular

MI.[20] Echocardiographic signs of this disorder include right ventricular dilation, right ventricular asynergy, and abnormal interventricular septal motion.[403] Echocardiography also is valuable to exclude pericardial tamponade because both right ventricular MI and pericardial tamponade may manifest with hypotension and elevated jugular venous pressure.[404]

The ACC/AHA guidelines emphasize the importance of maintenance of right ventricular preload, reduction of right ventricular afterload, inotropic support of the right ventricle, maintenance of atrioventricular (AV) synchrony, and early reperfusion of the IRA.[24] Volume loading plus dobutamine, but not volume loading alone, has been shown to improve cardiac index in patients with acute right ventricular infarction.[405] Systemic vasodilators are poorly tolerated, and hypotension after administration of sublingual nitroglycerin is a common event in patients with right ventricular MI. Short-term inhalation of nitric oxide, a selective vasodilator of the pulmonary circulation, improved cardiac index by 24% in a series of 13 patients with right ventricular infarction and cardiogenic shock.[406] In patients with right ventricular MI complicated by cardiogenic shock and refractory low cardiac output and hypotension, insertion of a percutaneous right ventricular assist device should be considered as a therapeutic option.[407]

The status of right atrial function is an important determinant of the hemodynamic consequences of right ventricular MI.[408] Hemodynamic compromise may result if the atrial contribution to ventricular filling is lost in patients with right ventricular MI. Therefore high-grade AV block, other bradyarrhythmias, and AF are common causes of hypotension in patients with right ventricular MI. Ventricular pacing may not increase cardiac output in such patients, although atrial pacing and AV sequential pacing have been shown to improve cardiac output.[409,410] AF associated with hemodynamic compromise is an indication for electrical cardioversion.

The elevated right atrial pressure in patients with right ventricular MI may cause refractory hypoxemia as a result of increased right-to-left shunting in patients with an atrial septal defect or patent foramen ovale.[406,411] Inhalation of nitric oxide reduced right-to-left shunting by 56% in a series of three patients with right ventricular MI.[406] Right-to-left shunting in patients with right ventricular MI also can be treated by percutaneous closure of the patent foramen ovale.[411]

Some evidence indicates that reperfusion of the IRA improves right ventricular function and clinical outcome in patients with MI. Successful PCI of an occluded RCA in patients with right ventricular infarction has been associated with improved right ventricular wall motion within 1 hour[412] and a reduction in right atrial pressure within 8 hours.[413] Three to 5 days after successful PCI, right ventricular function was normal in 95% of patients.[412] In a study of the data for 49 patients with shock and right ventricular MI enrolled in the SHOCK trial registry, the in-hospital mortality rate was found to be 65.2% among patients who did not undergo revascularization, compared with 42.3% among patients who underwent PCI or CABG surgery.[398]

Mechanical Causes of Congestive Heart Failure or Low Cardiac Output

Mitral Regurgitation

Among 1976 patients with acute MI who were not in cardiogenic shock and underwent cardiac catheterization within 12 hours of symptom onset, left ventriculography demonstrated mild MR in 192 patients (9.7%) and moderate or severe MR in 58 patients (2.9%).[61] By multivariate analysis, mild MR and moderate or severe MR were the two strongest independent predictors of 1-year mortality. The HRs were 2.40 (95% CI 1.31–4.42; $P = 0.005$) for mild and 2.82 (95% CI 1.34–5.92; $P = 0.006$) for moderate or severe MR. The 1-year mortality rates were 2.9% for patients with no MR ($n = 1726$), 8.5% for patients with mild MR ($n = 192$), and 20.8% for patients with moderate or severe MR ($n = 58$).

Acute severe MR accounted for 6.9% of patients with cardiogenic shock among 1422 patients with acute MI who were enrolled in either the SHOCK registry or the randomized trial.[373] The median time from the onset of MI to shock was 12.8 hours.[414] In a postmortem series of 20 cases of papillary muscle rupture, the posteromedial papillary muscle was ruptured in 16 patients and the anterolateral papillary muscle was ruptured in 4 patients.[415] The greater tendency of the posteromedial papillary muscle to rupture is reflected by the distribution of the IRA in a series of 98 patients with acute MR and cardiogenic shock who were enrolled in the SHOCK studies. The location of the index MI was anterior in 34% of patients and nonanterior in 66%.[414]

The diagnosis of acute severe MR should be suspected in patients with acute onset of pulmonary edema or hypotension. The absence of a loud murmur does not exclude severe MR. The diagnosis can be confirmed by transthoracic or transesophageal echocardiography. The treatment of acute severe MR should include inotropic support, afterload reduction, an IABP, and emergency mitral valve surgery, but mortality is high despite surgical treatment. Among the patients with acute severe MR and cardiogenic shock who were enrolled in the SHOCK registry or the randomized trial, the in-hospital mortality rate was 40% among 43 patients who underwent valve surgery, compared with 71% among 51 patients who did not.[414]

Ventricular Septal Rupture

Among 41,021 patients with STEMI who were enrolled in the GUSTO-I trial, the incidence of VSR was only 0.2% (84/41,021 patients).[416] Acute VSR accounted for 3.9% of patients with cardiogenic shock among 1422 patients with acute MI who were enrolled in either the SHOCK registry or randomized trial.[373]

The clinical manifestations of VSR may include chest pain, dyspnea, and hypotension. A harsh holosystolic murmur may be audible. Cardiogenic shock occurred in 67% of patients in the GUSTO-I trial in whom VSR developed.[416] The diagnosis of VSR can be confirmed by Doppler echocardiography or right heart catheterization to measure the oxygen saturation in the right atrium, right ventricle, and PA. The median time from MI to diagnosis of VSR was 16 hours among a series of patients with VSR and cardiogenic shock.[417] The electrocardiographic location of the MI was inferior in 26 patients, anterior in 22, both anterior and inferior in 3, and apicolateral in 1 patient.[417] Only 35 of 55 patients underwent coronary angiography, and the IRA was identified in only 26 patients: the RCA in 12, the LAD in 11, and the left circumflex coronary artery in 3 cases.

The location of the IRA may be an important determinant of survival in patients with VSR.[416,418] Among a series of 25 patients with this diagnosis, mortality was greater among patients with inferior MI than among patients with anterior MI.[418] At least two factors may explain the differential outcome of patients with inferior and anterior MI complicated by VSR. First, the right ventricular volume overload caused by the left-to-right shunt may be less tolerated in the presence of ischemia or infarction of the right ventricle, both of which are more common with an inferior MI than an anterior MI. Second, histopathologic studies have shown that complex septal defects that are more difficult to repair surgically are more common in patients with an inferior MI.[419]

An IABP has been shown to decrease the shunt and increase systemic cardiac output in patients with VSR.[420] Therefore vasodilator therapy and an IABP often are used to stabilize patients before surgical repair of the rupture. The overall in-hospital survival rate among patients with VSR in the SHOCK registry was only 13% (7/55).[417] Although six of the seven survivors underwent surgical repair, mortality was 81% (25/31) in the group of patients who underwent surgery. In the GUSTO-I trial, patients whose rupture was repaired surgically had better 30-day mortality (47%) than patients who received medical treatment (94%).[416] Percutaneous closure of acute VSR may be an option in the future.

Left Ventricular Free Wall Rupture

Rupture of the left ventricular free wall may manifest in any of several ways: pericardial tamponade with acute hemodynamic collapse and immediate death, gradual onset of tamponade and hypotension, or subacute formation of a pseudoaneurysm.[421] Although a 6% rate of cardiac rupture among patients with acute MI often is quoted, reports suggest that the rate probably is lower, at least among patients who receive reperfusion therapy. A total of 65 (1.7%) cases of cardiac rupture occurred among 3759 patients with STEMI who received fibrinolytic therapy and were randomly assigned to receive either adjunctive heparin or hirudin.[422] The prevalence of cardiac rupture or pericardial tamponade was 2.3% (28/1190) among patients with cardiogenic shock in the SHOCK registry; 13 patients had both rupture and pericardial tamponade, 9 had tamponade alone, and 6 had rupture alone.[423]

It has been suggested that the incidence of cardiac rupture may be lower after primary PCI than after fibrinolytic therapy. The overall incidence of left ventricular free wall rupture was 2.5% (n = 34) among 1375 patients with STEMI who underwent primary PCI (55.4%) or fibrinolytic therapy (44.6%).[424] In a multivariate analysis, primary PCI was independently associated with a lower incidence of rupture, but no significant difference was observed in the incidence of rupture after primary PCI or fibrinolytic therapy (1.8% vs. 3.3%; $P = 0.686$).

The timing of reperfusion therapy may affect both the risk and the timing of free wall rupture. Death from cardiac rupture appears to occur earlier in patients given fibrinolytic therapy than among patients who do not undergo reperfusion therapy.[425] Honan and associates[426] analyzed the relationship between the risk of cardiac rupture and the timing of fibrinolytic therapy for 58 cases of cardiac rupture among 1638 patients enrolled in four randomized trials that compared intravenous streptokinase with no fibrinolytic therapy (in the control group). The OR of cardiac rupture increased significantly with increasing delay in the time to treatment. Regression analysis suggested that treatment within 7 hours after symptom onset reduces the risk of cardiac rupture, whereas treatment later than 17 hours after symptom onset increases the risk of cardiac rupture.[426] Thus it was hypothesized that early fibrinolytic therapy reduces the risk of rupture by reducing the extent of myocardial necrosis, whereas late fibrinolytic therapy increases the risk of rupture by promoting hemorrhagic infarction.

The antemortem diagnosis of free wall rupture, pericardial tamponade, and left ventricular pseudoaneurysm usually is confirmed by an echocardiogram. An echocardiogram was obtained in 20 of the 28 patients in the SHOCK registry who had rupture or pericardial tamponade. A pericardial effusion was observed in 15 (75%) and a myocardial tear was detected in 39%.[423] Six patients underwent pericardiocentesis alone, and 21 had surgical repair of the rupture. The in-hospital survival rate was 39.3%.

Cardiac Arrhythmias and Heart Block

Both atrial and ventricular arrhythmias are common in patients with acute MI. The incidence AF was 10.4% among 40,891 patients who were enrolled in the GUSTO-I trial.[328] Patients in whom AF developed after admission were more likely to have a stroke or die within 30 days after acute MI. New-onset AF developed during hospitalization in 6.3% of the 5466 patients with STEMI who underwent primary PCI and were enrolled in the APEX-AMI trial.[329] New-onset AF was independently associated with 90-day mortality (HR 1.81; 95% CI 1.06–3.09; $P = 0.029$.[329] Management of atrial arrhythmias is discussed in another chapter.

A meta-analysis of 15 randomized trials of fibrinolytic therapy for acute MI confirmed that the likelihood of primary VF is not altered by fibrinolytic therapy, with an incidence of VF during the first hospital day of 2.99% for both the fibrinolytic treatment and placebo groups.[334] Some evidence, however, suggests that fibrinolytic therapy exerts a protective effect against secondary VF (occurring in patients with acute MI complicated by HF or shock).[331,334] Management of ventricular arrhythmias is discussed in Chapter 32.

The incidence of second-degree or third-degree AV block was 6.9% among 75,993 patients with STEMI who received fibrinolytic therapy and were enrolled in a database that combined four randomized clinical trials.[427] Inferior MI was the strongest independent predictor of AV block (OR 3.3; 95% CI 3.1–3.5). In comparison with patients without AV block, adjusted mortality was greater at 30 days, 6 months, and 1 year among patients with AV block. The adjusted mortality ORs at 1 year were 2.4 (95% CI 2.2–2.6) for patients with AV block and inferior MI and 3.3 (95% CI 3.0–3.7) for patients with AV block and anterior MI.

Among 2073 patients with STEMI who underwent primary PCI at one Danish hospital during a 4-year period, second-degree or third-degree AV block occurred in 67 patients (3.2%) during the hospitalization, 91% within 48 hours after admission.[428] The incidence was 7% among patients with an RCA culprit, compared with 1% among patients with an LAD culprit.[428] Compared with patients without second-degree or third-degree AV block, patients with second-degree or third-degree AV block had higher mortality 30 days after STEMI (33% vs. 5%), but the landmark analysis of survival in patients who were alive 30 days after MI showed that the mortality rate was similar for the two groups.[428]

It is unclear whether reperfusion therapy has decreased the incidence of heart block in patients with STEMI. A total of 2,273,853 patients with STEMI were included in the U.S. National Inpatient Sample databases from 2003 to 2012.[429] Although the proportion of STEMI patients who did not undergo reperfusion decreased from 43.0% in 2003 to 20.1% in 2012, the incidence of complete heart block was relatively constant: 2.1% in 2003 and 2.3% in 2012.[429] In-hospital mortality was significantly higher among patients with complete heart block than among patients without complete heart block (20.4% vs. 8.7%; adjusted OR 2.47; 95% CI 2.41–2.53; $P < 0.001$).[429]

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Clinical Manifestations

Definition

In 2014 the American Heart Association and the ACC jointly issued a full revision of the clinical practice guideline for non–ST-elevation

acute coronary syndromes (NSTE-ACS).[1] As noted earlier, the distinction between UA and NSTEMI is determined by the detection of cardiac markers indicative of myocardial necrosis. Therefore as the sensitivity of troponin assays increases, patients with biomarker-negative ACS (i.e., UA) will be less common.[50]

Clinical History

The GRACE registry analyzed the presenting symptoms of 20,881 patients with STEMI, NSTEMI, or UA.[15] Among the patients with UA and NSTEMI, 5.7% and 12.3%, respectively, presented with symptoms other than chest pain. Patients with UA or NSTEMI who presented with atypical symptoms were less likely to undergo coronary angiography, PCI, or CABG surgery and were less likely to receive heparin, aspirin, or β-blockers. The absence of chest pain among patients with ACS was predictive of an increased risk of in-hospital death.

Several risk-stratification models have been developed to evaluate patients with suspected ACS. The TIMI risk score uses seven variables to calculate a score that is predictive of the risk of death and ischemic events in patients with suspected ACS.[430] Four of the seven variables are derived from the clinical history: age 65 years or older, at least three risk factors for CAD (family history of CAD, hypertension, hypercholesterolemia, diabetes, cigarette smoking), two or more anginal events within the previous 24 hours, and use of aspirin within the previous 7 days.[430] The GRACE risk score and a PURSUIT risk model also have been shown to have predictive power in patients with suspected ACS.[431,432]

Physical Examination

As in patients with STEMI, evidence of HF at the time of initial presentation has prognostic importance in patients with NSTE-ACS. In a database accrued from studies in 26,090 patients with UA or NSTEMI, heart rate, systolic blood pressure, and Killip class were independent predictors of mortality at 30 days and 6 months.[433] Patients in Killip class II, III, or IV constituted only 11% of the population but accounted for 30% of the deaths. Among a cohort of 13,707 patients with a confirmed diagnosis of ACS without prior HF or cardiogenic shock at the time of presentation to the hospital, HF (Killip class II or III) was present at hospital admission in 1778 patients (13%), and HF developed later during hospitalization in an additional 869 patients (6.3%).[388] The incidence of HF was similar in patients with STEMI (15.6%) or NSTEMI (15.7%) but less frequent in patients with UA (8.2%). HF at the time of admission was associated with a fourfold increase in crude in-hospital mortality rates across all three ACS subsets. The cumulative 6-month mortality rate was greater among patients in whom HF developed during hospitalization (25.3%) than among patients who had HF at admission (20.7%) or patients who did not have HF (5.9%).

A pooled patient-level analysis of seven large clinical trials included 46,519 patients with NSTE-ACS, and 4910 (10.6%) had HF at the time of presentation, whereas an additional 1194 (2.9%) developed HF during hospitalization.[434] The patients who presented with or developed HF during hospitalization had a higher risk of death at 30 days than patients without HF (adjusted OR 1.74; 95% CI 1.35–2.26).[434]

Diagnostic Approach

Electrocardiogram

The admission ECG has prognostic value in patients with ACS.[435,436] Although normal or nonspecific findings on the initial ECG confer a better prognosis than ST-segment depression or elevation seen on the ECG, such findings do not predict a benign outcome in patients with suspected ACS.[436] The risk of death or reinfarction at 30 days or 6 months is similar in patients with ST-segment elevation and in those with ST-segment depression; the risk is lower among patients with isolated T-wave inversion.[435] The GUSTO-IIb clinical trial enrolled 12,142 patients with symptoms of cardiac ischemia at rest and electrocardiographic signs of myocardial ischemia.[435] After adjustment for factors associated with an increased risk of death or reinfarction, the odds of death or reinfarction at 30 days were 1.68 (95% CI 1.36–2.08) in those with ST-segment elevation and 1.62 (95% CI 1.32–1.98) in those with ST-segment depression compared with those who had T-wave inversion only on the admission ECG.[435]

Among 1198 patients with isolated anterior (leads V_1-V_4) ST-segment depression who were enrolled in the TRITON-TIMI 38 trial, 314 (26.2%) had TIMI 0 or 1 flow and an elevated serum troponin.[437] The left circumflex coronary artery was the occluded culprit artery in 48.4% of the patients with an occluded artery, compared with the LAD coronary artery in 33.8% and the RCA in 17.8%.[437]

The impact of invasive management on outcome in patients with ACS is predicted by the presence or absence of ST-segment depression on the admission ECG. Among patients with ACS who were enrolled in the Fast Revascularization during InStability in Coronary Artery Disease (FRISC II) randomized trial comparing early invasive management and a noninvasive strategy, ST-segment depression was present at enrollment in 45.5% of patients.[438] Among the patients who presented with ST-segment depression, the invasive strategy reduced the risk of death or MI at 12 months from 18.2% to 12% (RR 0.66; 95% CI 0.50–0.88; $P = 0.004$). Mortality was reduced from 5.8% to 3.3% (RR 0.58; 95% CI 0.33–1.01; $P = 0.050$). Among the patients without ST-segment depression, the corresponding rates of death or MI were 10.4% and 8.9% ($P = 0.36$), and the mortality rates were 2% and 1.2% ($P = 0.26$). A similar dichotomy was found in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 randomized trial of early invasive versus conservative strategies in patients with ACS.[439] Thus according to the ACA/AHA Practice Guidelines for the management of patients with UA and NSTEMI, new or presumably new ST-segment depression is a class I indication for use of an invasive strategy.[1]

The magnitude[440,441] and the location[442] of ST-segment depression also provide independent prognostic information in patients with UA and NSTEMI. Among 1846 patients who were enrolled in the TACTICS-TIMI 18 trial, the magnitude of ST-segment depression was a predictor of unsuccessful medical therapy in patients who were randomly assigned to the conservative strategy.[441] The magnitude of ST-segment depression was an independent predictor of the extent of CAD among patients who were randomly assigned to the early invasive strategy. After adjustment for baseline characteristics and the degree of troponin elevation, the benefit of an early invasive strategy was greater among patients with ST-segment depression of 0.10 mV or greater, compared with patients with 0.05 to 0.09 mV of ST-segment depression.

Among a cohort of 432 patients with a first NSTEMI, patients with ST-segment depression in two or more lateral leads (I, aVL, V_5, or V_6) had lower LVEFs, more frequent left main coronary artery or three-vessel CAD, and greater in-hospital mortality.[442] Although isolated T-wave inversion on the admission ECG is associated with a better prognosis than ST-segment depression or elevation, negative T waves in leads V_2 and V_3 are associated with

critical stenosis of the proximal LAD and stunning of the myocardium supplied by the LAD.[443,444]

Biochemical Markers

The distinction between NSTEMI and UA is based on the blood assays for biochemical markers of myocardial necrosis. As noted previously, a typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB are required to diagnose an acute, evolving, or recent MI.[2] Although troponin has become the preferred biomarker for myocardial necrosis, the serum troponin is frequently elevated in patients with HF[10] or chronic kidney disease.[49] Numerous other causes of an elevated troponin have been recognized, and several may be associated with chest pain or ST-segment elevation.[50]

Symptoms consistent with ACS are a class I indication for measurement of cardiac-specific troponin (troponin I or T) at the time of presentation and 3 to 6 hours after symptom onset to identify a rising and/or falling pattern.[1] Another class I recommendation is that "additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with normal troponin on serial examination when electrocardiographic changes and/or clinical presentation confer an intermediate or high index of suspicion for ACS."[1] Biochemical markers such as troponin or CK-MB provide both diagnostic and prognostic information, but CK-MB (and myoglobin) are now regarded as class III (no benefit) assays for the diagnosis of ACS.[1] Among 1404 patients with UA or NSTEMI who were enrolled in the TIMI IIIB trial, the mortality rate at 42 days was 3.7% (21/573) for patients with a baseline troponin I 0.4 ng/mL or greater, compared with 1% (8/831) for patients with a troponin I less than 0.4 ng/mL ($P < 0.001$).[445] There were significant increases in mortality with increasing levels of troponin I. An elevated troponin in patients with suspected ACS confers a greater risk of death or reinfarction even among patients without significant angiographic CAD.[446] Patients with ACS who have an elevated troponin level, even if the elevation is minor, derive greater benefit from platelet GP IIb/IIIa inhibitors[447,448] or invasive management[449] than do patients without an elevated troponin level.

Another biochemical marker that provides prognostic information is brain natriuretic peptide. An elevated brain natriuretic peptide at the time of presentation or after hospital discharge in patients with ACS is an independent predictor of death or new-onset HF during follow-up.[450,451]

Coronary CT Angiography

Several randomized trials have been performed to evaluate the utility of coronary CT angiography (CCTA) in "low-risk" patients with chest pain. Sixteen emergency departments enrolled 749 patients in a multicenter, randomized study called the Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) trial.[452] The patients were randomly assigned to either CCTA ($n = 361$) or rest-stress myocardial perfusion imaging ($n = 338$). The time to diagnosis and costs of care were less in the patients who were randomly assigned to CCTA.[452] A larger study randomly assigned low- to intermediate-risk patients with possible ACS, in a 2:1 ratio, to undergo CCTA or traditional care.[453] None of the 640 patients with a negative CCTA died or had an MI within 30 days.[453] A multicenter trial that randomly assigned 1000 patients with suspected ACS but no ischemic electrocardiographic changes and a normal initial serum troponin found that patients evaluated by CCTA were discharged sooner than patients who underwent standard evaluation.[454] The patients who were randomly assigned to CCTA, however, underwent more downstream testing and had greater radiation exposure.[454] The 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes includes a class IIa recommendation that "In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia."[1]

Approach to Management

Fig. 29.8 presents an algorithm for the treatment of UA and non–ST-segment elevation myocardial infarction. Specific components of management are discussed next.

Antiischemic Therapy

Nitrates

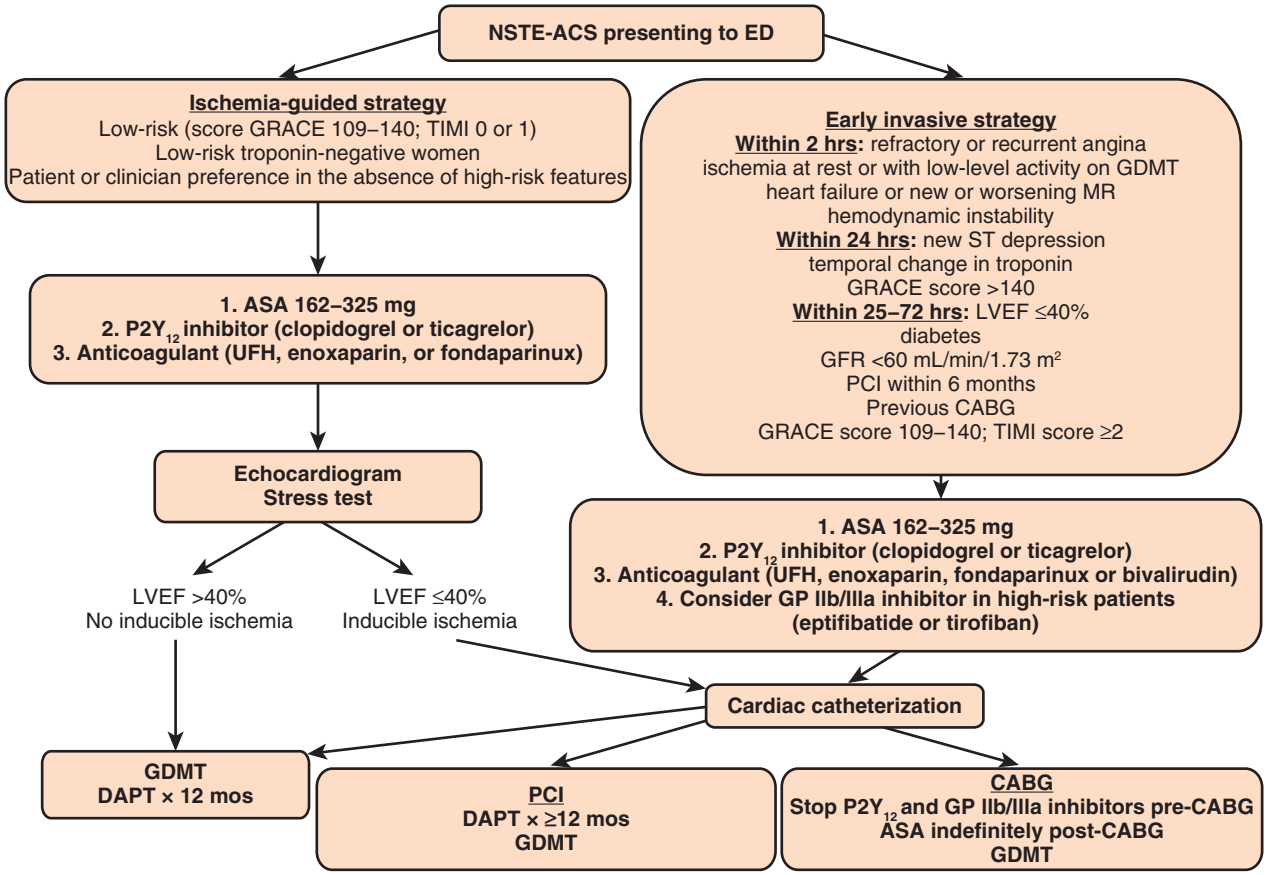
The class I recommendations for antiischemic therapy in patients with NSTE-ACS include nitroglycerin administered initially as a sublingual tablet or spray, followed by intravenous infusion for patients with persistent ischemia, HF, or hypertension.[1] Although nitroglycerin often relieves chest pain in patients with ACS, nitrates have not been shown to reduce clinical events in patients with NSTE-ACS. Abrupt cessation of intravenous nitroglycerin may be associated with rebound myocardial ischemia in patients with ACS.[455] After intravenous infusion of nitroglycerin for longer than 24 hours the development of tolerance may require an increase in the dose to maintain efficacy, but 200 μg/min usually is considered the maximum dose.

β-Blockers

The class I recommendations for antiischemic therapy in patients with NSTE-ACS include the administration of a β-blocker within the first 24 hours for patients who do not have signs of HF, evidence of a low output state, increased risk for cardiogenic shock, or other relative contraindications to β-blockade.[1] Nevertheless, many patients who are eligible for β-blocker therapy do not receive it, possibly because there are limited data regarding the efficacy of β-blockers in patients with NSTE-ACS.[456] Clinical trials that evaluated β-blockers in patients with UA were not adequately powered to demonstrate reductions in mortality. A pooled analysis of randomized trials in patients with threatened or evolving MI concluded that β-blockers reduce the risk of MI by 13%.[457] A report from the GRACE registry analyzed the outcomes of 7106 patients with NSTEMI.[456] β-Blocker therapy was initiated within 24 hours of admission in 76% of patients without contraindications. After multivariable logistic regression analysis to adjust for presence of comorbidity, both in-hospital mortality (OR 0.58; 95% CI 0.42–0.81) and 6-month mortality (OR 0.75; 95% CI 0.56–0.997) were lower among patients who received β-blockers than among patients who did not.

Calcium Antagonists

The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) found that nifedipine alone increased the risk of MI or recurrent angina, relative to placebo, by 24% in patients with UA.[458] The 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes includes a class III recommendation that "Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy."[1]



• **Fig. 29.8** Algorithm for the treatment of unstable angina or non–ST-segment elevation myocardial infarction. *Note:* Enoxaparin is not recommended for use in patients with known bleeding disorders or significant renal insufficiency (serum creatinine ≥2 to 2.5 mg/dL). *ASA,* Acetylsalicylic acid (aspirin); *CABG,* coronary artery bypass graft surgery; *DAPT,* dual antiplatelet therapy; *ED,* emergency department; *GDMT,* guideline-directed medical therapy; *GFR,* glomerular filtration rate; *GRACE,* Global Registry of Acute Coronary Events; *LVEF,* left ventricular ejection fraction; *GP,* glycoprotein; MR, mitral regurgitation; *NSTE-ACS,* non–ST-segment elevation acute coronary syndrome; *PCI,* percutaneous coronary intervention; *TIMI,* Thrombolysis in Myocardial Infarction study; *UFH,* unfractionated heparin. (From Amsterdam EZ, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e139–e228.)

The Multicenter Diltiazem Postinfarction Trial (MDPIT) randomly assigned 2466 patients to receive diltiazem or placebo 3 to 15 days after acute MI.[346] Approximately 70% of patients met ECG criteria for a Q-wave MI, and 25% had non–Q-wave MI. The percentage of patients with STEMI or NSTEMI was not reported. Total mortality rates for the two treatment groups were nearly identical, but treatment with diltiazem was associated with increased mortality in patients with either radiographic evidence of pulmonary congestion or an LVEF less than 40%. Also, diltiazem was associated with an increased risk of late-onset HF in patients with an LVEF less than 40%.[347]

Gibson and colleagues[459] performed a post hoc subset analysis of the 817 patients with non–Q-wave MI and no pulmonary congestion who were enrolled in two clinical trials: MDPIT and the second Danish Verapamil Infarction Trial (DAVIT-II).[459] The adjusted all-cause mortality was lower among patients who were given diltiazem or verapamil than among those who received placebo (RR 0.65; 95% CI 0.40–1.05). Nevertheless, calcium antagonists are not considered first-line therapeutic agents in patients with ACS and are reserved for patients with recurrent ischemia, but no severe left ventricular dysfunction, who have a contraindication to β-blockers.

Intraaortic Balloon Counterpulsation

Intraaortic balloon counterpulsation is believed to increase myocardial oxygen supply by increasing diastolic pressure and to reduce myocardial oxygen demand by afterload reduction of the left ventricle. The indications for an IABP in patients with NSTE-ACS include refractory ischemia, hypotension, and cardiogenic shock, although this modality should be considered an adjunct to definitive therapies such as percutaneous or surgical myocardial revascularization.

Antiplatelet Therapy

Aspirin

The 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes includes a class I recommendation that "Non-enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation,

and a maintenance dose of aspirin (81 mg/day to 325 mg/day) should be continued indefinitely."[1] The recommendation is based on the results of four small randomized trials. A pooled analysis of the results concluded that aspirin reduces the risk of death or MI by 50% in patients with UA. The optimal dose of aspirin in patients with ACS is uncertain.[460] An aspirin dose of 75 mg/day reduced the risk of MI or death after 1 year in patients with UA or non–Q-wave MI who were enrolled in a prospective, randomized, double-blind, placebo-controlled multicenter trial (RR 0.52; 95% CI 0.37–0.72).[461] Among 20,521 patients with ACS who were enrolled in the GUSTO IIb and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials, an aspirin dose of 150 mg or greater was associated with a lower risk of MI at 6 months, compared with an aspirin dose less than 150 mg (HR 0.79; 95% CI 0.64–0.98; $P = 0.03$).[462] The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomly assigned 12,562 patients with ACS to aspirin plus clopidogrel 75 mg daily or aspirin plus placebo.[463] The study protocol recommended an aspirin dose of 75 to 325 mg and the dose was left to the discretion of the local investigator. In both arms of the study, higher doses of aspirin were associated with an increased risk of major bleeding but clinical event rates were not reduced by higher doses of aspirin. PCI-CURE was a substudy of the CURE trial that consisted of the 2658 patients who underwent PCI.[464,465] A post hoc analysis of the patients who were enrolled in PCI-CURE found that the moderate-dose (101 to 199 mg) and high-dose (≥200 mg) aspirin groups had similar rates of cardiovascular death, MI, or stroke compared with the low-dose (≤100 mg) aspirin group, but high-dose aspirin was associated with an increased risk of major bleeding.[464,465]

The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) Trial was the first randomized trial to compare two different doses of aspirin in patients with ACS.[466,467] The primary results have been published in two complementary articles in the September 2, 2010, issue of the *New England Journal of Medicine* and the October 9, 2010, issue of *Lancet*.[466,467] The *NEJM* article presents an analysis of the entire enrollment of 25,086 patients, including patients who did not undergo coronary angiography or PCI, whereas the *Lancet* article describes a prespecified analysis of the 17,263 patients who underwent PCI. Among the entire cohort of 25,086 patients there was no significant difference between the higher dose of aspirin (300–325 mg daily) and the lower dose of aspirin (75 to 100 mg daily) with respect to the primary composite end point of cardiovascular death, myocardial infarction, or stroke at 30 days. Although the rates of major bleeding were 2.3% for both doses of aspirin, there was significantly less minor bleeding among the patients who received the lower dose of aspirin (4.4% versus 5%; HR 1.13; $P = 0.04$).

Based on an analysis of the PLATO trial, the label for ticagrelor, a platelet $P2Y_{12}$ receptor inhibitor, includes a black box warning that maintenance doses of aspirin reduce the effectiveness of ticagrelor. The practice guidelines for PCI include a class IIa recommendation that it is reasonable to prescribe a maintenance aspirin dose of 81 mg daily in preference to higher doses.[468]

Inhibitors of the Platelet $P2Y_{12}$ Receptor

Inhibitors of the platelet $P2Y_{12}$ receptor have been shown to improve outcomes in patients with NSTE-ACS.[469,470] An open study that randomly assigned patients with UA to ticlopidine or conventional therapy (excluding aspirin) demonstrated a 46% reduction in the risk of vascular death and nonfatal MI.[469] Clopidogrel has a more rapid onset of action and a better safety profile than ticlopidine. The CURE trial demonstrated that the combination of clopidogrel and aspirin, compared with aspirin alone, improved outcomes among patients with ACS without ST-segment elevation.[470]

There is extensive evidence that platelet inhibition by clopidogrel is influenced by both drug interactions and certain genotypes that affect the metabolism of clopidogrel, a prodrug that is converted to an active metabolite by CYP 2C19 activity, a hepatic cytochrome P450 enzyme.[471,472] Coadministration of clopidogrel and drugs metabolized by CYP 2C19, such as some proton pump inhibitors, may inhibit the formation of clopidogrel's active metabolite, resulting in diminished platelet inhibition. On November 17, 2009, the U.S. FDA issued a public alert regarding updated labeling of clopidogrel that included that following statement: "New data show that when clopidogrel and omeprazole are taken together the effectiveness of clopidogrel is reduced." There is also evidence, however, that proton pump inhibitors may be associated with an increased risk of adverse cardiovascular events in the absence of clopidogrel.[473] Concomitant use of proton pump inhibitors and thienopyridines was discussed in detail in an expert consensus document published by the ACCF, the American College of Gastroenterology, and the AHA.[474]

Genetic polymorphisms that affect CYP 2C19 activity are common and are associated with variability in the bioavailability of clopidogrel's active metabolite, affecting platelet inhibition and clinical outcomes, including the risk of stent thrombosis. On March 12, 2010, the FDA approved a new label for clopidogrel that contained a boxed warning regarding the drug's decreased efficacy in patients with impaired capacity to convert clopidogrel to an active metabolite, prompting publication of a document by the ACCF/AHA.[475]

The drug interactions and genetic polymorphisms that affect clopidogrel's metabolism can be approached using several strategies. One potential strategy is to use genetic testing to identify patients who are heterozygous or homozygous for loss-of-function alleles that impair metabolism of clopidogrel, but genetic testing is expensive and has not gained widespread acceptance. Another approach is alternative dosing regimens of clopidogrel. Numerous studies have found that a 600-mg loading dose of clopidogrel, compared with a 300-mg loading dose, reduces the risk of major adverse cardiovascular events after PCI without increasing the risk of major bleeding.[476] Also, increased loading and maintenance doses of clopidogrel produces greater platelet inhibition in patients who are heterozygous for the CYP 2C19*2 loss-of-function allele.[477,478] High residual platelet activity during clopidogrel therapy is associated with an increased risk of ischemic events in patients with ACS who undergo PCI, but a randomized trial that compared standard- and high-dose clopidogrel regimens in patients with high residual platelet activity failed to show a reduction in the incidence of cardiovascular deaths, nonfatal MI, or stent thrombosis 6 months after PCI with drug-eluting stents.[479,480]

The CURRENT-OASIS 7 trial compared two regimens of clopidogrel in patients with ACS.[466,467] The double-dose patients received a clopidogrel loading dose of 600 mg and a daily maintenance dose of 150 mg on days 2 to 7, then 75 mg daily, whereas the standard-dose group received a loading dose of 300 mg followed by a daily maintenance dose of 75 mg. The frequency of major bleeding was greater among the patients who were randomly assigned to receive the higher dose of clopidogrel. Although the double-dose regimen was associated with a reduction in cardiovascular events and stent thrombosis in ACS patients

who underwent PCI, it is uncertain whether the higher maintenance dose that was administered for only 6 days provided any additional benefit beyond the documented benefit of the 600-mg loading dose.

A third approach is to prescribe other $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor. Cytochrome P450 genetic polymorphisms do not affect drug metabolite concentrations, inhibition of platelet aggregation, or clinical event rates in patients treated with prasugrel[481,482] or ticagrelor.[483] Also, compared with the combination of aspirin and clopidogrel, the combination of aspirin and ticagrelor reduced the risk of death in patients with ACS.[113]

Among the 11,080 patients with NSTE-ACS who were randomly assigned to receive ticagrelor or clopidogrel in the PLATO trial, 5366 patients were alive and had not undergone revascularization 10 days after randomization.[484] Whether the patient did or did not undergo revascularization during the first 10 days did not significantly affect the reduction by ticagrelor of the either the primary endpoint (HRs 0.86 for revascularization vs. 0.85 for no revascularization; interaction $P = 0.93$) or all-cause death (HRs 0.75 for revascularization vs. 0.73 for no revascularization; interaction; $P = 0.89$).[484] However, in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) study, among 9326 patients with NSTE-ACS who were randomly assigned to received clopidogrel or prasugrel and managed medically without revascularization for the first 10 days, after a median follow-up of 17 months there was no significant difference in the rate of the primary endpoint, a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke among patients younger than age 75 (HR in the prasugrel group 0.91; 95% CI 0.79–1.05; $P = 0.21$).[485] The combinations of clopidogrel, prasugrel, or ticagrelor with aspirin were included in the class I recommendations for dual antiplatelet therapy in the 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes.[1] The guideline also added a class IIa recommendation that "it is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy."[1] The ESC guidelines include several additional recommendations regarding selection of specific $P2Y_{12}$ inhibitors.[22] Ticagrelor is preferred in patients at moderate to high ischemic risk (class I recommendation), and the ESC guidelines recommend against treatment with prasugrel when the coronary anatomy is unknown.[22]

Whenever possible clopidogrel and ticagrelor should be discontinued at least 5 days before CABG surgery, and prasugrel should be stopped at least 7 days before CABG surgery, to attenuate the increased perioperative bleeding associated with inhibition of platelet $P2Y_{12}$ receptors.[1] Therefore some practitioners prefer to withhold platelet $P2Y_{12}$ receptor inhibitors until the results of diagnostic cardiac catheterization are known, but this approach ignores the proven benefit of pretreatment in patients with ACS who undergo PCI or CABG.[486,487] Also, CABG surgery can usually be deferred for 5 to 7 days, and percutaneous revascularization is more frequent than surgical revascularization in patients with ACS.[486] The CURE investigators concluded that the increased bleeding risk in patients who may require CABG surgery is outweighed by the overall reduction in ischemic events among all patients.[486] Also, among patients who were enrolled in the TRITON-TIMI 38 trial and underwent CABG, patients who were randomly assigned to receive prasugrel had a lower rate of death after CABG, compared with the rate among patients who were randomly assigned to receive clopidogrel, despite an increase in bleeding, platelet transfusion, and surgical reexploration for bleeding.[487] Thus a policy of withholding $P2Y_{12}$ antagonists until after coronary angiography may harm more patients than a policy of starting a $P2Y_{12}$ antagonist upon admission to the hospital. If an intravenous $P2Y_{12}$ antagonist with a short half-life, such as cangrelor, is used instead of one of the oral $P2Y_{12}$ antagonists before the coronary anatomy is known, patients who need CABG would be able to undergo surgery sooner, whereas patients who are treated with PCI can be switched to an oral agent.[488] The 2014 AHA/ACC NSTE-ACS guideline did not include any recommendations regarding cangrelor, but the 2015 ESC Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation included a IIb recommendation for cangrelor: cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI[1,22]

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Discontinuation of either UFH or LMWH in patients with UA is associated with a rebound increase in thrombin generation,[489] which may underlie the increase in death and MI that has been observed during the 12 hours after heparin is stopped in patients with ACS.[490,491] Compared with patients who were randomly assigned to a placebo group, patients who were randomly assigned to treatment with a GP IIb/IIIa antagonist, eptifibatide, experienced significantly fewer deaths and MIs during the 12 hours after heparin was terminated.[491]

A retrospective analysis of the PURSUIT trial found that treatment with eptifibatide was associated with improved outcome among patients in whom cardiogenic shock developed during hospitalization for ACS without persistent ST-segment elevation.[492] Although randomization to eptifibatide treatment did not affect the occurrence of shock, patients with shock who received eptifibatide had significantly reduced adjusted odds of death at 30 days (OR 0.51; 95% CI 0.28–0.94; $P = 0.03$). It is unlikely that improved outcome after PCI was responsible for the beneficial effect of eptifibatide because only 25% of the patients with shock in PURSUIT underwent PCI.

Boersma and colleagues[493] performed a meta-analysis of the individual patient data from six trials that randomly assigned 31,402 patients with ACS without persistent ST-segment elevation to a GP IIb/IIIa inhibitor treatment group (abciximab, eptifibatide, lamifiban, or tirofiban) or to a control group. Overall, there was a 9% reduction in the odds of death or MI at 30 days (10.8% vs. 11.8%; OR 0.91; 95% CI 0.84–0.98; $P = 0.015$).[493] The baseline troponin value was available in a subset of 11,059 patients (35% of the entire cohort). Among the 45% of patients with a troponin T or I level 0.1 ng/mL or greater, there was a 15% reduction in the odds of death or MI at 30 days compared with that for the control group (10.3% vs. 12%; OR 0.85; 95% CI 0.71–1.03). No risk reduction was observed among patients with negative troponin levels (GP IIb/IIIa inhibitor 7% vs. control 6.2%; OR 1.17; 95% CI 0.94–1.44). Another meta-analysis of the same six trials found that the impact of GP IIb/IIIa antagonists on outcome varied with the revascularization strategy.[494] The reduction of ischemic events was greater among patients who underwent PCI during the index hospitalization (OR 0.82; $P = 0.01$) than among patients who were managed medically (OR 0.95; $P = 0.27$).[494] The corresponding number of events (death or MI at 30 days) prevented per 1000 patients treated was 20 for patients who underwent PCI compared with 4 for patients treated medically.[494] The GUSTO IV ACS trial failed to show a benefit of abciximab among patients with ACS who did not undergo early coronary revascularization.[495]

The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial compared two strategies of GP IIb/IIIa administration in 9492 patients with ACS without ST-segment elevation who were assigned to an invasive strategy.[496] The patients were randomly assigned to either early eptifibatide beginning ≥12 hours before coronary angiography, or a matching placebo infusion with provisional, delayed use of eptifibatide after angiography. At 30 days the rate of death or MI was 11.2% in the early-eptifibatide group compared with 12.3% in the delayed-eptifibatide group (OR 0.89; 95% CI 0.79–1.01; $P = 0.08$). The rates of bleeding and red blood cell transfusion, but not severe bleeding, were significantly higher in the early-eptifibatide group. A meta-analysis that included 12 clinical trials that evaluated a strategy of so-called upstream administration of GP IIb/IIIa inhibitors concluded that upstream use was associated with an 11% reduction in the combined endpoint of death or myocardial infarction (OR 0.89; 95% CI 0.83–0.95), no significant mortality effect (OR 0.93; 95% CI 0.83–1.05), and a 23% higher risk of major bleeding (OR 1.23; 95% CI 1.02–1.48).[497]

The 2014 AHA/ACC NSTE-ACS Guideline contains several recommendations regarding the use of platelet GP IIb/IIIa inhibitors.[1] The class I recommendation states "In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) who are not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI."[1] The class IIa recommendation states "In patients with NSTSE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI."[1] The class IIb recommendation states "In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban."[1]

GP IIb/IIIa antagonists increase the risk of bleeding, frequently involving the access site used for cardiac catheterization, but the risk of intracranial hemorrhage is not increased.[493] The meta-analysis performed by Boersma and colleagues[493] found that the risk of major bleeding was 2.4% among patients who were randomly assigned to receive a GP IIb/IIIa antagonist compared with 1.4% among control patients (OR 1.62; 95% CI 1.36–1.94; $P < 0.0001$). One preventable cause of bleeding is excess dosing of a GP IIb/IIIa antagonist, which occurred in 26.8% of patients with NSTE-ACS who were enrolled in the CRUSADE registry by 387 hospitals in 2004.[498]

A complete blood cell count including platelet count should be included in monitoring during administration of GP IIb/IIIa antagonists. A review of eight large placebo-controlled, randomized trials, however, concluded that abciximab, but not eptifibatide or tirofiban, increases the incidence of thrombocytopenia.[499]

Antithrombin Therapy

Unfractionated Heparin

At least seven randomized, placebo-controlled trials have compared UFH plus aspirin with aspirin alone in patients with UA, but none of them was adequately powered to detect a reduction in the rate of death or MI during hospitalization. A meta-analysis of six of the trials concluded that the addition of UFH to aspirin reduced the risk of death or MI during treatment by 33% (RR 0.67; 95% CI 0.44–1.02; $P = 0.06$).[500] Therefore the ACC/AHA Practice Guidelines include intravenous UFH in the list of class I recommendations for patients NSTE-ACS.[1] During treatment with UFH the platelet count and the hemoglobin or hematocrit should be measured daily because of the increased risks of bleeding and thrombocytopenia. An analysis of patients who were enrolled in the CRUSADE registry in 2004 found that bleeding was related to excess dosing of UFH, which occurred in 32.8% of patients who received UFH.[498]

As discussed earlier, a rebound increase in thrombin generation with reactivation of UA has been observed after the discontinuation of UFH. One clinical trial observed an eightfold increase in death and a twofold increase in MI during the 12 hours after heparin was discontinued.[491] The rate of events during the 12 hours after heparin was terminated was significantly lower among patients who were randomly assigned to treatment with eptifibatide than among patients in the placebo group.[491]

Low-Molecular-Weight Heparin

The FRISC study randomly assigned 1506 patients with UA or non–Q-wave MI to receive placebo or dalteparin, an LMWH, twice daily for 6 days, followed by once daily for 35 to 45 days.[501] A 63% reduction in the risk of death or MI occurred during the first 6 days (4.8% vs. 1.8%; $P = 0.001$). Subsequently, 21,946 patients with non-ST-segment elevation ACS were enrolled in six randomized trials that compared enoxaparin, another LMWH, with UFH. A meta-analysis of the trials found no significant difference in death at 30 days for enoxaparin versus UFH (3% vs. 3%; OR 1.00; 95% CI 0.85–1.17).[502] A statistically significant reduction was observed in the combined endpoints of death and nonfatal MI at 30 days for enoxaparin versus UFH (10.1% vs. 11%; OR 0.91; 95% CI 0.83–0.99).

Although it had been hypothesized that the risk of bleeding would be less during treatment with LMWH than during treatment with UFH, the meta-analysis performed by Petersen and colleagues[502] found no significant difference between enoxaparin and UFH in the rates of blood transfusion or major bleeding at 7 days after initiation of the study treatment. The risk of bleeding during treatment with LWMH may be increased by excess dosing, which occurred in 13.8% of patients who were enrolled in the CRUSADE registry in 2004 and received LMWH.[498]

The current ACC/AHA guideline for NSTE-ACS states that "In patients with NSTE-ACS, anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy."[1] The options include intravenous UFH for 48 hours or until PCI is performed, and enoxaparin for the duration of hospitalization or until PCI is performed.[1]

Direct Thrombin Inhibitors

Direct thrombin inhibitors, such as hirudin and bivalirudin, have been evaluated in patients with NSTE-ACS. The ACUITY trial was an open-label, randomized, multicenter trial that compared heparin plus a GP IIb/IIIa antagonist, bivalirudin plus a GP IIb/IIIa antagonist, and bivalirudin alone in patients with moderate-risk or high-risk NSTE-ACS who were undergoing an early invasive strategy.[503–505] NSTEMI was present in 59% of patients, and 41% had UA. Compared with patients who received a GP IIb/IIIa antagonist plus UFH or enoxaparin, patients who received bivalirudin alone experienced significantly less non–CABG-related major bleeding (3% vs. 5.7%; RR 0.53; 95% CI 0.43–0.65). Compared with heparin plus a GP IIb/IIIa antagonist, bivalirudin alone resulted

in a noninferior rate of the composite ischemia endpoint (7.3% vs. 7.8%, respectively; RR 1.08; 95% CI 93–1.24; $P = 0.32$). Administration of bivalirudin plus a GP IIb/IIIa antagonist, as compared with heparin plus a GP IIb/IIIa antagonist, resulted in noninferior 30-day rates of the composite ischemia endpoint (7.7% vs. 7.3%, respectively; RR 1.07; 95% CI 0.92–1.23; $P = 0.39$) and major bleeding (5.3% vs. 5.7%, respectively; RR 0.93; 95% CI 0.78–1.10; $P = 0.38$). Bivalirudin is a class I anticoagulant in patients with NSTE-ACS only in patients who are selected for an early invasive strategy.[1]

In addition, the 2014 AHA/ACC guideline for NSTE-ACS includes a class IIa recommendation that "In patients with NSTSE-ACS undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist."[1]

Factor Xa Inhibitors

Several factor Xa inhibitors, fondaparinux,[506] apixaban,[507,508] and rivaroxaban,[509] have been studied in patients with NSTE-ACS. The OASIS-5 trial compared fondaparinux with enoxaparin for a mean of 6 days in 20,078 patients with ACS.[506] The rate of major bleeding at 9 days was lower with fondaparinux than with enoxaparin (2.2% vs. 4.1%; HR 0.52; $P < 0.001$). Also, the number of deaths at 30 days was significantly reduced by fondaparinux compared with enoxaparin (295 vs. 352; $P = 0.02$). Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant during PCI, and an additional anticoagulant with antifactor IIa activity should be administered.[1]

In patients with a recent ACS, treatment with rivaroxaban, compared with placebo, significantly reduced the primary efficacy endpoint of death from cardiovascular causes, MI, or stroke (8.9% vs. 10.7%, respectively; HR in the rivaroxaban group 0.84; 95% CI 0.74–0.96; $P = 0.008$), but rivaroxaban increased the risk of major bleeding and intracranial hemorrhage.[509] Treatment with apixaban also increased bleeding in high-risk ACS patients, but it did not reduce recurrent ischemic events, regardless of whether concomitant antiplatelet therapy consisted of aspirin alone or aspirin plus clopidogrel.[507,508]

Angiotensin-Converting Enzyme Inhibitors

Little information is available regarding the administration of ACE inhibitors to patients with NSTEMI because most of the ACE inhibitor trials did not report subgroup analyses of patients with STEMI or NSTEMI. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study enrolled 1556 patients with acute anterior MI who were not eligible for fibrinolytic therapy.[510] The patients were randomly assigned to receive 6-week courses of placebo or zofenopril, an ACE inhibitor. Among the 526 patients with ECG criteria for NSTEMI, death or severe HF occurred in 10.3% (28/273) of placebo patients and 3.6% (9/253) of zofenopril patients (RR reduction 65%; 95% CI 20–80; $P = 0.003$).[511] The 1-year mortality rate also was significantly reduced by zofenopril (7.9% vs. 15.8%; RR reduction 43%; 95% CI 14–57; $P = 0.036$).

Lipid-Lowering Therapy

Numerous randomized trials have investigated the effects of statins on outcomes in patients with ACS. Compared with placebo, treatment with atorvastatin 80 mg daily beginning 24 to 96 hours after hospital admission for UA or non-Q-wave MI reduced the rate of recurrent ischemic events at 16 weeks.[512] As discussed earlier, the 4S,[348] CARE,[349] and LIPID[350] trials have established the long-term benefits of starting statin therapy 3 months or later after hospitalization for an MI or UA. Analysis of the LIPID trial showed that initiation of pravastatin 40 mg daily 3 to 36 months after hospitalization for UA significantly reduced the risk of several endpoints, including death (RR 0.74; 95% CI 0.50–0.91; $P = 0.004$) and nonfatal MI (RR 0.67; 95% CI 0.51–0.88; $P = 0.004$).[513]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study compared atorvastatin 80 mg daily with pravastatin 40 mg daily started within 10 days of hospitalization for an ACS.[514,515] The median LDL cholesterol during treatment was 95 mg/dL in the pravastatin group and 62 mg/dL in the atorvastatin group ($P < 0.001$). The primary endpoint was a composite of death, MI, UA, revascularization, and stroke. For the entire study population of 4162 patients, the rates for the primary endpoint at 2 years were 22.4% in the atorvastatin group and 26.3% in the pravastatin group, representing a 16% reduction in the HR in favor of atorvastatin (95% CI 5–26; $P = 0.005$). For the patients with unstable angina the rates for the primary endpoint at 2 years were 26.5% for the atorvastatin group and 31.4% for the pravastatin group. For the patients with NSTEMI the rates for the primary endpoint were 19.0% for the atorvastatin group and 24.1% for the pravastatin group. For the entire study population of 4162 patients, during a median follow-up of 24 months, hospitalization for HF more than 30 days after randomization was significantly less frequent among patients who were treated with atorvastatin than among patients who were treated with pravastatin (1.6% vs. 3.1%; HR 0.55; 95% CI 0.35–0.85; $P = 0.008$).[515]

It appears that patients who are treated with statins may be adversely affected if statin therapy is discontinued after hospitalization for an ACS.[516,517] A retrospective analysis of the outcomes in 1616 patients with ACS concluded that statin pretreatment is associated with improved clinical outcome, whereas the discontinuation of statins after symptom onset is associated with an increased risk of death and nonfatal MI within 30 days.[516] Similarly, multivariate analysis of the 13,871 patients in the NRMI 4 database who were receiving statin therapy before hospitalization for a NSTEMI found that withdrawal of statin therapy in the first 24 hours of hospitalization was associated with a statistically significant increased risk of hospital death compared with those who continued statin therapy.[517]

At least two meta-analyses of relevant randomized controlled trials have been performed to estimate the effects of early treatment with statins on short-term outcomes in patients with ACS.[518,519] One analysis of 12 randomized trials concluded that statin therapy initiated within 14 days of hospital admission does not reduce the risk of death, MI, or stroke during the first 4 months after ACS.[518] Another meta-analysis of 13 randomized trials concluded that early statin therapy reduces the rates of death and cardiovascular events after 4 months of treatment.[519]

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) randomly assigned 18,144 patients who were hospitalized for an ACS within the preceding 10 days to either simvastatin 40 mg/day or simvastatin 40 mg/day and 10 mg/day of ezetimibe, a nonstatin that reduces intestinal absorption of cholesterol.[520] The index event was a NSTE-ACS in the majority of patients: NSTEMI in 47%, STEMI in 29%, and UA in 24%. The median time-weighted average LDL cholesterol during the study was 53.7 mg/dL in the simvastatin-ezetimibe group compared with 69.5 mg/dL in the simvastatin monotherapy group ($P < 0.001$). At 7 years, the event rate for the primary endpoint—a composite of cardiovascular death, nonfatal MI,

rehospitalization for UA, coronary revascularization within 30 days of randomization, or nonfatal stroke—was 2.0 percentage points lower for the combination group (32.7% vs. 34.7%; HR 0.936; 95% CI 0.89–0.99; $P = 0.016$).[520]

Invasive versus Conservative Management

At least eight randomized trials have compared early invasive and early conservative management strategies for patients with NSTE-ACS. Patients who are managed by an early conservative strategy undergo coronary angiography if evidence points to spontaneous recurrent ischemia or if results of stress testing are strongly positive despite medical therapy. Patients who are managed using an early invasive strategy undergo routine coronary angiography and coronary revascularization as indicated. Three relatively large trials demonstrated better short-term and long-term outcomes among patients randomly assigned to the early invasive strategy compared with the early conservative strategy: FRISC II,[521–523] TACTICS-TIMI 18,[439] and the Randomized Intervention Trial of Unstable Angina-3 (RITA-3).[524–526] The FRISC II[521–523] and TACTICS-TIMI 18[439] trials randomly assigned 2457 and 2220 patients, respectively, with UA or NSTEMI to either an early conservative or an early invasive strategy. Both trials found that the early invasive strategy was associated with a lower risk of death or MI at 6 months compared with the early conservative strategy: 9.4% versus 12.1% (RR 0.78; 95% CI 0.62–0.98; $P = 0.031$) for FRISC II and 7.3% versus 9.5% (OR 0.74; 95% CI 0.54–1.00; $P < 0.05$) for TIMI 18. The early invasive strategy also was associated with a reduced rate of rehospitalization for ACS in both trials. After follow-up for 5 years in the FRISC II trial, patients who were randomly assigned to the early invasive arm experienced a lower rate of MI (12.9% vs. 17.7%; RR 0.73; 95% CI 0.60–0.89; $P = 0.002$) but not overall mortality (9.7% vs. 10.1%; RR 0.95; 95% CI 0.75–1.21; $P = 0.693$).[523] The RITA-3 study randomly assigned 1810 patients with NSTE-ACS to early invasive or early conservative treatment.[524–526] After a median follow-up period of 5 years, 142 (16.6%) patients randomly assigned to the early intervention group and 178 (20%) patients assigned to the early conservative group died or had a nonfatal MI (OR 0.78; 95% CI 0.61–0.99; $P = 0.044$). The death rates were 12% for the interventional group versus 15% for the conservative group (OR 0.76; 95% CI 0.58–1.00; $P = 0.054$). The advantage of the routine early invasive strategy that was observed at 5 years was not sustained, and after follow-up for 10 years there were no differences between the routine invasive and selective invasive groups in either all-cause mortality (25.1% vs. 25.4%; $P = 0.94$) or cardiovascular mortality (15.1% vs. 16.1%; $P = 0.65$).[526] An editorial that was co-published with the 10-year results of the RITA-3 Trial speculated that a possible explanation for the attenuation of benefit is that the advantage of the routine invasive strategy observed at 5 years probably influenced the management decisions that were made when the patients who were enrolled in the study experienced ischemic events between 5 and 10 years after enrollment.[527]

A meta-analysis of the 5-year outcomes of three large trials found that cardiovascular death or MI occurred in 14.7% (389/2721) of patients randomly assigned to a routine invasive strategy versus 17.9% (475/2746) of patients who were randomly assigned to a selective invasive strategy (HR 0.81; 95% CI 0.71 to 0.93; $P = 0.002$).[528] The absolute risk reductions for the combined endpoint of cardiovascular death or MI were 2%, 3.8%, and 11.1% for the low-, moderate-, and high-risk patients.

The early invasive strategy confers the greatest benefit in patients who are characterized by high-risk indicators such as ST-segment depression[438,439] or elevated troponin levels.[449] Therefore elevated troponin T or I levels and new or presumably new ST-segment depression are included in a list of 15 high-risk indicators that warrant an early invasive strategy in patients with UA or NSTEMI (Box 29.7).[1] A meta-analysis of nine randomized trials that compared an invasive versus a conservative strategy in patients with NSTE-ACS included 1789 patients with diabetes mellitus.[529] Compared with the conservative strategy, the invasive strategy was associated with a 3.7% absolute risk reduction of nonfatal MI and a 5.1% absolute risk reduction of death, MI, or rehospitalization with ACS among patients with diabetes.[529] Consequently, diabetes is included in the list of 15 high-risk indicators that warrant an early invasive strategy in patients with NSTE-ACS.[1]

Both women and men with NSTE-ACS benefited from an early invasive strategy in the TACTICS-TIMI 18 trial.[530] The adjusted OR for the primary composite endpoint of death, MI, or rehospitalization for ACS at 6 months was 0.72 (95% CI 0.47–1.11) for women and 0.64 (95% CI 0.47–0.88) for men who were randomly assigned to the invasive strategy.[530] The benefit of invasive therapy was magnified in women with elevated troponin T levels.[530] A meta-analysis of 8 trials included 3075 women and 7075 men

• BOX 29.7 Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTE-ACS

Immediate Invasive (Within 2 h)

Refractory angina
Signs or symptoms of heart failure or new or worsening mitral regurgitation
Hemodynamic instability
Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
Sustained VT or VF

Early Invasive (Within 24 h)

None of the above, but GRACE risk score >140
Temporal change in troponin (evidence for a serial increase or decrease ≥20% is required if the initial value is above the 99th percentile of the upper reference level)
New or presumably new ST-segment depression

Delayed Invasive (Within 25–72 h)

None of the above but diabetes mellitus
Renal insufficiency (GFR <60 mL/min per 1.73 m^2)
Reduced LVEF (≤40%)
Early postinfarction angina
PCI within 6 months
Prior CABG surgery
GRACE risk score 109–140; TIMI score ≥2

Ischemia-Guided Strategy

Low-risk score (e.g., TIMI 0 or 1, GRACE <109)
Low-risk troponin-negative female patients
Patient or clinician preference in the absence of high-risk features

CABG, *Coronary artery bypass graft;* GFR, *glomerular filtration rate;* GRACE, *Global Registry of Acute Coronary Events;* LVEF, *left ventricular ejection fraction;* PCI, *percutaneous coronary intervention;* TIMI, *thrombolysis in myocardial infarction;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia. From Amsterdam EZ, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;64:e139–e228.*

with NSTE-ACS who were randomly assigned to an invasive or a conservative strategy.[531] The OR for the composite of death, MI, or ACS for the invasive versus the conservative strategy was 0.81 (95% CI 0.65–1.01; 21.1% vs. 25.0%) in women and 0.73 (95% CI 0.55–0.98; 21.2% vs. 26.3%) in men.[531] Among biomarker-positive women an invasive strategy was associated with a 33% lower odds of death, MI, or ACS (OR 0.67; 95% CI 0.50–0.88), but an invasive strategy was not associated with a significant reduction in the triple composite endpoint in biomarker-negative women (OR 0.94; 95% CI 0.61–1.44).[531]

There are limited data regarding the impact that age should have on the decision whether to recommend an early invasive or early conservative strategy in patients with NSTE-ACS. Among patients with NSTE-ACS who were randomly assigned to an invasive strategy or a conservative strategy in the TACTICS-TIMI 18 trial benefit of the invasive strategy was observed only in patients 65 years of age or older.[532] The absolute reduction of death or MI at 6 months was 4.8 percentage points (8.8% vs. 13.6%; $P = 0.018$) among patients 65 years or older, but among patients younger than 65 years the rates of death or MI at 6 months were 6.1% for the invasive strategy compared with 6.5% for the conservative strategy ($P > 0.2$). Among patients older than 75 years the early invasive strategy was associated with a 56% relative reduction in death or MI at 6 months and an absolute reduction of 10.8 percentage points (10.8% vs. 21.6%; $P = 0.016$). A meta-analysis of patient-pooled data from the FRISC II, ICTUS, and RITA-3 trials found that a routine invasive strategy was associated with a lower hazard of the 5-year composite of cardiovascular death or MI in patients aged 65 to 74 years (HR 0.72; 95% CI 0.58–0.90) and in patients 75 years or older (HR 0.71; 95% CI 0.55–0.91), but not in those younger than 65 years (HR 1.11; 95% CI 0.90–1.38).[533] The After Eighty study was conducted at 16 hospitals in Norway and randomly assigned 457 patients 80 years or older with NSTE-ACS to an invasive strategy or a conservative strategy.[534] During a median follow-up of 1.5 years, the primary outcome—a composite of MI, need for urgent revascularization, stroke, and death—occurred in 93 (40.6%) of 229 patients assigned to the invasive group and 140 (61.4%) of 228 patients assigned to the conservative group (HR 0.53; 95% CI 0.41–0.69; $P = 0.0001$).[534]

Several studies have attempted to determine the optimal timing of revascularization with PCI among patients with NSTE-ACS who are selected for early invasive management. The Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial randomly assigned 3031 patients with NSTE-ACS to two groups: routine early intervention (coronary angiography ≤24 hours after randomization) or delayed intervention (coronary angiography ≥36 hours after randomization).[535] The median time to coronary angiography was 14 hours for the early intervention group and 50 hours for the delayed-intervention group. Early intervention improved the primary composite endpoint of death, MI, or stroke at 6 months in the one-third of patients who were at highest risk (HR 0.65; 95% CI 0.48–0.89), but not in the two-thirds of patients at low or intermediate risk (HR 1.12; 95% CI 0.81–1.56). PCI was performed in 7749 patients with NSTE-ACS who were enrolled in the ACUITY randomized trial.[536] Delay to PCI more than 24 hours after presentation was associated with a significant increase in the mortality and MI rates at 30 days. A delay to PCI more than 24 hours after presentation was an independent predictor of both 30-day and 1-year mortality.

The outcome in invasively managed patients with ACS is affected by numerous factors, including the access route. Two reviewers identified 17 randomized trials that compared radial versus femoral access in invasively managed patients with ACS.[537] The pooled data from four trials that were judged to be high-quality, multicenter trials included patients with either STEMI or NSTE-ACS; all of the trials included patients with STEMI, whereas only two of the trials included patients with NSTE-ACS.[537] For the total population of 17,133 patients with STEMI or NSTE-ACS, radial access was associated with reduced mortality (RR 0.73; 95% CI, 0.59–0.90; $P = 0.003$), major adverse cardiovascular events (RR 0.86; 95% CI 0.75–0.98; $P = 0.025$), and major bleeding (RR 0.57; 95% CI 0.37–0.88; $P = 0.011$). There is evidence that radial access, compared with femoral access, is associated with less major bleeding and reduced mortality in patients with STEMI.[538,539] A subgroup analysis of the Radial Vs femorAL access for coronary intervention trial (RIVAL) trial did not show a mortality benefit of radial access in patients with NSTE-ACS.[538] An observational cohort study of 10,095 patients with NSTEMI concluded that a 1-year mortality benefit of radial access, compared with femoral access, was demonstrated in high-volume radial centers (HR 0.70; 95% CI 0.51–0.97; $P = 0.031$) but not in the low-volume centers (HR 0.80; 95% CI 0.47–1.38; $P = 0.428$).[540] Finally, a meta-analysis of eight randomized trials that compared bivalirudin to heparin in patients with ACS concluded that radial access reduces bleeding risk in patients treated with heparin (OR 0.57; 95% CI 0.43–0.77; $P < 0.001$) but not in patients treated with bivalirudin (OR 0.96; 95% CI 0.65–1.41; $P = 0.83$).[541] The 2014 AHA/ACC NSTE-ACS guideline did not include any recommendations regarding vascular access, but the 2015 ESC Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation included a class I recommendation: "In centres experienced with radial access, a radial approach is recommended for coronary angiography and PCI."[1,22]

A pooled cohort analysis of the individual data from 37,555 participants with NSTE-ACS who were enrolled in four trials found that sudden cardiac death accounted for approximately one-third of the cardiovascular deaths, and the risk of sudden death was reduced in patients who underwent revascularization with either PCI or CABG surgery (HR 0.75; 95% CI 0.58–0.98; $P = 0.03$).[542] According to the 2014 AHA/ACC NSTE-ACS Guideline, the following factors should influence the choice of PCI or CABG surgery for revascularization in patients with NSTE-ACS: the extent and complexity of CAD, the short-term risk and long-term durability of PCI, operative mortality, diabetes mellitus, chronic kidney disease, completeness of revascularization, left ventricular systolic dysfunction, previous CABG, and the ability of the patient to tolerate and comply with dual antiplatelet therapy.[1] Although the guidelines do not specify a preference for PCI or CABG surgery in patients with a non–Q-wave MI, periprocedural mortality was greater after CABG surgery than after PCI in the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial.[543] Thirty-day mortality was 11.6% after CABG surgery (11/95 patients) compared with 0% after PCI (0/98 patients).[543]

Long-Term Medical Therapy

Prescription of evidence-based medical therapy at the time of hospital discharge has a major impact on outcome in patients with ACS. Mukherjee and coworkers[544] calculated an appropriateness score based on the use of antiplatelet agents, β-blockers, ACE inhibitors, and lipid-lowering agents in patients with an indication for each class of drugs. The use of combination evidence-based medical therapies was independently associated with lower 6-month

mortality among a cohort of 1358 patients with ACS (55% NSTEMI, 30% UA, and 15% STEMI). The OR for death for prescription of all indicated medications versus none of the indicated medications was 0.10 (95% CI 0.03–0.42; $P < 0.0001$).

A comparison of the 2014 AHA/ACC and 2015 ESC guidelines for NSTE-ACS determined that the AHA/ACC document included a total of 168 recommendations, 100 class I, 35 class IIa, 17 class IIb, and 16 class III, whereas the ESC document included fewer total recommendations (95) and fewer class I recommendations (75).[545] The 2014 AHA/ACC and 2015 ESC guidelines for NSTE-ACS include multiple class I recommendations for long-term medical therapy (Box 29.8).[1,22] High-intensity statin therapy—that is, statin regimens that reduce LDL cholesterol by approximately 50%—should be initiated as early as possible and continued indefinitely in all patients with NSTE-ACS and no contraindications to its use. According to the ESC guideline, in patients with LDL cholesterol of 70 mg/dL or higher despite a maximally tolerated statin dose, further reduction in LDL cholesterol with ezetimibe should be considered (class IIa recommendation).[22]

An ACE inhibitor should be continued indefinitely for all patients with a, LVEF of 40% or less, or HF, hypertension, diabetes, or stable chronic kidney disease unless contraindicated. An ARB is an alternative for patients who do not tolerate ACE inhibitors. A mineralocorticoid receptor antagonist, preferably eplerenone, is recommended in patients with an LVEF or 35% or less and either HF or diabetes but no significant renal dysfunction or hyperkalemia (serum potassium <5.0 mmol/L; serum creatinine <2.5 mg/dL for men and <2.0 mg/dL for women).[22]

As discussed earlier, the class I recommendations for antiischemic therapy in patients with NSTE-ACS include the administration of a β-blocker within the first 24 hours for patients who do not have signs of HF, evidence of a low output state, increased risk for cardiogenic shock, or other relative contraindications to β-blockade.[1] In patients with concomitant NSTE-ACS, stabilized HF, and reduced left ventricular systolic function, treatment should include one of the three drugs proven to reduce mortality in HF: sustained-release metoprolol succinate, carvedilol, or bisoprolol. The ESC guideline recommends long-term β-blocker therapy in patients with an LVEF or 40% or less, but neither the 2014 AHA/ACC nor the 2015 ESC guidelines for NSTE-ACS provide a recommendation regarding the duration of treatment in patients without HF or impaired left ventricular systolic function.[1,22]

Aspirin should be continued indefinitely.[1] The maintenance dose should be 81 mg in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients. A $P2Y_{12}$ inhibitor should be continued for up to 12 months in all patients with NSTE-ACS without contraindications. The options include clopidogrel 75 mg daily or ticagrelor 90 mg twice daily in patients who are managed with an ischemia-guided strategy, and clopidogrel 75 mg daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg daily in patients who receive a stent (either bare metal or drug-eluting).

The optimal duration of DAPT is an area of active investigation and has been the subject of a systematic review and a guideline focused update by the ACC/AHA Task Force on Clinical Practice Guidelines.[546,547] The addition of clopidogrel to aspirin decreased the risk of the primary endpoint of cardiovascular death, MI, or stroke in patients with a history of MI who were enrolled in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (6.6% vs. 8.3%; HR 0.774; 95% CI 0.61–0.98; $P = 0.031$).[548] The DAPT study, a double-blind, placebo-controlled randomized trial, compared 30 months with 12 months of dual antiplatelet therapy (aspirin plus clopidogrel or prasugrel) after coronary stenting.[549] The study population included 3576 patients who had an MI at the time of enrollment (47% STEMI, 53% NSTEMI) and were randomly assigned 12 months after MI to receive aspirin plus placebo or aspirin plus continued thienopyridine. The rates of stent thrombosis and MI were lower among the patients randomly assigned to extended DAPT than among the patients assigned to aspirin alone. Long-term use of ticagrelor in patients with a prior MI was investigated in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.[550] Ticagrelor, administered

• BOX 29.8 Class I Recommendations for Long-Term Medical Therapy for Patients With NSTE-ACS

1. All patients should be given sublingual or spray nitroglycerin.
2. Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81–325 mg daily in all other patients.
3. Unless contraindicated, patients should be treated with a $P2Y1_{12}$ inhibitor as follows:
   For patients treated with an ischemia-guided strategy, clopidogrel 75 mg daily or ticagrelor 90 mg twice daily for up to 12 months
   For patients receiving a stent, clopidogrel 75 mg daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg daily for at least 12 months
4. β-Blockers are indicated for all patients recovering from UA/NSTEMI unless contraindicated. Treatment should begin within a few days of the event, if not initiated acutely, and should be continued indefinitely. Patients recovering from NSTE-ACS with moderate or severe LV failure should receive β-blocker therapy with a gradual titration scheme.
5. ACE inhibitors should be given and continued indefinitely for patients recovering from NSTE-ACS with heart failure, LV dysfunction (LVEF < 0.4), hypertension, or diabetes mellitus, unless contraindicated.
6. An angiotensin receptor blocker should be prescribed at discharge to those NSTE-ACS patients who are intolerant of an ACE inhibitor and who have either clinical or radiologic signs of heart failure and LVEF <0.4.
7. Long-term aldosterone receptor blockade should be prescribed for NSTE-ACS patients without significant renal dysfunction (estimated creatinine clearance should be >30 mL/min) or hyperkalemia (potassium should be ≤5 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have an LVEF ≤0.4, and have either diabetes mellitus or symptomatic heart failure.
8. The following lipid recommendations are beneficial:
   Lipid management should include assessment of a fasting lipid profile for all patients, within 24 hours of hospitalization.
   High-intensity statin therapy, in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-NSTE-ACS patients, including postrevascularization patients.
   For hospitalized patients, lipid-lowering medications should be initiated before discharge.

ACE, *Angiotensin-converting enzyme;* ACS, *acute coronary syndrome;* LDL-C, *low-density lipoprotein cholesterol;* LV, *left ventricular;* LVEF, *left ventricular ejection fraction;* NSTE-ACS, *non–ST-segment elevation acute coronary syndrome;* NSTEMI, *non–ST-segment elevation myocardial infarction;* UA, *unstable angina;*

Modified slightly from Amsterdam EZ, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. *2014; 64:e139–e228.*

in a dose of either 60 mg twice daily or 90 mg twice daily, reduced the composite of cardiovascular death, MI, or stroke in patients who had a STEMI or NSTEMI 1 to 3 years earlier.[550] A meta-analysis that included the CHARISMA and PEGASUS-TIMI 54 data and four additional trials was performed to compare long-term DAPT with aspirin alone in patients with a history of prior MI.[551] A total of 33,435 patients were followed for a mean of 31 months during treatment with aspirin alone or DAPT with aspirin plus clopidogrel, prasugrel, or ticagrelor. Extended DAPT for more than 1 year after an MI resulted in a 22% RR reduction and 1.1% absolute risk reduction in major adverse cardiovascular events, and significant reductions of cardiovascular death (2.3% vs. 2.6%; RR 0.85; 95% CI 0.74–0.98; $P = 0.03$), MI, stroke, and stent thrombosis. Although there was an increased risk of major bleeding (1.85% vs. 1.09%; RR 1.73; 95% CI 1.19–2.50; $P = 0.004$), intracranial hemorrhage and fatal bleeding events were infrequent and were not significantly different between extended DAPT and aspirin alone. According to the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease, in patients with ACS who are treated with either medical therapy alone or PCI, continuation of DAPT for longer than 12 months may be reasonable if DAPT has been tolerated without bleeding complications and there is not a high bleeding risk (class IIb recommendation).[547] In patients with ACS who are treated with DAPT after DES implantation, discontinuation of $P2Y_{12}$ therapy after 6 months may be reasonable in patients who develop a high risk of bleeding, are at high risk of severe bleeding, or develop significant overt bleeding (class IIb recommendation).[547]

Key Points

- Patients with suspected STEMI should have an ECG performed and interpreted within 10 minutes of presentation, and serial ECGs should be performed at intervals of 5 to 10 minutes in patients with a nondiagnostic initial ECG and clinical findings strongly suggestive of STEMI. Right-sided lead tracings should be obtained to screen for right ventricular MI in patients with inferior STEMI.
- Fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact.
- Fibrinolytic therapy should be initiated within 30 minutes of presentation.
- Intracranial hemorrhage should be ruled out in any patient with a change in neurologic status during or after fibrinolytic therapy.
- Nitrates are indicated for relief of ischemic discomfort in patients with STEMI, but large clinical trials did not demonstrate a reduction in mortality among patients who received nitroglycerin over prolonged periods after acute MI.
- Aspirin has been shown to reduce mortality in patients with acute MI or UA. Patients with STEMI should receive 162 to 325 mg of non–enteric-coated aspirin, and the aspirin tablets should be chewed.
- The addition of clopidogrel to aspirin has been shown to improve angiographic and clinical outcomes in patients with STEMI or ACS without ST-segment elevation.
- A meta-analysis of 23 randomized trials concluded that the rates of death over the short-term, nonfatal reinfarction, stroke, and the combined endpoint of all three were lower for primary coronary intervention than for fibrinolytic therapy in patients with STEMI.
- Balloon inflation should occur within 90 minutes of presentation in patients with STEMI who undergo primary coronary intervention.
- There are three class I indications for primary PCI in patients with STEMI who present initially to a PCI-capable hospital: (1) patients with ischemic symptoms of less than 12 hours' duration; (2) patients with ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from first medical contact; (3) patients with cardiogenic shock or acute severe HF, irrespective of time delay from MI onset.
- In patients with acute MI, the early administration of β-blockers reduces the rate of reinfarction and chronic administration improves long-term survival.
- An ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF less than 40% in the absence of hypotension.
- An angiotensin receptor blocker should be administered to patients with STEMI who are intolerant of ACE inhibitors and have either HF or an LVEF less than 40%.
- Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF of 40% or less, and have either diabetes or symptomatic HF.
- Diltiazem and verapamil are contraindicated in patients with STEMI and associated systolic left ventricular dysfunction and HF.
- High-intensity statin therapy is indicated at the time of hospital discharge in all patients with ACS.
- Patients with NSTE-ACS should be treated with both an anticoagulant (UFH, enoxaparin, or fondaparinux) and at least dual antiplatelet therapy with aspirin and an antagonist of the platelet $P2Y_{12}$ receptor (clopidogrel, prasugrel, or ticagrelor).
- An early invasive strategy is favored in patients with NSTE-ACS who have any of the following high-risk indicators: recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy; early postinfarction angina; refractory angina; signs or symptoms of HF or new or worsening MR; hemodynamic instability; temporal change in troponin; new or presumably new ST-segment depression; LVEF less than 40%; sustained ventricular tachycardia; ventricular fibrillation; diabetes mellitus; renal insufficiency (glomerular filtration rate <60 mL/min per 1.73 meters squared); PCI within the past 6 months; prior CABG surgery; or a high risk score (TIMI ≥2, GRACE ≥109).

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Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 ACC/AHA guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *J Am Coll Cardiol*. 2016;68:1082–1115.

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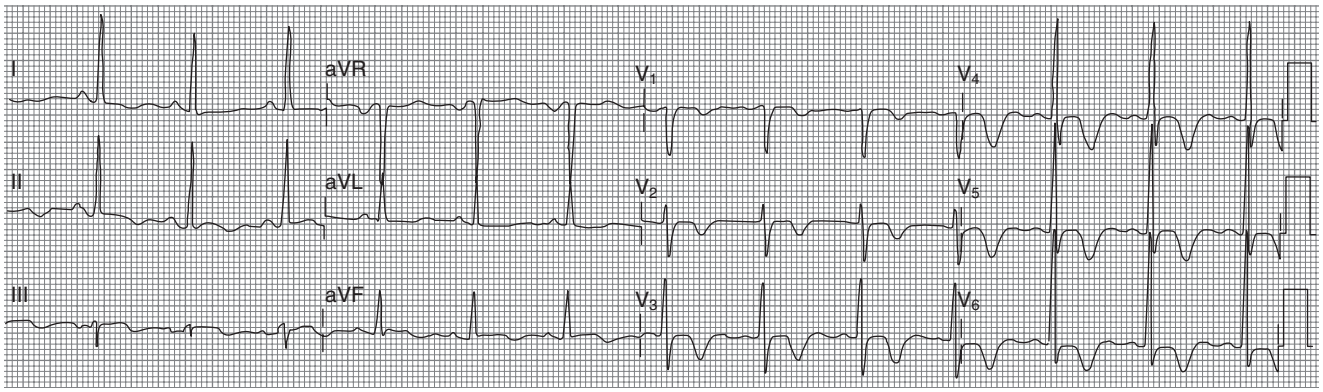
Review Questions

1. A 56-year-old woman presents to the emergency department (ED) 3 hours after the onset of severe dyspnea. The following electrocardiogram (ECG) was obtained at 1:55:

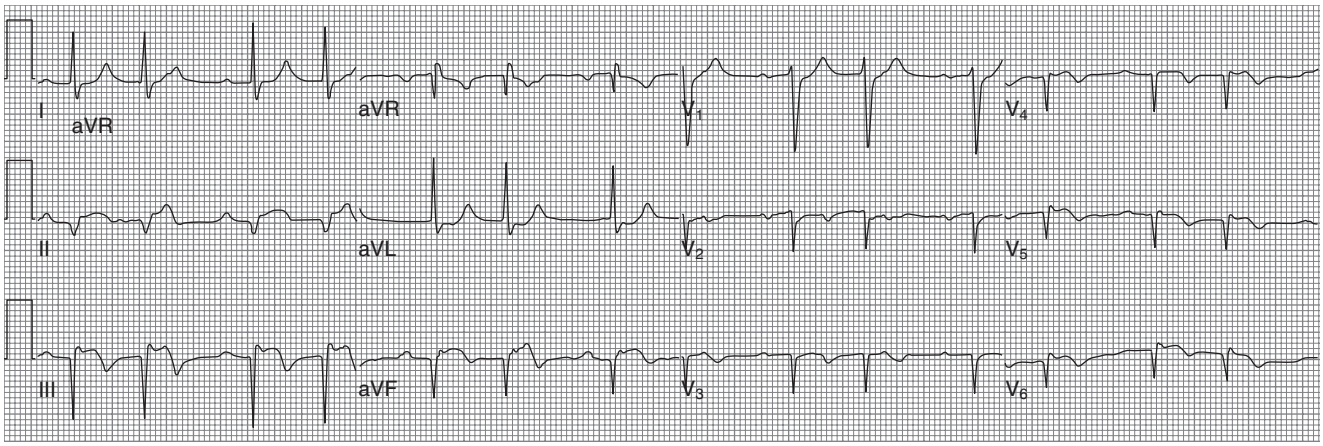


Which of the following should be recommended?

a. Repeat the ECG in 15 to 30 minutes
b. Order an immediate echocardiogram
c. Schedule an exercise echocardiogram
d. Schedule a dipyridamole nuclear stress test
e. Order an immediate computed tomography (CT) scan of the chest

Answer: a. Although the ECG is not diagnostic of an ST-segment elevation myocardial infarction (STEMI), it shows deep T-wave inversions in the precordial leads consistent with myocardial ischemia. It is common for patients to develop ST-segment elevation on subsequent ECGs. Therefore the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend repeating an ECG within 15 to 30 minutes in patients with an acute coronary syndrome if the initial ECG is nondiagnostic.[21]

2. A 75-year-old man with a history of a coronary artery stent and exertional angina has been admitted to the intensive care unit (ICU) after undergoing an open surgical repair of an abdominal aortic aneurysm. His aspirin and clopidogrel were discontinued 10 days before surgery. On the second postoperative day he complains of chest pain, his serum troponin is elevated, and the following ECG is obtained:

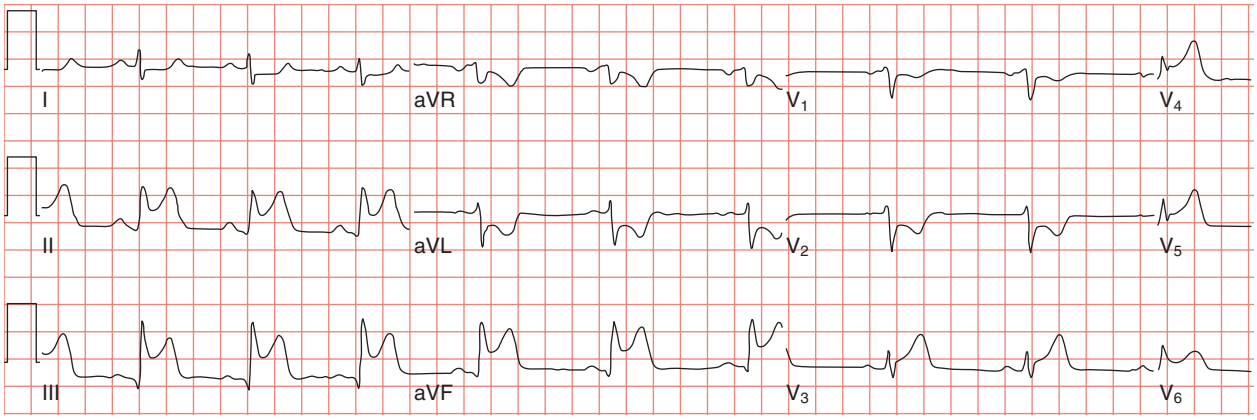


Which of the following management strategies is most appropriate?

a. His age is a contraindication to reperfusion therapy.
b. The Q waves are a contraindication to reperfusion therapy.
c. A fibrinolytic drug should be administered because his aortic aneurysm repair is a contraindication to cardiac catheterization.
d. Cardiac catheterization should be performed because his aortic aneurysm repair is a contraindication to fibrinolytic therapy.

Answer: d. The patient's age is not a contraindication to reperfusion therapy. Q waves are present on the initial ECG in approximately 50% of patients with an acute STEMI, and Q waves are not a contraindication to reperfusion therapy. The patient's recent surgery is a contraindication to fibrinolytic therapy, but it is not a contraindication to cardiac catheterization, which can be performed via the radial artery.

3. A 60-year-old man presents to the ED within 1 hour of the onset of chest pain. The following ECG was obtained:



Which of the following treatments is most appropriate?

a. A glycoprotein IIb/IIIa inhibitor while awaiting the serum troponin result
b. Sublingual nifedipine for treatment of coronary artery spasm
c. Aspirin, clopidogrel, and an intravenous fibrinolytic drug (tissue plasminogen activator, reteplase, or tenecteplase)
d. Transfer of the patient to a hospital 2 hours away for cardiac catheterization

Answer: c. Reperfusion therapy is indicated because the ECG shows an acute inferior STEMI. Transfer to another hospital for cardiac catheterization would be appropriate if percutaneous coronary intervention can be performed within 2 hours of arrival at the initial ED or if the patient has a contraindication to fibrinolytic therapy. According to the 2013 ACC/AHA STEMI Guideline, a fibrinolytic agent should be administered when the anticipated first medical contact to device time exceeds 120 minutes (see O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425). Therefore if this patient does not have a contraindication to fibrinolytic therapy, he should be treated with a fibrinolytic agent along with aspirin and clopidogrel. Treatment should not be delayed to obtain a serum troponin result. Sublingual nifedipine is contraindicated in a patient with a STEMI because of hypotension and reflex sympathetic activation with tachycardia.

4. In the Second International Study of Infarct Survival, after follow-up for 5 weeks, vascular death occurred in 804 of the 8587 (9.2%) patients who were randomly assigned to receive aspirin compared with 1016 of the 8600 patients who were randomly assigned to receive placebo (11.8%). Therefore how many patients with suspected myocardial infarction (MI) would need to be treated with aspirin to prevent one vascular death after 5 weeks?

a. 10
b. 20
c. 38
d. 50
e. 100

Answer: c. The number needed to treat = 1/(absolute risk reduction) = 1/(11.8% − 9.2%) = 1/2.6% = 1/0.026 = 38.46.

5. A 65-year-old woman is transferred to the ICU after having chest pain during hemodialysis. She has long-standing hypertension and chronic kidney disease, and she started hemodialysis recently. Her antihypertensive medications are clonidine, diltiazem, and hydralazine. Her blood pressure is 180/100 mm Hg. She has bibasilar rales and an S_3 gallop. Her serum troponin is mildly elevated. Her chest radiograph shows pulmonary congestion. The patient does not want to undergo invasive diagnostic studies. Which of the following medications is most appropriate?

a. Unfractionated heparin
b. Enoxaparin
c. Fondaparinux
d. Eptifibatide

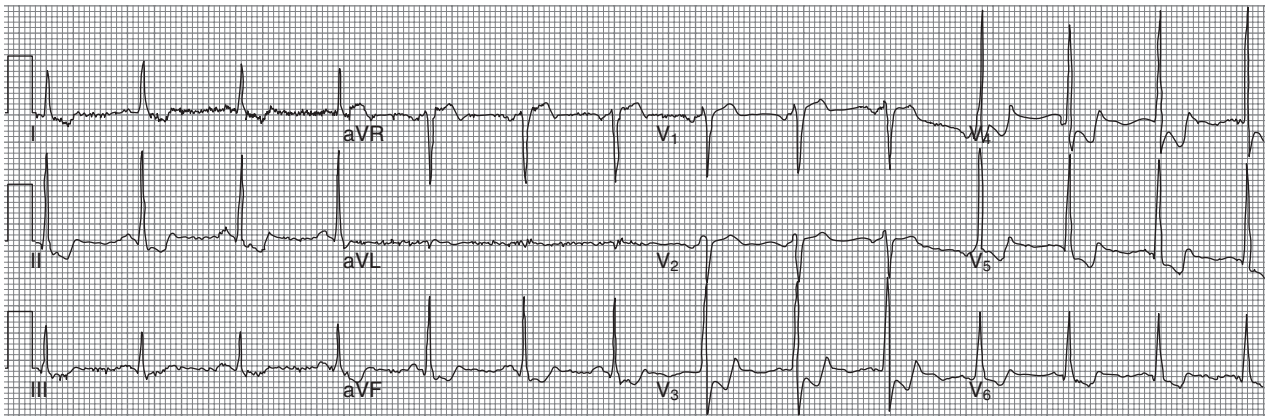
Answer: a. Enoxaparin, fondaparinux, and eptifibatide are contraindicated in patients treated with hemodialysis.

6. A 65-year-old woman is transferred to the ICU after having chest pain during hemodialysis. She has long-standing hypertension and chronic kidney disease, and she started hemodialysis recently. Her antihypertensive medications are clonidine, diltiazem, and hydralazine. Her blood pressure is 180/100 mm Hg. She has bibasilar rales and an S_3 gallop. Her serum troponin is mildly elevated. The patient does not want to undergo invasive diagnostic studies. Which of the following orders is most appropriate:

a. Aspirin 325 mg daily
b. Aspirin 325 mg daily and prasugrel 10 mg daily
c. Aspirin 325 mg daily and clopidogrel 75 mg daily
d. Aspirin 325 mg daily and ticagrelor 90 mg twice daily

Answer: c. Dual antiplatelet therapy with aspirin 325 mg daily and clopidogrel 75 mg daily is the correct therapy. Aspirin monotherapy is incorrect. Prasugrel is indicated only in patients who undergo PCI. Patients treated with ticagrelor should receive an aspirin dose <100 mg daily.

7. An 80-year-old man with diabetes presented to the ED with chest pain. He had a transient ischemic attack 1 year ago, and 6 months ago he was treated for upper gastrointestinal bleeding owing to gastritis. Results of his physical examination are normal. This ECG was obtained during chest pain:



Which of the following would you recommend:
a. A resting sestamibi scan
b. A nuclear stress test
c. An intravenous fibrinolytic drug
d. Cardiac catheterization
Answer: d. The patient's ECG shows diffuse ST-segment depressions consistent with myocardial ischemia. Therefore a cardiac catheterization is indicated. A fibrinolytic drug is not indicated because the patient's ECG does not show a STEMI or left bundle branch block. A stress test is contraindicated. A resting sestamibi scan would not be useful.

8. An 80-year-old man presented to the ED with chest pain. He had a transient ischemic attack (TIA) 1 year ago, and 6 months ago he was treated for upper gastrointestinal bleeding owing to gastritis. Coronary angiography showed a 90% stenosis of the left anterior descending coronary artery that was treated with a drug-eluting stent. Which of the following medication orders is most appropriate for this patient?
a. Aspirin 81 mg daily and omeprazole 40 mg daily
b. Aspirin 81 mg daily, prasugrel 10 mg daily, and omeprazole 40 mg daily
c. Aspirin 81 mg daily, ticagrelor 90 mg twice daily, and omeprazole 40 mg daily
d. Aspirin 325 mg daily, ticagrelor 90 mg twice daily, and omeprazole 40 mg daily
Answer: c. The patient received a drug-eluting stent and should be treated with dual antiplatelet therapy. He should also receive a proton-pump inhibitor because of his history of gastrointestinal bleeding. Prasugrel is contraindicated because of the patient's age and history of a TIA. Patients treated with ticagrelor should receive an aspirin dose less than 100 mg daily.

30

Valvular Heart Disease in Critical Care

ZOLTAN G. TURI, TILAK K.R. PASALA, AND CARLOS E. RUIZ

CHAPTER OUTLINE

Aortic Stenosis
- Pathophysiology
- Diagnosis
- Low-Gradient Aortic Stenosis
- Therapy

Aortic Insufficiency
- Pathophysiology
- Diagnosis
- Therapy

Mixed Aortic Valve Disease

Mitral Regurgitation
- Pathophysiology
- Diagnosis
- Therapy

Hypertrophic Obstructive Cardiomyopathy
- Pathophysiology
- Diagnosis
- Therapy

Mitral Valve Stenosis
- Pathophysiology
- Diagnosis
- Therapy

Prosthetic Heart Valves
- Pathophysiology
- Diagnosis
- Therapy

The profile of valvular heart disease (VHD) in the critical care setting has evolved substantially over the past several decades.[1] Aortic stenosis (AS), mitral regurgitation (MR), and aortic insufficiency (AI) are the most common and significant valve diseases seen in the intensive care unit, but hypertrophic cardiomyopathy (HCM) and mitral stenosis (MS) remain important entities as well, as are prosthetic valve dysfunction and paravalvular leak (PVL). Patients with VHD in critical care units typically fall into one of two categories: (1) those who are critically ill because of valvular dysfunction or (2) those in whom VHD represents an important comorbidity. Many patients present without prior diagnosis of VHD,[2] either because the progression has been insidious and the disease not previously diagnosed or because the onset has been acute. Improvements in technology and the ubiquitous availability of echocardiography have improved diagnosis, whereas clinician skills at integrating physical examination and other data have generally atrophied during this time frame.[3]

Diagnosis of VHD in critical care units is challenging, with lack of a quiet environment for auscultation; comorbidities that affect physical findings; and stress, infection, or metabolic abnormalities that result in tachycardia and shorter intervals for evaluation of heart sounds. The progression of VHD was redefined by the 2014 American College of Cardiology/American Heart Association (AHA/ACC) guidelines,[4] which abandoned the previous "mild," "moderate," and "severe" categories for a classification that describes four stages (A to D) that represent a progression from early anatomic findings (A) through progressive physiologic abnormalities (B) and then severe, clinically and physiologically important disease that is either asymptomatic (C) or symptomatic (D). In most cases, intervention is reserved primarily for patients with severe VHD Table 30.1.

Aortic Stenosis

With the aging of the population, AS has moved to the forefront in frequency of VHD encountered in the elderly. The prevalence is surprisingly high; in patients 85 years of age, more than 8% of a random general population survey had Doppler-derived aortic valve area estimates of 1 cm^2 or less (Fig. 30.1).[5] Thus AS should be considered in the differential diagnosis of every older critical care patient with hemodynamic instability. The possibility of AS should be dismissed only after considering physical examination and electrocardiographic and, when applicable, echocardiographic and invasive findings, all of which have potential limitations in achieving accurate diagnosis as discussed subsequently.[6]

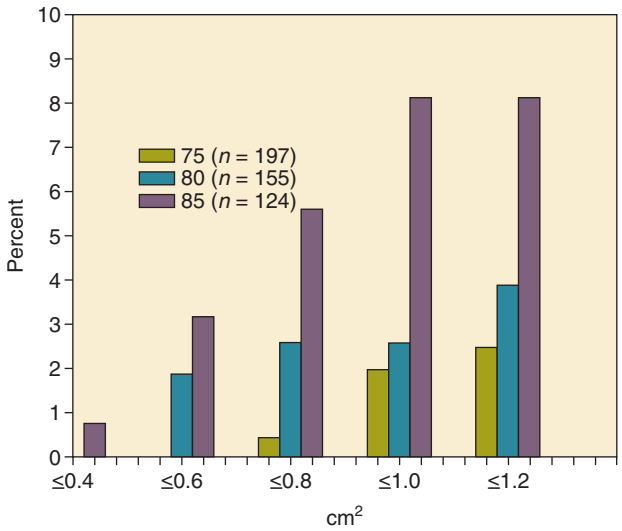
Pathophysiology

AS represents a continuum, from hemodynamically insignificant congenital and atherosclerotic disease to end-stage decompensation secondary to severe valvular obstruction. The congenital pathway is typically secondary to a bicuspid aortic valve, the most common congenital cardiac anomaly if mitral valve prolapse is excluded, occurring in approximately 1.5% of the population.[7] Bicuspid aortic valve disease is part of a larger aortopathy[8] syndrome with significant implications for the natural course of aortic valve disease.[9] The most common acquired anomaly is typically referred to as *degenerative disease,* an atherosclerotic process that represents a continuum from aortic valve sclerosis, which is not associated with a hemodynamically significant gradient, to a densely calcified aortic

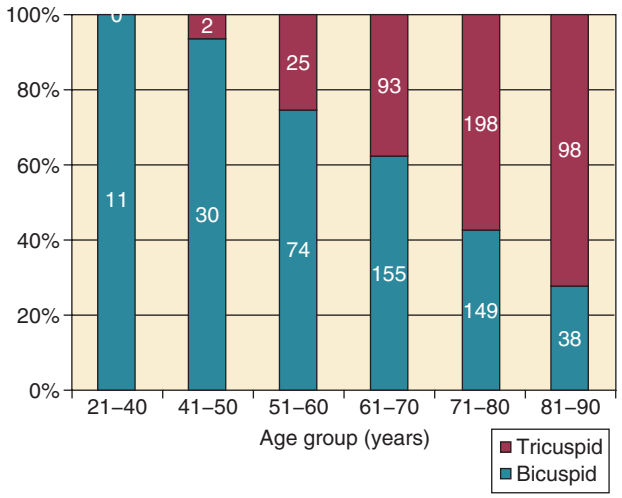
TABLE 30.1 Stages of Progression of Valvular Heart Disease

Stage	Definition	Description
A	At risk	Patients with risk factors for the development of VHD
B	Progressive	Patients with progressive VHD (mild to moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who reached the criteria for severe VHD C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patients who have severe VHD with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

VHD, Valvular heart disease.
From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:2440–2492.



• **Fig. 30.1** Doppler-derived estimates of aortic valve area at ages 75, 80, and 85 years from a randomized sampling of individuals in the general population. Bars represent percentages of individuals with valve areas at or below the thresholds on the abscissa (in square centimeters). (Data from Lindroos M, Kupari M, Heikkila J, et al. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993;21:1220–1225.)



• **Fig. 30.2** Distribution by age group of bicuspid versus tricuspid aortic valves in patients undergoing aortic valve replacement for aortic stenosis. (Modified from Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation.* 2005;111:920–925.)

valve with severe outflow obstruction. Although the etiology of aortic valve stenosis in patients undergoing aortic valve replacement (AVR) has shifted to calcific tricuspid aortic valve disease from bicuspid and rheumatic disease, this remains an age-related phenomenon, with a predominance of bicuspid aortic valve disease in patients younger than 70 years of age (Fig. 30.2).[10]

Aortic Valve Sclerosis

Aortic valve *sclerosis* is an important disease entity, although usually not because of hemodynamic considerations. Defined as calcification and thickening of the aortic valve without significant outflow obstruction (gradient <20–25 mm Hg), it is present in nearly 30% of the population older than age 65 and nearly 50% by age 85[11] and is associated with a 50% increase in 5-year cardiovascular mortality rate.[12] Its incidence is as high as 15-fold greater than aortic valve stenosis; the two diagnoses can be differentiated from one another by hemodynamics and physical examination findings discussed subsequently. In keeping with the primary atherosclerotic nature of aortic sclerosis, it is associated with increasing age, male gender, hypertension, smoking, elevated low-density lipoprotein and lipoprotein(a) levels, and diabetes.[11] The primary importance of aortic valve sclerosis is that it provides a window on the overall presence of vascular disease, in particular coronary artery disease (CAD).[13] Thus there should be a high index of suspicion of vascular disease in any patient with aortic valve sclerosis managed in the critical care setting.

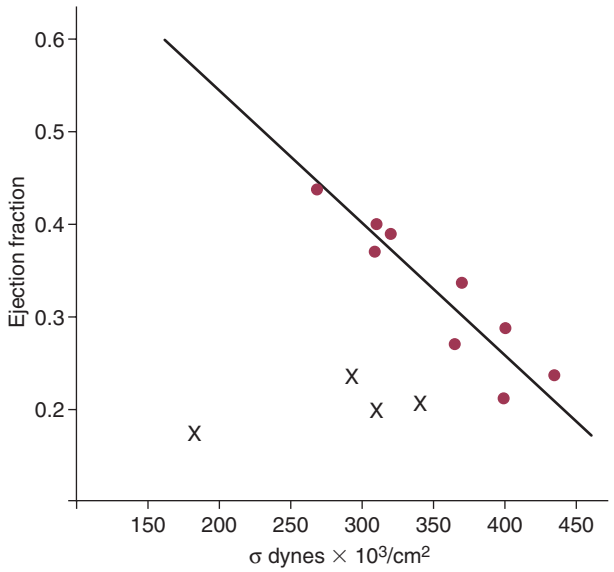
Patients with aortic sclerosis do progress to aortic valve stenosis; a study of more than 2000 patients with valve thickening showed progression to severe AS in 2.5% over an average time interval of 7 years,[14] with a more recent meta-analysis of 22 studies showing a nearly 2% annual rate of progression to severe AS and a 69% increased risk of cardiovascular mortality.[15] The fact that so-called degenerative disease of the aortic valve is absent in nearly half of octogenarians is also important to consider because it implies that

it is not only aging but other factors that result in leaflet thickening, calcification, and stenosis. In the Helsinki Aging Study from which data are reflected in Fig. 30.1, additional analysis demonstrated that not only age but also hypertension and low body mass index independently predicted calcification of the aortic valve, and age and serum ionized calcium were independently associated with valvular stenosis.[16] In general, the process of sclerosis and then stenosis of the aortic valve appears, like atherosclerosis in general, to be an active inflammatory process, with deposition of lipoproteins, local inflammation with T-lymphocyte and macrophage infiltration, fibroblast proliferation, and eventually osteoblast and bone formation.[17] Similar to other vascular disease, endothelial disruption likely leads to the initial lipid deposition in the leaflet tissues. The areas of early focal plaque formation appear at the loci of greatest stress: on the aortic side of the leaflets at the flexion points. Because bicuspid valves have greater mechanical stress, the average age at presentation of patients with bicuspid aortic valve stenosis is significantly lower than in the tricuspid aortic valve stenosis that is typically seen in an elderly population.[18]

An important element in understanding calcific AS is the relatively lower contribution of commissural fusion to the overall obstruction; unlike rheumatic mitral valve stenosis, in which fusion of the commissures is the primary cause of obstructive disease, lack of mobility of the aortic valve leaflets is the primary cause of obstruction in AS. Rheumatic AS is associated with commissural fusion but is now a rare finding, even in countries where rheumatic heart disease is prevalent, and is usually associated with mitral valve involvement and typically AI as well. More obscure causes, such as unicuspid and quadricuspid aortic valve disease, are uncommon, although presentation can be delayed to adulthood. In the case of unicuspid aortic valves there is a strong association with AS,[19] whereas with quadricuspid aortic valves there is a high incidence of significant aortic insufficiency.[20]

Normal aortic valve area ranges from 3 to 4 cm^2. Significant resistance to outflow does not occur until the valve orifice is reduced more than 50%. Based on the simple hydraulic principle of Poiseuille's law, a 50% reduction in valve diameter results in approximately a 16-fold increase in resistance. In practice, as the resistance to outflow rises, the left ventricle is subject to pressure overload, resulting in compensatory hypertrophy. This in turn normalizes wall stress because the latter is proportional to chamber diameter times pressure divided by wall thickness (the LaPlace principle). The degree of wall thickness is variable: In patients with inadequate hypertrophic response, wall stress is inordinately high and there is early dilation and dysfunction.[21] In patients with a profound hypertrophic response disproportionate to valvular resistance, wall stress actually falls below normal and ejection fraction (EF) becomes supranormal,[22] a phenomenon that appears to be more common in women with AS. The EF for any degree of wall stress is predictable,[21] and patients who have disproportionately poor ejection phase indices (afterload mismatch) typically manifest left ventricular (LV) dysfunction beyond the depression that would be associated with high wall stress (Fig. 30.3),[23] a phenomenon described under low-gradient, low-output AS that follows.

LV hypertrophy, although it reduces wall stress, has several features that may be deleterious. With progressive hypertrophy, diastolic pressures may rise as LV compliance decreases, resulting in increased LV filling pressures. In addition, the myocardial supply-demand relationship is deleteriously affected by hypertrophy in this setting. With increased wall stress and increased wall mass, myocardial oxygen demand is increased; at the same time coronary flow reserve is decreased in AS,[24] and in later stages of the disease

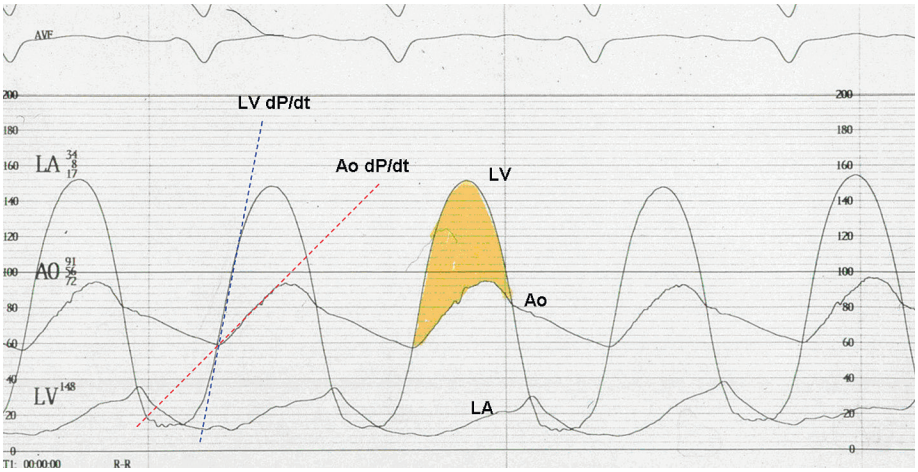


• **Fig. 30.3** The relationship between ejection fraction and wall stress in patients with aortic stenosis. The patients (each represented by an "X") whose ejection fraction was disproportionately lower than the regression line had a poor overall outcome. In these patients ejection phase indices were depressed despite a low transvalvular gradient, a phenomenon suggesting intrinsic contractile dysfunction. (From Carabello BA, Green LH, Grossman W, et al. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. *Circulation.* 1980;62:42–48.)

diastolic perfusion pressure is lowered. Because of abnormal flow reserve, conventional testing for ischemia in the setting of significant aortic valve stenosis (fractional flow reserve) has less specificity to identify the presence or absence of hemodynamically significant concomitant CAD.[25]

Other features associated with AS that are important in the critical care setting include abnormal platelet function and decreased levels of von Willebrand factor,[26] with associated bleeding risk that improves with AVR. Another associated cause of bleeding is gastrointestinal angiodysplasia (Heyde syndrome) associated with aortic valve stenosis,[27] possibly exacerbated by the concomitant presence of von Willebrand syndrome.

The progression of AS is highly variable, but with the onset of moderately severe disease, the estimated mean decrease in valve area is on the order of 0.1 cm^2/yr.[28] It is important to note that the rate of progression is quite variable in individual patients, with some demonstrating accelerating progression while others remain stable for years. Certain demographics and noninvasive findings appear to predict more rapid progression, including age and severity of valve calcification.[29] The issue of progression is particularly important in patients who are asymptomatic of the disease, because AVR before it is necessary is undesirable but must be weighed against the risk of sudden death. The latter has been investigated in a number of longitudinal studies and is rare if patients' conditions are followed prospectively. The patients who are most likely to require early intervention are those with peak Doppler systolic velocities greater than 4 m/s or who have a rapid increase in serial transvalvular Doppler velocity measurements.[28,29] This threshold has been confirmed by other series.[30] Once patients become symptomatic, with a classic triad of heart failure, angina, or syncope, hemodynamic deterioration can be rapid with significant associated mortality risk.[31]



• **Fig. 30.4** Left ventricular *(LV)*, aortic *(Ao),* and left atrial *(LA)* pressure on 200-mm Hg scale, 100-mm/s paper speed. The aortic valve gradient is filled in *yellow.* The dramatic difference in the slope of left ventricular (*LV dP/dt, dashed blue line*) and aortic pressure upstroke *(Ao dP/dt, dashed red line*) and the low pulse pressure (≈30 mm Hg) in this patient with classic severe aortic valve stenosis is demonstrated.

An important consideration relates to patients with moderate AS (AVA 1.0–1.5 cm^2) and LV systolic dysfunction (LV ejection fraction [LVEF] <50%) who are symptomatic (New York Heart Association [NYHA] class III or IV); these patients appear to be at high risk of all-cause death and hospitalization for heart failure.[32] Whether AVR in this group improves clinical outcomes is the subject of the ongoing Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure trial (TAVR UNLOAD) comparing transcatheter aortic valve replacement (TAVR) to optimal heart failure therapy.

Diagnosis

Physical Examination

The hallmarks of the physical examination relate to the contour of the aortic pressure upstroke, with a low volume and delayed carotid upstroke (pulsus parvus et tardus), a late peaking systolic ejection murmur, and a diminished or absent aortic second sound. Fig. 30.4 demonstrates the hemodynamics that manifest in an abnormal carotid pulse contour; unlike the brisk upstroke of LV pressure over time (dP/dt), the aortic pressure is slow to rise and of significantly lower volume. An ejection click may be present in young patients with congenital AS, but with increasing calcification of the valve, mobility decreases to a point at which an ejection click becomes unlikely. The aortic component of the second heart sound, reflecting deceleration and closure of the aortic valve, is diminished or absent in severe AS where the thickened aortic valve leaflets are poorly mobile, have little deceleration, and drift rather than snap shut. In contrast, if pulmonary hypertension is present, the P2 component may be exaggerated and can potentially mask the diminished A2. The murmur of AS is characteristically a crescendo-decrescendo murmur that is late peaking, consistent with the timing of the peak gradient as seen in Fig. 30.4, and is typically best heard over the right upper sternum and clavicle. It reflects the high-velocity systolic jet directed into the ascending aorta. In the critical care setting, where patients have a low output state and end-stage AS, the murmur may be relatively quiet or absent altogether. A second component, described by Gallavardin as a musical component, is best heard at the left lower sternal border. The latter confounds diagnosis because the murmur is suggestive of mitral regurgitation (MR), but in its true form it is purely secondary to aortic valve stenosis. Because handgrip raises resistance to LV ejection, the murmur should decrease if it is a true Gallavardin phenomenon, whereas when it is secondary to MR, it should increase.[33]

Unfortunately, none of these findings has sufficiently high sensitivity or specificity for AS or for differentiating moderate from severe disease.[3] Many patients with AS, particularly the elderly with stiff noncompliant vessels, have a wide pulse pressure even with declining cardiac output (CO) and may have systolic hypertension. Hypotension may not be seen until late stages of the disease. The loudness of the murmur, which correlates to some degree with severity, is also not specific because body habitus and a variety of other factors affect the acoustics transmitted across the chest. Most importantly, in severe AS, as the CO drops, the gradient generated decreases as well. In this setting the murmur may be quite soft, although sometimes still high-pitched because of the high velocity across a tight constriction. A useful means of differentiating aortic sclerosis from stenosis is that in the former the systolic ejection murmur heard over the right sternum is typically mid-peaking and mild to moderate in intensity, and it features a well-preserved aortic second heart sound. Although the physical findings described are variable, the presence of a preserved aortic second heart sound tends to exclude severe calcific AS.[34]

Noninvasive Evaluation

In contrast to the physical examination, echocardiographic techniques have progressively improved over the past several decades and availability in the critical care setting in industrialized nations is ubiquitous. The characteristic echocardiographic features of AS are decreased valve leaflet mobility, calcification in all except congenital AS in adolescents and young adults, and an augmented Doppler velocity that generally allows accurate estimation of the gradient. In congenital bicuspid AS in young adults, when commissural fusion is dominant, a characteristic doming pattern is seen, but this disappears with progressive valve calcification. The severity of calcification correlates with extent of obstruction by middle age, and typically Doppler signal velocity with peak and mean pressure gradient and valve area by continuity equation provide an accurate overall assessment. However, the gradient is

TABLE 30.2 Stages of Valvular Aortic Stenosis

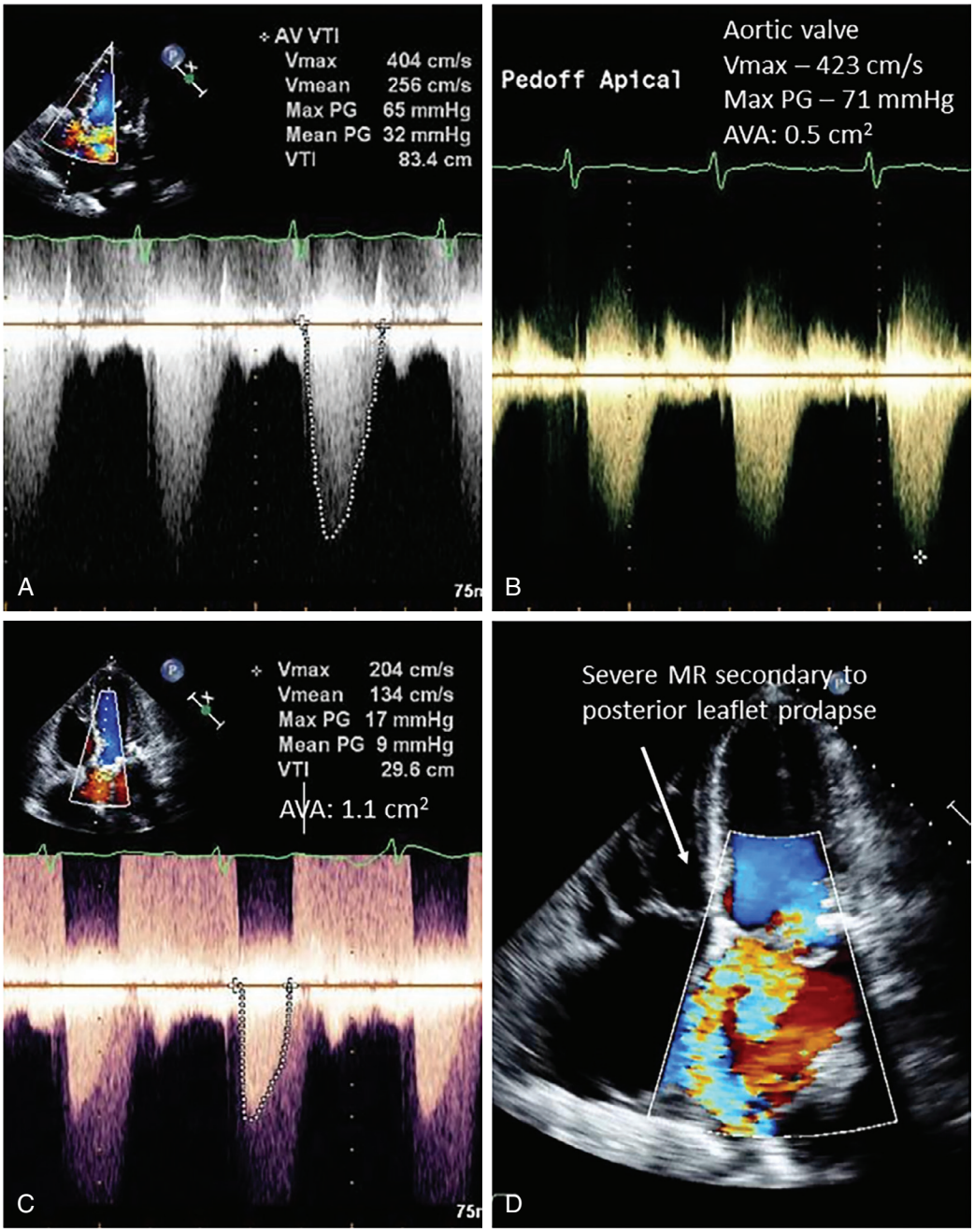
Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
C: Asymptomatic Severe AS					
C1	• Asymptomatic severe AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) • Very severe AS is an aortic V_{max} ≥5 m/s, or mean ≤P ≥60 mm Hg	• LV diastolic dysfunction • Mild LV hypertrophy • Normal LVEF	• None—exercise testing is reasonable to confirm symptom status
C2	• Asymptomatic severe AS with LV dysfunction	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg • AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2)	• LVEF <50%	• None
D: Symptomatic Severe AS					
D1	• Symptomatic severe high-gradient AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic V_{max} ≥4 m/s, or mean ΔP ≥40 mm Hg • AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2), but may be larger with mixed AS/AR	• LV diastolic dysfunction • LV hypertrophy • Pulmonary hypertension may be present	• Exertional dyspnea or decreased exercise tolerance • Exertional angina • Exertional syncope or presyncope
D2	• Symptomatic severe low-flow, low-gradient AS with reduced LVEF	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg • Dobutamine stress echo shows AVA ≤1 cm^2 with V_{max} ≥4 m/s at any flow rate	• LV diastolic dysfunction • LV hypertrophy • LVEF <50%	• HF • Angina • Syncope or presyncope
D3	• Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	• Severe leaflet calcification with severely reduced leaflet motion	• AVA ≤1 cm^2 with aortic V_{max} <4 m/s, or mean ΔP <40 mm Hg • Indexed AVA ≤0.6 cm^2/m_2 and stroke volume index <35 mL/m^2 • Measured when the patient is normotensive (systolic BP <140 mm Hg)	• Increased LV relative wall thickness • Small LV chamber with low stroke volume • Restrictive diastolic filling • LVEF ≥50%	• HF • Angina • Syncope or presyncope

AR, Aortic regurgitation; *AS,* aortic stenosis; *AVA,* aortic valve area; *AVAi,* aortic valve area indexed to body surface are; *BP,* blood pressure; *HF,* heart failure; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *ΔP,* pressure gradient; V_{max}, maximum aortic velocity.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:2440–2492.

highly dependent on flow across the valve, and in low-output states the gradient may result in underestimation of severity of disease; in high-output states such as in patients with augmented CO caused by inotropic stimulation, endogenous high catecholamine states, and sepsis, the gradient may be disproportionately higher than the severity of stenosis would suggest. The latest AHA/ACC guidelines[4] describe the threshold for severe AS as antegrade jet velocity greater than 4 m/s, mean gradient greater than 40 mm Hg, and aortic valve area less than 1 cm^2 (valve area index less than 0.6 cm^2) with the caveat that the gradient and jet velocity depend on the overall transvalvular flow (Table 30.2). Importantly, antegrade flow across the aortic valve does not equal CO in patients with confounding conditions, including aortic insufficiency; thus, for example, a patient with mild to moderate AS and moderate AI may have a transvalvular gradient suggestive of severe AS. Finally, although many practitioners do not index the valve area, it is important to appreciate that in a patient with a large body surface area (BSA), disease that might be considered moderate in smaller patients may be functionally severe.

Several caveats need to be considered before acceptance of noninvasive data in the critical care setting. Inadequate acoustic windows in some patients and difficulty in positioning patients supported by respirators and with multiple lines in place do limit echocardiographic imaging. Technical errors in recording and interpretation result in significant misdiagnosis; errors in recording angle, inadvertent imaging of MR jets instead of aortic outflow (Fig. 30.5), assessing proximal velocity instead of the transvalvular signal, and selecting signals in the setting of arrhythmias that are not representative of mean heartbeats can all lead to skewed assessment of valve disease severity.[35] Further, a number of other potential



• **Fig. 30.5** Noninvasive findings in a symptomatic patient who was referred for aortic valve intervention. A, Continuous Doppler across the aortic valve showed a peak velocity of 4.0 m/s, suggesting severe aortic stenosis. B, Pedoff apical Doppler confirmed peak velocity above 4.0 m/s. C, However, a repeat continuous Doppler with care to avoid mitral regurgitant flow showed the true aortic velocity of 2.0 m/s. D, Color Doppler showed severe mitral regurgitation in the same patient. Therapy was directed to correcting mitral regurgitation instead. *AV,* Aortic valve; *AVA,* aortic valve area; *MR,* mitral regurgitation; *PG,* gradient; *Vmax,* peak aortic jet velocity; *VTI,* time-velocity integral.

confounding variables can lead to overestimation or underestimation of the severity of AS,[6,36] and valve area calculations by the continuity equation in a low-flow setting may be inaccurate.[37] Because the continuity equation depends on measurement of the LV outflow tract (LVOT) dimension, which is prone to inaccuracy, another measure of AS severity—the dimensionless index (the ratio of blood flow velocity across the LVOT to that across the aortic valve)—has been widely adopted.[38] A number of other techniques for determining the severity of AS supplement the most commonly used noninvasive tools, including three-dimensional echocardiography, computed tomography (CT),[39] and magnetic resonance imaging (MRI).[40] Overall, there has been a major a shift in the gold standard from catheter-derived to noninvasive-derived determination of AS severity, and cardiac catheterization is no longer indicated for hemodynamic assessment of aortic valve disease severity when noninvasive findings are unequivocal.[4]

The echocardiogram provides important additional information including severity of LV hypertrophy, LV function and size, and concomitant disease of other heart valves. The presence of regional wall motion abnormalities, in the absence of a conduction disturbance, suggests concomitant CAD. The electrocardiogram (ECG) in AS is typically abnormal and frequently features LV hypertrophy, with ST-segment abnormalities in the lateral leads typically described as a strain pattern.[41] Although occasionally mistaken for anterior ischemia or infarction, with loss of R voltage across the precordium and occasionally with narrow QS complexes, the ECG is not specific for severity of AS. With increasing calcification of the perivalvular tissues, heart block and other conduction disturbances are seen, representing a significant issue in the management of patients after surgical AVR (SAVR) or TAVR.

Cardiac Catheterization

Cardiac catheterization *is* indicated in patients in whom the noninvasive data are equivocal (Box 30.1). In addition, coronary angiography before heart surgery is indicated in patients with an increased likelihood of CAD and those with functional MR; coronary CT angiography (CTA) is a potential alternative.[4] The hemodynamics of AS are best recorded with a catheter or catheters placed simultaneously on either side of the aortic valve.[6,42] Unfortunately, most laboratories record femoral artery pressure in lieu of central aortic pressure or do a catheter pullback in lieu of simultaneous pressure tracings; both techniques can result in significant misinterpretation of the severity of aortic valve disease.[43] A variety of other errors in catheterization laboratory pressure measurements makes the catheter-derived valve area generally more variable than desirable in all except a few laboratories; such errors include inherent errors in estimating rather than measuring oxygen consumption and in assuming that the Gorlin constant (originally established for a limited subset of patients[44]) and the valve area itself remain constant under varying loading conditions.[37] In the catheterization laboratory as well, transvalvular flow may be underestimated if there is concomitant AI, resulting in overestimation of the severity of aortic valve disease.

In addition to echocardiography, high-resolution CTA is an increasingly used tool to assess VHD. Planimetry on CTA has been shown to agree well with valve area derived from transesophageal echocardiography (TEE) in high-risk subjects.[45] Valve area (Fig. 30.6) can be traced and calcium scoring can be useful in determining the need for intervention in certain subsets of patients with AS.

Low-Gradient Aortic Stenosis

The critical care unit patient with a low to moderate gradient across the aortic valve, especially in the setting of low CO, represents an important conundrum (and should be differentiated from the patient with aortic *sclerosis*). There are at least three types of low-gradient severe AS that need to be considered[46] (Fig. 30.7): type D2 ("classical" low-flow, low-gradient AS), which incorporates patients with depressed EF and requires differentiation between

• BOX 30.1 Indications for Cardiac Catheterization in Patients With Valvular Heart Disease

General Indications

1. When noninvasive findings are inconclusive or discordant with clinical findings or inadequate imaging is obtained. Class I
2. Exercise hemodynamics in symptomatic patients with chronic primary MR when there is a discrepancy between symptoms and severity of MR at rest (alternatively Doppler echocardiography may be used). Class IIa
3. Right-sided heart catheterization when clinical decision making will be influenced by hemodynamics not otherwise obtainable. (Not in guidelines)

Specific Indications for Coronary Angiography

Class I

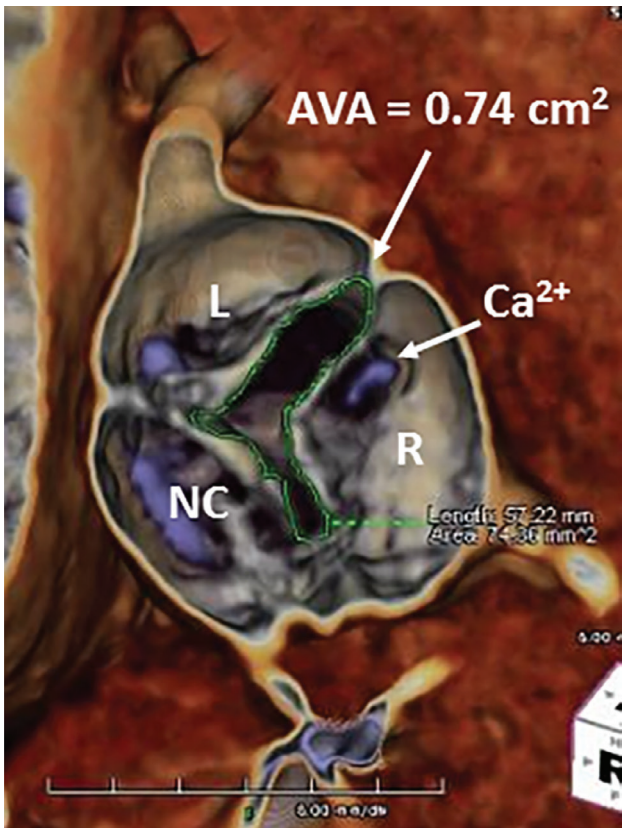
1. Before valve intervention in patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men older than 40 years of age and postmenopausal women).
2. Coronary arteriography is useful to establish etiology of chronic secondary MR and/or to assess myocardial viability.

Class IIa

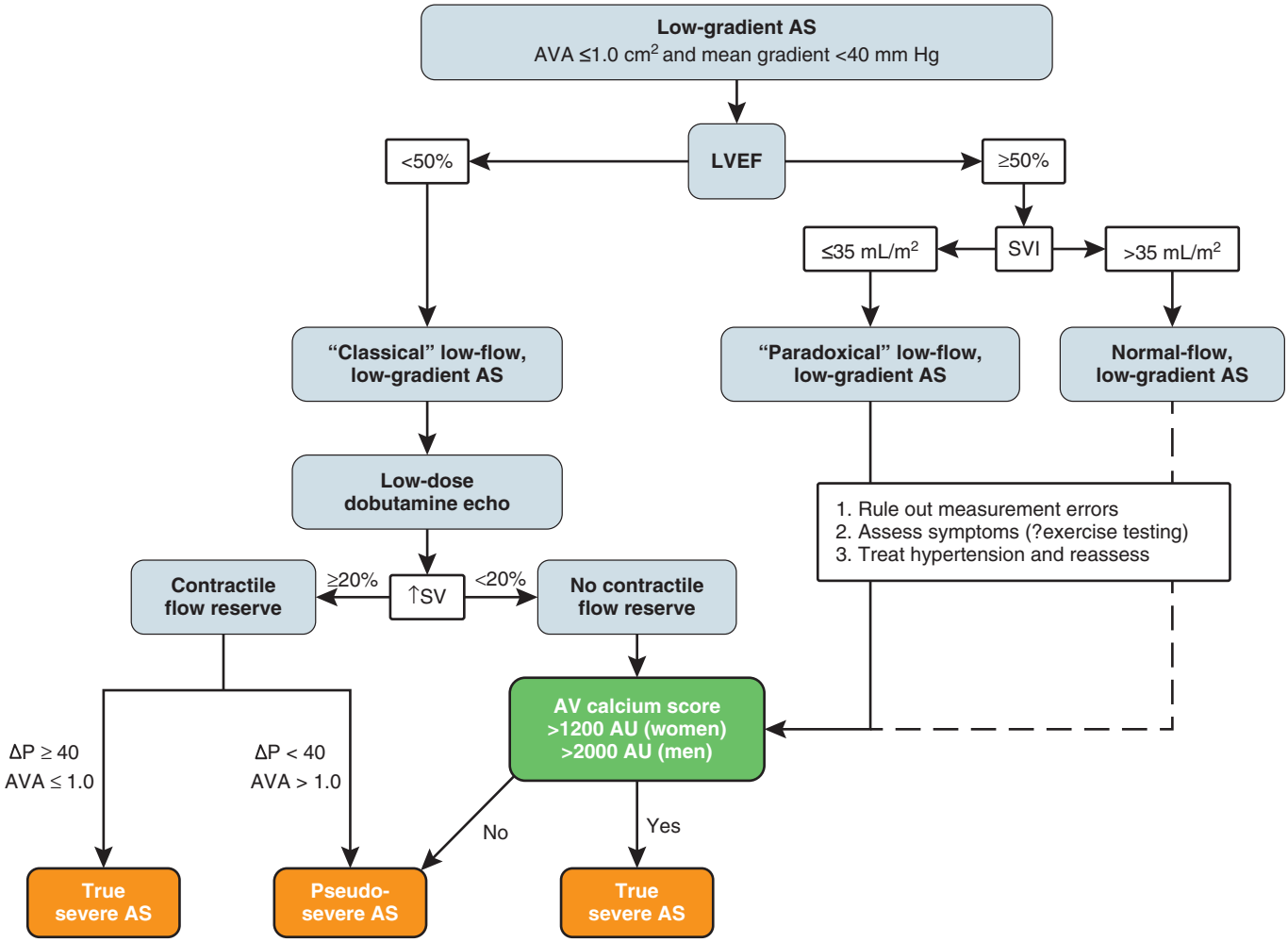
1. Surgery without coronary angiography is reasonable for patients requiring emergency valve surgery for acute valve regurgitation, disease of the aortic sinuses or ascending aorta, or infective endocarditis.
2. CT coronary angiography is reasonable to exclude the presence of significant obstructive CAD in selected patients with a low/intermediate pretest probability of CAD. A positive coronary CT angiogram can be confirmed with invasive coronary angiography.

CAD, *Coronary artery disease*; CT, *computed tomography;* LV, *left ventricular;* MR, *mitral regurgitation.*

Modified from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. *2014;129:2440–2492.*



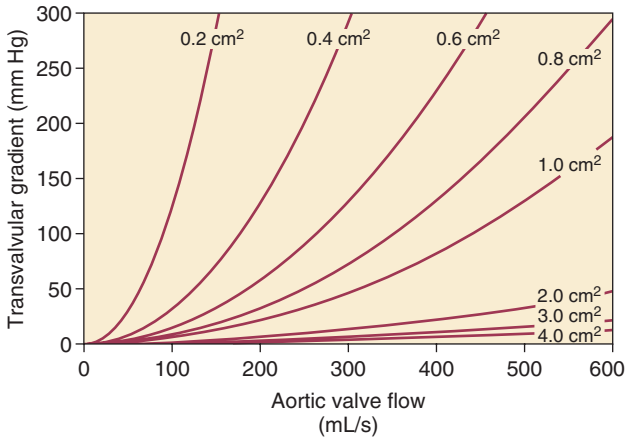
• **Fig. 30.6** Three-dimensional–rendered image of the trileaflet aortic valve showing severe aortic stenosis (aortic valve area *[AVA]* = 0.74 cm^2). There is significant calcification *(blue color)* in the aortic cusps. Ca^{2+}, Calcium; *L,* left; *R,* right; *NC,* noncoronary.



• **Fig. 30.7** Low-gradient aortic stenosis can be further classified based on the left ventricular ejection fraction and the stroke volume ("Classical" low-flow, low-gradient AS; "Paradoxical" low-flow, low-gradient AS; and normal-flow, low-gradient AS). It is important to distinguish between true severe aortic stenosis and pseudo-severe aortic stenosis. *AU,* Agatston unit; *AS,* aortic stenosis; *AV,* aortic valve; *LVEF,* left ventricular ejection fraction; *ΔP,* gradient in mm Hg; *SV*, stroke volume; *SVI,* stroke volume index. (Adapted from Clavel MA, Magne J, Pibator P. Low-gradient aortic stenosis. *Eur Heart J.* 2016;37:2645–2657.)

true severe AS and so called pseudo-severe AS; type D3 ("paradoxical" low-flow, low-gradient AS), where LV function is preserved, but the gradient is low because of a typically small left ventricle with very low stroke volume; and normal-flow low-gradient AS (proposed classification type D4). The approaches to these types of low-gradient AS are substantially different, including evaluation, management, and prognosis.

Patients with type D2 with true AS and depressed LV function generate a substantial rise in gradient with dobutamine infusion as long as they have contractile reserve. Because the rules of hydraulics demonstrate that valve area is proportional to flow divided by the square root of the gradient,[44] when the valve area is fixed, as in true severe AS, increased flow is associated with an exponential rise in gradient when valve areas are less than 1 cm^2 (Fig. 30.8). In these patients, the depressed LV function is related to high wall stress (see Fig. 30.3). In contrast, patients with pseudo-severe AS, where the left ventricle is depressed because of a cardiomyopathy and the stenosis is less than severe, inotropic increase in myocardial function results in an improvement in EF as well as an improvement in valve opening and valve area and minimal increase in gradient. The differentiation can be made with dobutamine infusion (typical peak dose 20 μg/kg per minute).[47] In addition to increasing flow across the valve in these patients,[48] the echocardiogram can be useful in several other ways[49]; valve calcification is suggestive of fixed outflow obstruction and, if severe, suggests that the underlying disease is severe AS rather than LV dysfunction. The stenosis is considered severe when the mean gradient with dobutamine rises to 40 mm Hg or higher with little to no change in aortic valve area (AVA). Preserved LV contractile reserve, with significant rise in stroke volume (>20%), peak velocity (>0.6 m/s), or mean transvalvular gradient (>10 mm Hg) at the time of dobutamine infusion is an additional useful marker. Patients with lack of contractile reserve, and hence no significant increase in contractility despite dobutamine, may have true severe AS despite lack of increase in gradient; this has been associated with lower operative survival rate[50] (68% vs. 95% in one study), although it should not be the sole parameter for the decision on whether or not to perform AVR, Patients who survive may manifest significant



• **Fig. 30.8** The relationship between transvalvular flow and transvalvular gradient for given valve areas. An exponential rise in gradient occurs when flow is increased with valve areas in the severe stenosis range (<1 cm^2). The curve demonstrates that change in gradient is proportional to the square of change in flow; thus doubling the flow rate results in a fourfold increase in gradient. (From Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J.* 1951;41:1–29.)

recovery in LV function postoperatively.[51] Low contractile reserve should not always preclude AVR in patients who do have severe fixed obstruction because their prognosis without surgery is abysmal.[52] Aortic valve calcium scoring (calculated on multidetector computed tomography [MDCT]) may help in distinguishing true from pseudo-AS as well.[53]

Patients with type D3 AS (paradoxical low-flow, low-gradient AS with preserved EF) are characterized by low-flow (stroke volume index <35 mL/m^2), small hypertrophied ventricles with impaired LV filling, and calcification with small valve areas. Dobutamine echocardiography is somewhat controversial in this setting, but MDCT calcium scoring can be useful, and dimensionless index by echocardiography can also provide adjunctive evidence. Although a burgeoning evidence base does show improved results with AVR compared with medical therapy,[54] the overall outcome for these patients has been inferior to patients with classic severe AS, and at best comparable to those seen with AVR in low-flow, low-gradient depressed EF (type D2) AS.[55] Finally, patients with normal-flow low-gradient AS have an AVA less than 1.0 cm^2 (indexed AVA <0.6 cm^2) with mean gradient less than 40 mm Hg, LVEF of 50% or higher but normal flow (stroke volume index >35 mL/m^2). In these patients, a true severe AS may be masked by decreased gradient owing to reduced aortic compliance with high aortic systolic pressure. Reassessment of these patients after controlling hypertension should be performed as a significant proportion of these patients may have true severe AS. Calcium scoring on MDCT is preferred over dobutamine stress echo in these patients to distinguish true severe AS.[56]

Therapy

Medical Management

Medical management is aimed solely at patient stabilization because pharmacologic intervention has never been shown to prolong life and can achieve modest hemodynamic improvement at best. In the critical care setting the approach to the patient with AS normally parallels treatment of corresponding degrees of heart failure, albeit with caution, because the normal therapeutic approach to heart failure can be deleterious or fatal in the setting of severe AS. The traditional heart failure therapies—particularly, diuretics and vasodilators—need to be used with care because reduction in preload can cause hypotension, decreased CO, and a downward spiral into refractory shock. In patients with small-volume hypertrophic left ventricles, CO is particularly preload dependent.

Atrial arrhythmias—particularly atrial fibrillation (AF)—can lead to abrupt and severe decompensation because of loss of the atrial contraction component of LV filling. Cardioversion in the critical care setting is particularly helpful in severely decompensated patients, and maintenance of sinus rhythm in patients who are otherwise suitable (e.g., left atrium <6 cm, recent onset of AF, and absence of clot in the left atrium by TEE) should be a priority.

Despite the caveats, vasodilator therapy, including nitroprusside, has been used in the critical care setting in patients with severe LV dysfunction and severe AS.[57] In a select group of patients not dependent on inotropes, CO rose significantly and there was overall hemodynamic improvement. Similarly, intraaortic balloon pumping (IABP) has been used, although there are only small series with modest demonstration of hemodynamic benefit.[58] As would be expected, both nitroprusside and IABP result in afterload reduction and some increase in transvalvular flow along with some increase in aortic valve gradient.

Hemodynamic monitoring is essential for the pharmacologic management of decompensated patients with severe AS in the critical care setting. Because of the dependence on preload, a fine threshold exists between optimal filling pressures and pulmonary edema. Vasodilator therapy as described earlier results in peripheral vasodilation, but because of the fixed obstruction to outflow it may not provide sufficient increase in stroke volume and CO to maintain systemic blood pressure. Inotropic agents are frequently required, and patients with inadequate contractile reserve may show limited improvement. β-Blockers are relatively dangerous, although tachycardia is hemodynamically unfavorable, even in sinus rhythm. β-Blockade, if used, should be used with great caution. β-Blockers decrease contractility and, in addition, an increase in heart rate (HR) may be the only remaining compensatory mechanism for low stroke volume because of the fixed resistance to outflow. Patients with severe AS can enter a "death spiral" in which hemodynamic recovery becomes impossible.

Lipid-lowering therapy and converting enzyme inhibitors have been the subject of substantial investigation, although their role is in the chronic setting rather than during critical care. Two prospective randomized trials failed to show clear benefits of a statin[59,60] in slowing disease progression; overall the evidence base has not been compelling.[61] Some preliminary evidence suggests potential benefits of angiotensin-converting enzyme (ACE) inhibitors in decreasing progression of aortic valve calcification,[62,63] but the available clinical data do not show slowing of AS progression. Both lipid-lowering and converting enzyme inhibitors need to be tested in larger populations earlier in the course of aortic valve disease.

Percutaneous Interventions

Balloon Valvuloplasty

Balloon aortic valvuloplasty (BAV) is a temporizing measure for patients who are hemodynamically unstable and are at high risk for AVR. Although the procedure is therapeutic and indicated in congenital AS in children and young adults, the risk/benefit ratio as a stand-alone procedure in patients older than their 20s is usually unfavorable. Because calcific AS is associated with open commissures

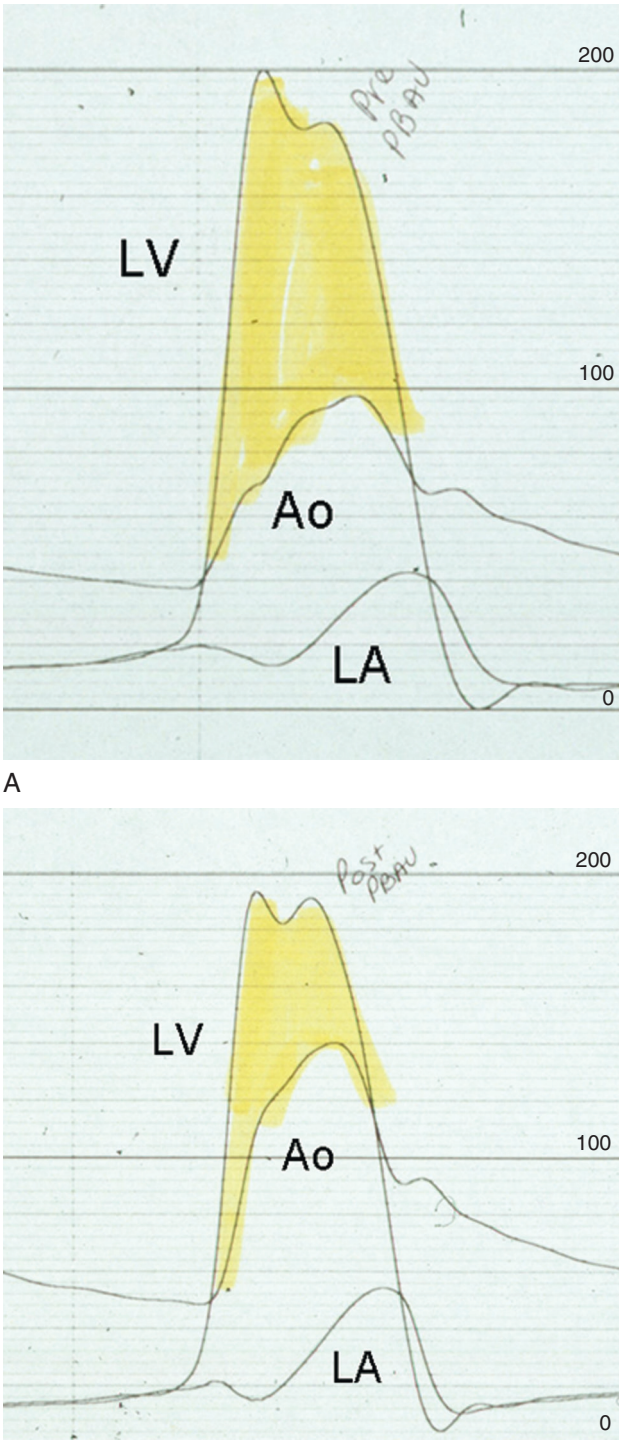
and ossified leaflets, abrupt balloon inflation exerts its effect by improving leaflet compliance through the formation of multiple, usually microscopic, fracture lines in the calcified tissues. Stretching of the commissures is temporary, and any hemodynamic benefit of the latter resolves within hours. The leaflets lose their improved compliance within weeks to months, and the AVA typically returns to baseline.

The acute hemodynamic results (Fig. 30.9) are poor compared with those of AVR, with a 50% reduction in gradient and an increase in AVA of only 0.2 to 0.3 cm^2.[64] The in-hospital mortality rate was close to 10% in the National Heart, Lung and Blood Institute registry[65] and is substantially higher in patients with hemodynamic decompensation and multiorgan failure. Most valves have restenosed within a few months, and the overall outcomes if no additional intervention is performed are very poor; one series reported an 87% mortality rate after a median period of less than 7 months.[66] No benefit for long-term outcomes has been shown. Indeed, the overall clinical course is not influenced by BAV alone.[67] Nevertheless, it can serve as a bridge to TAVR or SAVR in select patients with multiple comorbid conditions and is an alternative but low efficacy measure for patients who are not candidates for TAVR or AVR. It is not an alternative to TAVR or surgery for patients who can undergo valve replacement, even for most patients at relatively high risk for the latter.

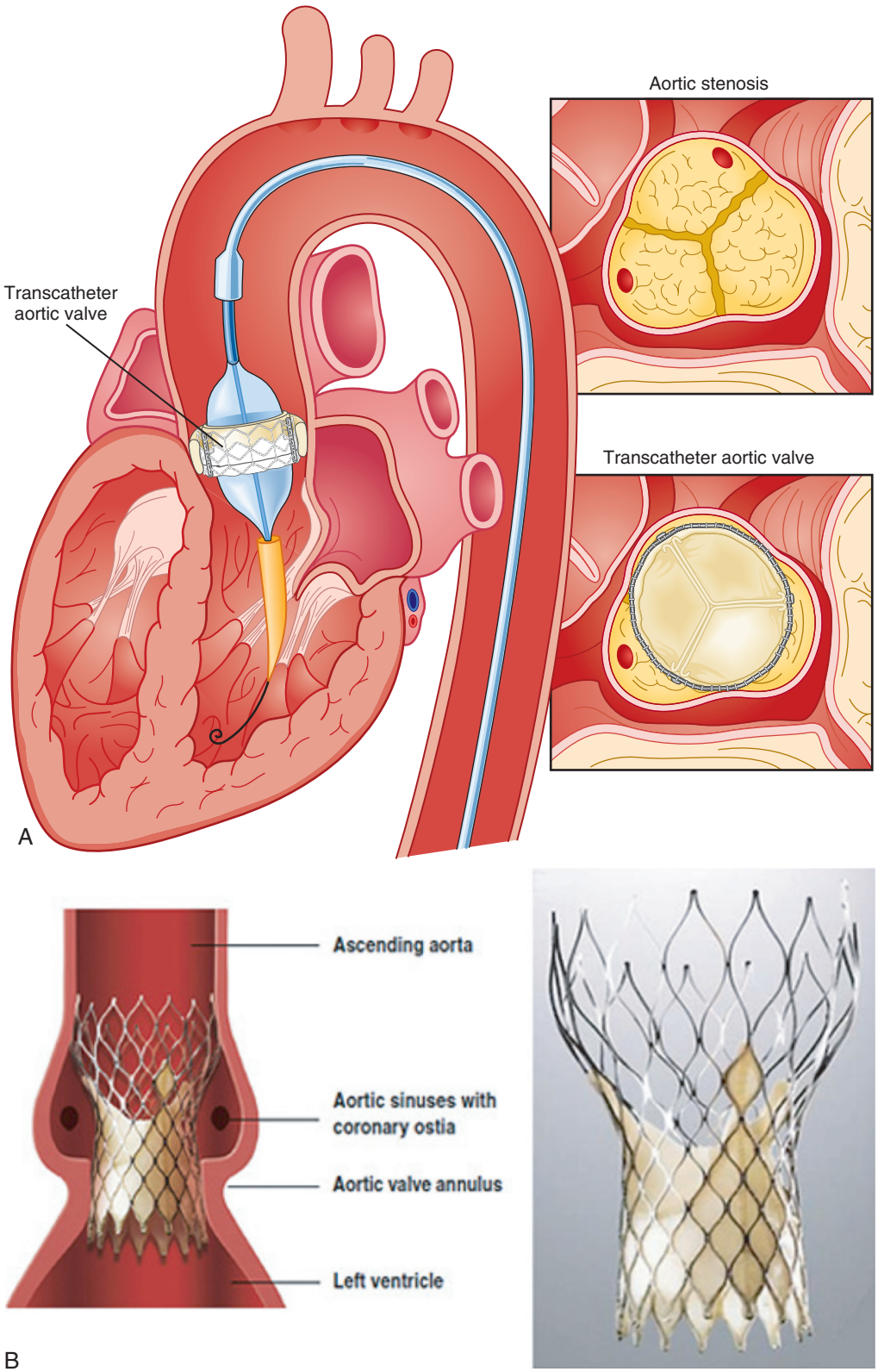
Several settings in which BAV was previously considered to have a role are no longer included as indications in the 2014 AHA/ACC guidelines.[4] These include preoperative balloon dilation in patients undergoing noncardiac surgery[68]; in general all but decompensated patients can withstand general anesthesia as long as careful hemodynamic monitoring and anesthesia management are performed.[69] Patients who require urgent noncardiac surgery in the setting of severe symptomatic AS do have a significant perioperative risk,[70] and preoperative TAVR or AVR should be considered if at all possible. In severely hemodynamically compromised patients, BAV has been performed successfully with a variety of hemodynamic support devices, including IABP as well as the Impella device (Abiomed, Danvers, MA).[71,72] BAV has also been proposed as a tool to differentiate less than severe AS with severe myocardial dysfunction from severe AS combined with secondary LV dysfunction in low-gradient, low-output AS.[73] The latter patients typically demonstrate substantial improvement in stroke volume and EF after balloon dilation, but dobutamine stress testing is usually a safer, less morbid screening tool. With the growth of TAVR, the use of BAV as a therapeutic test has gained traction.[74] The 2014 guidelines[4] describe only one (class IIb) indication for BAV: as a bridge to TAVR or AVR. Nevertheless, because of the widespread availability of TAVR and resultant exponential rise in percutaneous AS interventions that include BAV, BAV techniques have improved[75] and the proper role of BAV remains under active debate.[76]

Transcatheter Aortic Valve Replacement

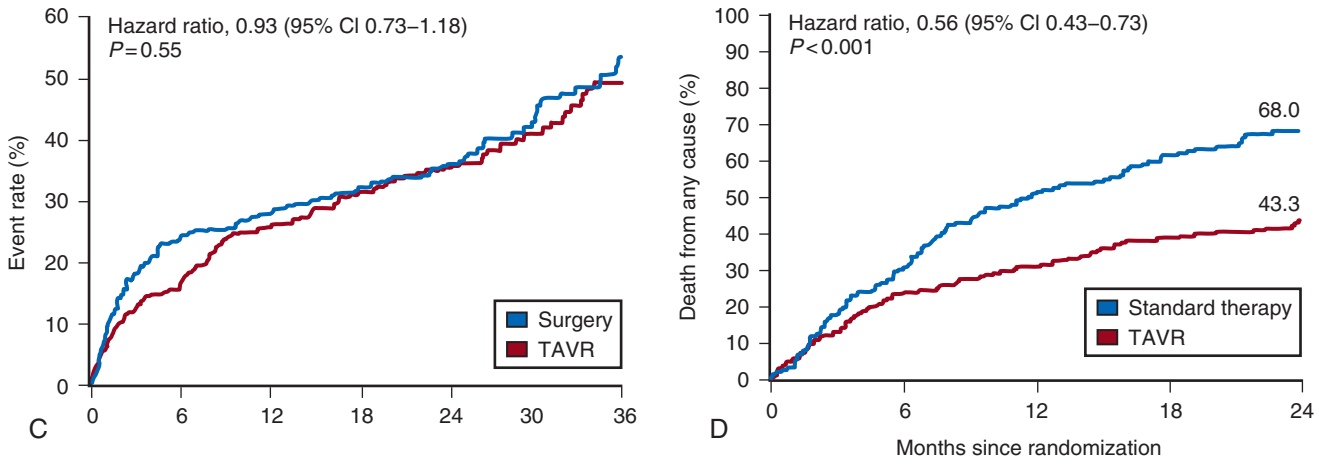
TAVR, a technology developed in the past 2 decades, has revolutionized the treatment of AS. The procedure is of increasing importance in the critical care setting. Tissue valves are sewn to either balloon expandable or self-expanding stents, which are crimped onto a catheter and advanced across the stenotic native valve. Both balloon expandable and self-expanding technologies are widely available (Fig. 30.10A and B). The landmark PARTNER (Placement of AoRtic TraNscathetER valves) study had two cohorts: PARTNER A enrolled high-risk but operable patients, whereas PARTNER B enrolled patients deemed inoperable. PARTNER A randomly



• **Fig. 30.9** Hemodynamic response to percutaneous balloon aortic valvuloplasty *(PBAV)*. Tracings show before (A) and after (B) balloon dilation on a 200-mm Hg scale. A successful 50% reduction in gradient occurs, but residual gradient remains at 50 mm Hg, still in the severe category. The pulse pressure has increased from 60 to 90 mm Hg, the peak aortic systolic pressure has increased to 140 mm Hg from 100 mm Hg, and the aortic pressure upslope can be seen to have improved dramatically. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.



• **Fig. 30.10** A, Percutaneous aortic valve (SAPIEN, Edwards Life Sciences, Irvine, CA) shown in place immediately after transcatheter deployment with the balloon still inflated. B, CoreValve (Medtronic). C and D, Results of the Placement of Aortic Transcatheter Valves (PARTNER) Trial.



• **Fig. 30.10, cont'd** C, Death from any cause or stroke in the A cohort, the high-risk but operable patients who were randomly assigned to surgical aortic valve replacement (*n* = 351) versus either transfemoral (*n* = 244) or transapical (*n* = 104) transcatheter deployment depending on the suitability of the femoral and iliac circulation. There were no differences in mortality rate or stroke. D, Mortality in the B cohort, showing substantial survival advantage among the 179 patients undergoing transcatheter aortic valve replacement over the 179 patients treated with medical therapy. (A and C, From Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187–2198. B, Courtesy Medtronic Inc., Minneapolis, MN. D, From Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med.* 2012;366:1696–1704.)

assigned patients to SAVR versus two approaches to TAVR: transfemoral if the iliac and femoral vasculature was suitable for accommodating the large catheter shafts or transapical if not.[77] The results of TAVR compared with SAVR were similar, with published follow-up through 2 years; however, vascular complications and stroke were higher with TAVR and major bleeding and AF were higher with SAVR (see Fig. 30.10C). PARTNER B randomly assigned patients with suitable vasculature to transfemoral TAVR versus medical therapy.[78] Patients who received only medical therapy (with or without balloon valvuloplasty) had a 51% 1-year mortality rate compared with those inoperable patients randomly assigned to TAVR, who had a 31% 1-year mortality rate, an approximately 40% relative reduction (see Fig. 30.10D). Thus TAVR appears to be among the most dramatically successful of all modern cardiac interventions. It is noteworthy that the residual mortality rate in inoperable patients, whether treated with TAVR or medical therapy, remained very high (the 5 year mortality was 93.6% vs 71.8%),[79] reflecting the severe comorbidities in patients who met inoperability criteria. There was an initially higher stroke risk in TAVR patients,[78] but because of the greater ongoing stroke rate in patients treated only with medical therapy, the disparity resolved by 24 months. In general, the risk of stroke appeared to be largely related to patient comorbid conditions that increase stroke risk, rather than the type of valve replacement.[80] Indeed, the risk of stroke in subsequent TAVR trials has been the same or lower than with surgery.[81] The U.S. Food and Drug Administration (FDA) initially approved TAVR for inoperable patients based on the results of PARTNER B and subsequently approved the high-risk population treated in PARTNER A. Thereafter two randomized controlled trials comparing TAVR versus SAVR in intermediate-risk patients with severe AS showed that TAVR was noninferior to SAVR[82,83]; the AHA/ACC 2017 Guidelines Update has given TAVR a class IIa recommendation for patients with intermediate surgical risk, and class I for patients with high surgical risk and those who are inoperable.[84] In addition, there have been excellent results with valve-in-valve (ViV) TAVR for patients with bioprosthetic valve dysfunction (owing to either stenosis or insufficiency).[85,86] The likelihood that transcatheter ViV replacement will eventually supplant reoperation is changing the algorithm for choice of tissue versus mechanical AVR during heart surgery, with a lowering of the recommended age when tissue valves should be considered (rather than mechanical ones) from 60 to 50 years of age.[87] In addition, percutaneous ViV replacement rather than reoperation is now a class IIa indication for both bioprosthetic AS and AR.

The management of TAVR patients after valve replacement initially took place in a critical care unit or open heart recovery area; in the current era of "minimalist" TAVR, there is a shift toward performing TAVR procedures under monitored anesthesia care (MAC) instead of general anesthesia with recovery in step-down units. Nevertheless, critical care physicians and staff remain involved in the immediate postprocedure management and early mobilization and discharge of TAVR patients even as length of stay declines.[88] The persistent but now single-digit rate of major vascular complications[89] associated with TAVR requires careful monitoring for limb ischemia, retroperitoneal hemorrhage, and a variety of other vascular complications. Conduction disturbances, particularly after use of a self-expanding TAVR platform, and especially in patients with existing conduction disturbances, particularly right bundle branch block, continue to occur in a significant percentage of cases, requiring permanent pacemaker placement.[90] Pericardial tamponade can occur infrequently late after TAVR (owing to trauma secondary to wire and catheter manipulation) and should be suspected in patients with hemodynamic compromise. Most operators have treated TAVR patients with lifelong aspirin 75 mg to 100 mg daily plus clopidogrel for periods ranging from 1 to 6 months (class IIb per the 2017 Guidelines[84]). Evidence that thrombus formation takes place after TAVR[91] (and SAVR with bioprosthetic valves) has led to a class IIb indication for anticoagulation after TAVR

for at least 3 months and class IIa indication for 3 to 6 months anticoagulation after SAVR in patients at low risk of bleeding.[84] A number of issues, such as the use of dual antiplatelet therapy plus anticoagulation after TAVR in patients with AF, remain to be fully investigated, but these are associated with high bleeding risk; as such, non-AF patients treated with anticoagulation typically receive concomitant aspirin only.[92]

Surgical Aortic Valve Replacement

AVR remains the treatment of choice for severe AS in patients who are considered to have low operative risk. Class I indications are severe AS (valve area <1 cm^2) with symptoms or, regardless of symptoms, if patients have severe AS and are undergoing coronary artery bypass, are undergoing surgery of the aorta or other heart valves, or have LV dysfunction. A long list of class II indications generally focuses on patients who do not meet class I criteria but are thought to be at increased risk because of rapid disease progression, abnormal stress test results, or "very severe" AS (as defined by a maximum velocity ≥5 m/s or mean gradient threshold ≥60 mm Hg). In addition, patients with moderate AS who undergo other cardiac surgery generally have simultaneous AVR. Survival after AVR is excellent if LV function is preserved, with an operative mortality rate in ideal candidates as low as 1%. In these patients, age-matched survival is not significantly different from patients without AS.[93] In the setting of LV dysfunction, however, postoperative life expectancy is relatively poor.[94] Nevertheless, conservative therapy for severe AS remains an undesirable alternative. A review of 453 patients treated without intervention despite severe AS had 1-year, 5-year, and 10-year survival rates of only 62%, 32%, and 18%, respectively,[95] with the worst survival in patients with renal failure, pulmonary hypertension, age older than 75 years, diminished EF, and congestive heart failure.

A number of technological advances in the SAVR arena have decreased the morbidity of AVR along with shorter length of stay. These include minimally invasive surgery and the use of sutureless valve replacement,[96,97] both of which need formal high-level comparison to TAVR. The postoperative management of AVR patients includes antiplatelet and anticoagulation therapy as discussed earlier and in the 2017 guidelines; an important caveat is that anti-Xa anticoagulants are contraindicated for mechanical valves (class III harm). The level of anticoagulation after surgery is specific to prosthetic valve type and location.[84]

Aortic Insufficiency

The overall prevalence of moderate or severe AI in the United States, as shown in the Framingham Offspring Study, ranged from 0.3% in the fifth decade of life to 2.2% for patients aged 70 to 83.[98] The frequency is age and male gender related. The diagnosis of AI is more difficult and the treatment issues in many ways more complex than for AS, with a less clear dichotomy in the decision tree for valve replacement. AI needs to be considered in light of its acuity: Acute AI is usually associated with life-threatening comorbidities and the resultant acute regurgitation places great stress on the left ventricle and may itself be fatal. In contrast, it may take decades for chronic AI to evolve from clinically insignificant to requiring surgery. Unlike AS, it is not primarily a disease of the aging process (although it does occur more frequently with increasing age) and is typically secondary to one of an extensive list of systemic or structural pathologies that result in insufficiency of the aortic valve. Acute AI frequently requires urgent surgery, whereas chronic AI may be managed by watchful waiting and some limited options for medical therapy, although the trend is for operating earlier than in prior decades.

• BOX 30.2 Etiology of Acute and Chronic Aortic Insufficiency

Acute
- Infective endocarditis
- Aortic dissection
- Trauma

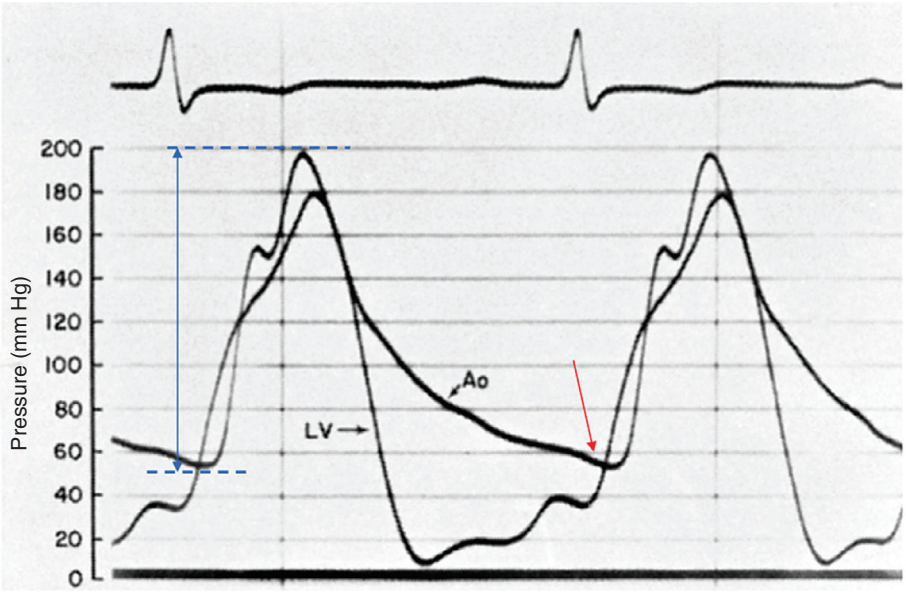
Chronic
- Dilation of the aorta
  - Systemic hypertension
  - Bicuspid aortic valve
  - Calcific degenerated aortic valve disease
  - Aortic dissection
  - Marfan syndrome
  - Trauma
  - Ankylosing spondylitis
  - Syphilis
  - Rheumatoid arthritis
  - Osteogenesis imperfecta
  - Giant cell aortitis
  - Ehlers-Danlos syndrome
- Rheumatic aortic valve disease
- Infective endocarditis
- Myxomatous degeneration
- Ventricular assist device use
- Subaortic stenosis
- Ventricular septal defect with cusp prolapse
- Anorectic drug reaction
- Prosthetic paravalvular leak

Pathophysiology

Acute AI is generally associated with leaflet involvement by endocarditis or disruption of the aortic valve's annular structure by dissection or trauma. Chronic AI, by contrast, is caused by congenital valve abnormalities, most importantly bicuspid aortic valve disease, or by the degenerative process described earlier associated with AS. Conditions that distort the annulus and aortic root including systemic hypertension have been considered as important causes of secondary AI, although the association between chronic AI and systemic hypertension remains to be confirmed.[99] Rheumatic AI, almost invariably associated with mitral valve involvement as well, remains prevalent in developing countries.

In general, causes of AI (Box 30.2) have been divided into those that affect the leaflets primarily and those that affect the root and annulus. The former group includes bicuspid and other aortic valve abnormalities, endocarditis, rheumatic aortic valve disease, the atherosclerotic process described earlier, connective tissue disorders, antiphospholipid syndrome (Libman-Sacks endocarditis), and toxicity from anorectic drugs.[100] The aortic root and annulus are affected by a variety of comorbidities that dilate the aortic root; Marfan and Ehlers-Danlos syndromes; osteogenesis imperfecta; chronic aortic dissection; syphilitic aortitis; connective tissue disorders; and, along with the valve leaflets, ankylosing spondylitis. AI is commonly seen in patients with long-term implantation of ventricular assist devices, with moderate or severe AI occurring in perhaps a third of these patients (see Chapter 7).[101]

In isolated acute AI, the sudden onset of regurgitation imposes a large-volume load on the left ventricle in diastole before an adaptive process is in place. The abrupt rise in pressure is reflected by parallel development of left atrial and pulmonary vascular hypertension, frequently resulting in pulmonary edema. Because the compliance of a previously unaffected left ventricle is not sufficient to allow adequate dilation to absorb the regurgitant volume, the ventricle operates on the steep portion of its pressure-volume curve, with inadequate stroke volume to accommodate the high regurgitant flow. The effective (net) forward stroke volume (antegrade flow minus retrograde filling) is therefore low,



• **Fig. 30.11** The hemodynamics of acute aortic insufficiency. The wide pulse pressure (150 mm Hg) difference between peak and minimum aortic pressure *(blue arrow)* and near diastasis of left ventricular and aortic pressure late in diastole *(red arrow)* are demonstrated. *Ao,* Aorta; *LV,* left ventricle. (Modified from Grossman W. Profiles in valvular heart disease. In Baim DS, ed. *Grossman's Cardiac Catheterization, Angiography and Intervention.* 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:654.)

compensated to some degree by tachycardia, but frequently insufficient to maintain normal CO. This phenomenon is exaggerated in patients with preexistent LV hypertrophy in whom the ventricle is already operating on the steep portion of its pressure-volume curve, and particularly severe decompensation is seen when the left ventricle is small and hypertrophic. Critical care settings for the latter unfortunately include many of the common scenarios for acute AI, including endocarditis in the setting of AS, and aortic dissection in patients with hypertension and a dilated aortic root.[4]

Acute severe AI results in near approximation of aortic and LV pressures at end diastole, with consequent deleterious effects on coronary perfusion of the subendocardium (Fig. 30.11). Because coronary perfusion pressure is the difference between diastolic pressure in the aortic root and subendocardial pressure in the LV cavity, the decrease in aortic diastolic pressure and rise in subendocardial pressure that are hallmarks of acute AI can result in profound subendocardial ischemia, especially in patients with preexistent hypertrophy or patients with underlying CAD. In addition, because afterload and wall stress in this setting are increased, there is a rise in myocardial oxygen demand simultaneous with a fall in supply, occasionally leading to cardiogenic shock and death. Acute AI also results in early closure of the mitral valve as LV diastolic pressure rises above left atrial pressure, a phenomenon that has potential protective benefits for the pulmonary circulation.

In contrast, chronic AI features a host of adaptive processes by the left ventricle, including progressive dilation, increased compliance, and hypertrophy. As with AS, hypertrophy results in lower wall stress, but AI features an increase in afterload combined with progressive LV dilation and somewhat less hypertrophy, resulting in significantly higher wall stress than seen in compensated AS.[102] End-diastolic dilation of the left ventricle allows for larger stroke volumes to compensate for regurgitant fractions, which may be in the range of 50% or greater. With combined pressure and volume overload, unique among the valve disorders discussed in this chapter, LV adaptations allow for maintenance of normal overall function until ventricular remodeling and hypertrophy are no longer sufficient to maintain forward stroke volume and EF. With increasing wall stress and LV dilation, LV contractility is eventually impaired, at which point filling pressures begin to rise (or rise further) and patients become symptomatic. Coronary flow reserve in AI, as with AS, is impaired and, combined with increased demand and the need for additional perfusion for a hypertrophic myocardium, may result in significant ischemia. The onset of symptoms may be abrupt, especially with new onset of atrial tachyarrhythmias or sudden increase in CO demand such as with exertion or infection.

Although acute AI represents a relative or absolute medical emergency, chronic AI may have an insidious course over decades. In a review of nine admittedly heterogeneous studies incorporating nearly 600 primarily asymptomatic or mildly symptomatic patients with AI, average progression to symptoms with or without LV systolic dysfunction was 4.3% annually, and sudden death occurred in 0.2% per year.[103] Although this rate of progression is modest, patients do not necessarily develop symptoms before developing LV dysfunction or sudden death.[104] Age, end-systolic dimensions,[105] and rate of deterioration of end-systolic dimension and EF[106] are more sensitive tools for predicting outcome in chronic AI.

In contrast, in the setting of *symptomatic* AI that does not fall in the acute severe category, an annual mortality rate of 6% to 25% has been described, depending on severity of symptoms. By the 10-year follow-up, 75% had undergone AVR or died.[107]

Diagnosis

Physical Examination

The hallmarks of *acute* severe AI include features consistent with congestive heart failure and low CO, including tachycardia, dyspnea,

and signs of impaired CO such as peripheral vasoconstriction. The wide pulse pressure that is a hallmark of AI may or may not be seen, in part because it is dependent on LV compliance. The classic AI murmur may not be heard because of the limited gradient between the aorta and left ventricle during diastole when LV diastolic pressures in some cases approach systemic diastolic pressures. Tachycardia and diminished effective forward flow in acute AI may offset the augmented systolic and wide pulse pressure seen in later stages of the disease, and these patients may have normal or occasionally diminished pulses, although more moderate acute AI may feature the more classic findings. Early closure of the mitral valve may result in a soft first heart sound, and distortions of leaflet anatomy may result in lack of a distinct aortic second heart sound. In some cases absence of a second heart sound in a patient presenting with cardiogenic shock may be the most prominent physical finding.[100]

The dramatic physical findings in *chronic* AI are among the most familiar to physicians and trainees. A wide pulse pressure results primarily because of increased stroke volume, which augments systolic pressure[108] and low aortic diastolic pressures because of volume runoff into the left ventricle. This in turn results in a large variety of associated eponymous physical findings, including bounding carotid and peripheral pulses (Corrigan and water-hammer pulses, respectively); Hill's sign (dramatically higher systolic pressure in the legs than the arms because of the exaggerated effect of harmonics on systolic pressure waveforms, variously described as having a 20 or 40 mm Hg threshold); Duroziez's sign (to-and-fro murmur over the femoral arteries); and Traube's sign ("pistol shot" sound over the femoral artery during simultaneous compression). With LV dilation, the apical impulse is displaced laterally.

The intensity and duration of the classic diastolic decrescendo murmur heard over the left midsternal border generally correlates well with the severity of AI,[109] although in later stages of decompensation (or in acute AI), when the gradient between the aorta and the left ventricle disappears in later stages of diastole, the murmur typically shortens. When the murmur is better heard over the right (rather than left) sternal border, the cause of the AI may be secondary to a dilated aortic root rather than a primary leaflet abnormality.[110] Two other murmurs are frequently heard with moderate to severe AI: a systolic ejection murmur consistent with increased transvalvular flow and on occasion an Austin Flint murmur. The latter is the apical diastolic rumble occasionally confused with MS and thought to originate from vibration of the anterior mitral leaflet caused by the diastolic regurgitant jet originating at the aortic valve; it has been described only in the setting of severe AI.[110] In rheumatic AI, if a diastolic rumble is heard, MS should be excluded. An S_3 gallop is most likely to be present when severe AI occurs in a setting of depressed LV function[111] but may merely reflect substantial volume loading; the finding is not specific.

Noninvasive Evaluation

As with AS, noninvasive assessment has replaced cardiac catheterization for determining severity of AI. It provides both structural and physiologic information, including visualization of the leaflets, annulus, and aortic root; semiquantitative assessment of the severity of AI; and characterization of LV size, hypertrophy, and function, as well as other structural heart disease. TEE has superior diagnostic sensitivity to transthoracic echocardiography for certain parameters, in particular for detection of valvular vegetations.[112] A wide range of techniques for measurement of AI severity, including width of the color Doppler jet compared to the size of the LVOT, width of the vena contracta, regurgitant volume, regurgitant fraction, pressure half-time, and regurgitant orifice area, are described in Chapter 8. Additional findings of importance are the rate of jet velocity deceleration as diastasis is achieved between aortic and LV diastolic pressures and duration of diastolic flow reversal in the aorta.[113] In addition to echocardiography, cine MRI can assess severity of AI, size of chamber volumes, LV mass, wall thickness, and systolic function[114] as well as regurgitant volume, with good reproducibility[115] and is indicated[4] (class I) when echocardiography data are equivocal. LV size and function have also been followed serially by radionuclide ventriculography.[116]

The size and function of the left ventricle have been used to set thresholds at which AVR should be considered. The AHA/ACC guidelines[4] and the European Society of Cardiology guidelines[117] largely correlate but have set slightly different values for class I and II recommendations.[118] The echocardiogram-based recommendations for AVR for severe asymptomatic AR include LV end-diastolic dimension thresholds of 65 mm or 70 mm and end-systolic dimension greater than 50 mm along with variable consideration of whether the LVEF is greater than 50%. An additional consideration relates to patients with aortic root dilatation (aortic root dimension >45 to 55 mm with the thresholds varying for patients with bicuspid valves or Marfan syndrome).[117] As the observational data have grown, these numbers have shifted slightly from the familiar "rule of 55s," which recommended surgery for asymptomatic patients with EF less than 55% or LV end-systolic dimension greater than 55 mm. An important consideration is that the end-systolic and end-diastolic dimensions should be adjusted downward for patients with small BSA. The rate of dilatation of the left ventricle and rate of deterioration in LV function are also important parameters. It is important to keep in mind that these threshold values can be confounded by comorbid conditions that affect chamber size and function, including ischemic and other forms of cardiomyopathy, as well as multivalvular disease.

The ECG was once an important tool in the serial assessment of patients with AI. Similar to AS, features of LV hypertrophy may be present. Progression of LV dilation and dysfunction were thought to correlate with development of an LV strain pattern on ECG, a phenomenon that has been confirmed.[119] As a result, because the use of digitalis glycosides (which has decreased substantially in general) can cause a similar strain pattern, it was discouraged to maintain relative specificity of the ECG finding. Conduction disturbances remain an important feature, particularly heart block in the setting of endocarditis, discussed subsequently.

Cardiac Catheterization

As with the other valvular diseases discussed in this chapter, cardiac catheterization (other than coronary angiography) is indicated only for patients with inconclusive noninvasive findings or when noninvasive findings are discordant with the rest of the clinical picture. Typical findings include a wide aortic pulse pressure and an exaggerated rise in LV diastolic pressure, reflecting continuous retrograde filling during diastole (see Fig. 30.11). Cardiac catheterization in this setting normally includes aortic root angiography, although the latter requires a significant dye load (typically ≥30 mL/s for up to 2 seconds) to be diagnostically accurate. The hallmark of severe AI is greater opacification of the left ventricle than the aorta. The indications for coronary angiography in this setting are listed in Box 30.1.

Therapy

Medical Management

In acute AI, medical therapy is targeted to stabilization pending urgent or emergent AVR. Nitroprusside has been the standard for

reducing peripheral vascular resistance and improving net forward flow across the aortic valve since the 1970s.[120] The use of arterial vasodilators is more complex when the patient is already hypotensive, and a combination of inotropes and afterload reduction should be considered. Although afterload reduction in this setting is highly beneficial, the otherwise optimal combination of afterload reduction and augmented diastolic pressure normally provided by IABP in cardiogenic shock (see Chapter 7) is normally not a viable choice in AI. Counterpulsation during diastole increases the severity of AI with potentially catastrophic consequences; it typically represents an absolute contraindication to the intraaortic balloon pump.

Besides vasodilator therapy, maneuvers to raise the HR may be helpful, especially in patients who are bradycardic or have a normal HR. Tachycardia disproportionately decreases the diastolic filling period, thereby decreasing the duration of regurgitation across the aortic valve. Both isoproterenol and electrical pacing to raise the HR have been used with therapeutic benefit.

In *chronic* AI, the evidence base is incomplete and somewhat controversial. The general consensus is that asymptomatic patients with mild to at most moderate AI with normal LV function who are not hypertensive do not require or benefit from vasodilator therapy.[104,106] Hypertension (systolic blood pressure > 140 mm Hg) should be treated with a dihydropyridine calcium channel blocker or an ACE inhibitor or angiotensin receptor blocker (class I indication), and if a patient is not a surgical candidate, vasodilators can be used in the setting of symptomatic heart failure and/or LV dysfunction (class IIa indication).[4] Class II indications are short-term treatment to optimize the patient's hemodynamic status before AVR and, more controversially, long-term therapy for asymptomatic patients with severe AI but preserved LV function. Two important studies with divergent results were performed. One study, using nifedipine, appeared to demonstrate some slowing of progression to need for AVR compared with patients using digoxin.[121] The second study, a placebo-controlled trial failed to demonstrate clear benefits of vasodilator therapy with either nifedipine or an ACE inhibitor,[122] but there are concerns regarding the size of the study, dose of drug used, and modest severity of disease at baseline.

Oral vasodilators that have been described as having potential therapeutic benefit include several dihydropyridine calcium channel blockers (nifedipine and felodipine), as well as hydralazine. The appropriateness of vasodilator therapy regardless of severity of disease is clearer in patients with systemic hypertension, in whom reduction of afterload has dual benefits. The dose of drug should be sufficient to show at least some reduction in systolic pressure. There is no evidence base to recommend other forms of medical therapy, such as nitrates or drugs commonly used to treat congestive heart failure, to prevent progression of disease in chronic asymptomatic AI. Nevertheless, there is a general consensus that ACE inhibitors or ARBs as well as β-blockers are reasonable in patients with severe symptomatic AI and/or those who have LV dysfunction[123]; β-blockers in general should be used with caution because of potential deleterious effects of negative chronotropy. In the critical care setting, inotropes and vasodilators are appropriate if patients have congestive heart failure, a low output state, or both.

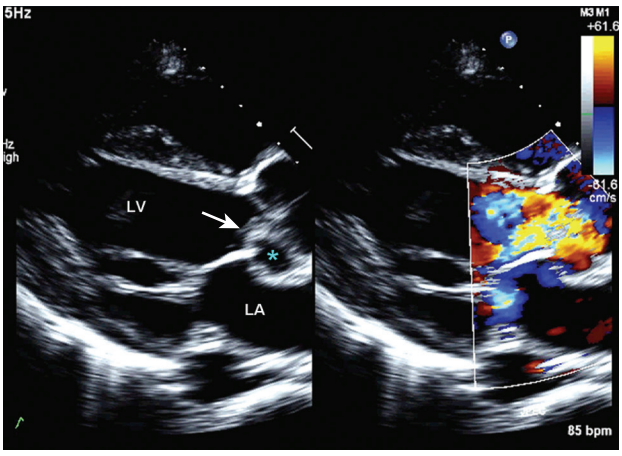
Aortic Valve Replacement

Two factors primarily determine when a patient should be referred for valve replacement for aortic insufficiency: the presence of symptoms and findings of LV systolic dysfunction.[4] Surgery results in superior long-term survival compared with medical therapy alone for symptomatic patients.[107,124] Similarly, patients with LV dysfunction have an inverse correlation between EF and mortality risk.[125] Three AHA/ACC class I indications for surgery, all for patients with severe AI, exist: (1) patients with symptoms regardless of LV function; (2) patients with LV systolic dysfunction (EF ≤ 50%) regardless of symptoms; and (3) patients undergoing coronary bypass surgery or surgery on other heart valves or the aorta. Several devices are being developed for TAVR for native aortic valve insufficiency; these typically attach by clipping onto the existing leaflets rather than attaching to leaflet calcification. The JenaValve (JenaValve Technology, Inc., Irvine, CA) is CE (European Conformity) marked for this indication.

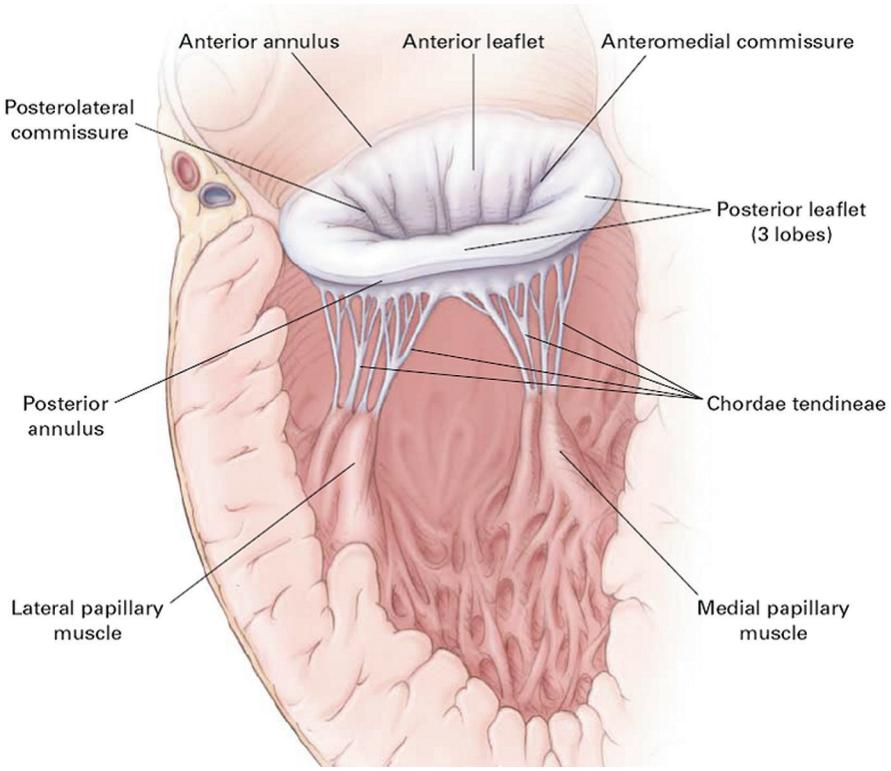
The AHA/ACC guidelines lowered the thresholds for AVR in 2014[4] for patients with chronic severe AI. For asymptomatic patients with preserved LVEF (≥50%) who show signs of LV dilatation, the threshold is set at 50 mm as the end-systolic threshold (class IIa) and 65 mm as the end-diastolic threshold (class IIb and assumes the patient is low surgical risk). Patients with only moderate (progressive) AI who are undergoing other cardiac surgery are also considered to have class II indications.

The question of whether it is ever too late to perform AVR in patients with AI has been raised.[108] Because the disease involves high afterload and wall stress, there is postoperative improvement in EF[126] even in patients with severe baseline LV dysfunction. In general, there is substantial reversal of the physiologic adaptations required by chronic severe AI in the postoperative state.[127] Nevertheless, delay in referring patients for surgery is deleterious, with significant negative impact on outcomes[128]; the prognosis is adversely affected both by the severity and duration of LV dysfunction.[129] This includes a fourfold increase in the operative mortality rate for patients with EF less than 35% (14%) compared with those with EF greater than 50% (3.7%). Thus the trend has been for earlier referral of symptomatic patients and more aggressive noninvasive monitoring for early detection of deterioration in LV function or dimensions.

Special consideration should be given to patients with acute aortic valve endocarditis. Deteriorating hemodynamics mandate early surgery,[84] as do the following conditions: extension of infection, as manifest by progressive heart block and ring abscess formation on echocardiography (Fig. 30.12); recurrent emboli and persistent vegetations despite antibiotics or mobile vegetations greater than 10 mm in length; infection with *Staphylococcus aureus* organisms,



• **Fig. 30.12** Vegetation *(arrow).* On the right is wide-open aortic insufficiency; the jet fills the outflow tract. The asterisk on the left refers to a walled-off echolucent abscess cavity. *LA,* Left atrium; *LV,* left ventricle.



• **Fig. 30.13** Structure of the mitral valve, its surrounding apparatus, and relationship to the left ventricle. Each component can contribute to the presence and extent of mitral regurgitation. (From Otto CM. Evaluation and management of chronic mitral regurgitation. *N Engl J Med*. 2001;345:740–746.)

fungi, or other highly resistant organisms[4]; or the occurrence of stroke without intracranial bleeding or extensive neurologic damage.[130,131] Despite the semielective nature of the operation (with an operative mortality rate close to 10%) and the theoretical risk of an infected prosthesis, the long-term outcomes have been satisfactory, with 75% 10-year survival rate after hospital discharge.[132]

Mixed Aortic Valve Disease

Mixed aortic valve disease (MAVD) denotes the presence of both AS and AI. This combination results in both pressure and volume overload that appears to have an additive effect on severity of symptoms as well as on outcomes. As such, the 2014 Guidelines[84] incorporate a higher valve area threshold (≥1.0 cm^2) for the class D1 category of severe AS (see Table 30.2). The prognosis and management of MAVD are less well studied than isolated aortic valve disease, but in general the available literature suggests an adverse effect on overall prognosis.[133] In a study from the Mayo Clinic,[134] patients with moderate MAVD demonstrated adverse event rates similar to those of patients with severe AS, and higher than in patients with either isolated moderate AS or AI. In addition, in a subset of MAVD patients with concentric hypertrophy, patients tended to become symptomatic, requiring AVR even in the absence of any progression of the severity of aortic valve disease. The recommendation is for closer echocardiographic and clinical follow-up in patients with MAVD.[84] In a multicenter registry of patients undergoing TAVR,[135] the incidence of MAVD was approximately 40% and MAVD was associated with lower device success and higher postprocedural AI; the latter was associated with increased cardiovascular mortality. TAVR is currently not FDA approved for treatment of predominant AI.

Mitral Regurgitation

Anatomically and physiologically, the mitral valve is the most complex of the heart valves, dependent for function on the interaction among leaflets, annulus, commissures, and the supporting apparatus consisting of chordae tendineae tethered to the papillary muscles (Fig. 30.13). Distortion or dysfunction of any of the elements and changes in function and geometry of the left ventricle and left atrium can all have a significant impact on flow across the mitral valve. In addition, unlike other valvulopathies, the mitral valve is highly dependent on the myocardial circulation. In contrast with the relatively passive nature of opening and closing of the aortic valve, mitral valve motion is an active process reflecting not only cyclical pressure variations but also tethering and dynamic interaction with the supporting apparatus. As with AI, MR has acute and chronic manifestations and chronic (rather than acute) insufficiency is more common. However, acute MR has a much larger variety of causes than acute AI and the overall incidence is higher. Data from the Framingham Offspring Study revealed a prevalence of moderate or greater MR from 0.9% of women in the fifth decade of life to 11.2% of men between ages 70 and 83, which was correlated with age, low body mass, and systemic hypertension.[98] As with AI, ventricular function predicts overall outcomes. Chronic MR can both cause and be the result of LV remodeling and heart failure and, when secondary to LV dysfunction, is associated with a significantly poorer overall prognosis than LV dysfunction without secondary MR.[136]

Pathophysiology

Fundamental understanding of the pathophysiology of MR has expanded substantially in the past two decades. In particular, awareness of the role of the subvalvular apparatus in preserving LV function and data demonstrating the need for earlier referral to surgery have resulted in significant changes in clinical and surgical practice, leading to substantial improvement in outcomes.[137]

As with AI, MR results in volume overloading of the LV. Unlike AI, the afterload is not increased and overall LV ejection is enhanced rather than impaired by loading conditions, although in significant MR half or more of the ejection is retrograde into the left atrium. The incompetent mitral valve acts as a second pathway for blood ejection, which reduces afterload in a setting in which preload is increased, thus potentiating ejection via the Frank-Starling mechanism. The combination ultimately may raise EF to supranormal early in the course of the disease. As a result, patients with "normal" EF may already have significant impairment in LV function.[138] Adaptations to the volume loading include lengthening of the myocytes, which increases LV volume. Progressive MR eventually results in contractile dysfunction. Relatively early in the course of the disease, the sympathetic nervous system is activated as a compensatory mechanism to volume loading and decreased forward ejection.[139] Chronic high sympathetic tone results in secondary myocardial damage[140] and has been postulated as the rationale for potential benefit from β-blockade in chronic MR.[141] Over time, although some hypertrophy develops, the predominant response to volume overload without pressure overload is enlargement of chamber size. Extrapolating the LaPlace relationship, which is manifestly protective of wall stress in AS, the progressive expansion of LV dimensions in MR without similar compensatory hypertrophy results in increasing wall stress, which in turn results in increasing MR. In a similar manner, a second vicious circle is caused by the effect of MR on LV chamber size, which, as it enlarges, results in stretching of the annulus, further exacerbating MR.[142] Thus chronic MR can both cause and be the result of LV remodeling and heart failure.

The causes of MR vary by geography, with mitral valve prolapse the most common cause in industrialized nations. Rheumatic MR remains common in developing countries. The causes of acute MR include ischemic MR, endocarditis, chordal rupture, papillary muscle dysfunction, and a variety of pathologies affecting prosthetic valves (Box 30.3). The most likely causes of acute MR in the critical care setting are ischemia, including acute myocardial

• BOX 30.3 Etiology of Acute and Chronic Mitral Insufficiency

Acute

Mitral Annular Disorders
Infective endocarditis (with abscess)
Trauma (e.g., valve surgery)
Paravalvular leak
- Surgical—suture interruption
- Infection

Mitral Leaflet Disorders
Infective endocarditis (with perforation or vegetation interfering with coaptation)
Trauma
Atrial myxoma
Myxomatous degeneration
Systemic lupus erythematosus (Libman-Sacks lesions)

Chordal Rupture
Spontaneous
Myxomatous degeneration
- Mitral valve prolapse
- Marfan syndrome
- Ehlers-Danlos syndrome

Infective endocarditis
Acute rheumatic fever
Trauma

Papillary Muscle Disorders
Coronary artery disease
Acute global left ventricular dysfunction
Infiltrative diseases (amyloidosis, sarcoidosis)
Trauma

Primary Mitral Valve Prosthetic Disorders
Bioprosthetic cusp perforation
Bioprosthetic cusp degeneration
Mechanical failure (e.g., strut fracture)
- Immobilized disk or ball

Chronic Disorders

Inflammatory
Rheumatic heart disease
Systemic lupus erythematosus
Scleroderma

Degenerative
Myxomatous degeneration (mitral valve prolapse)
Marfan syndrome
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Calcification of mitral valve annulus

Infective
Endocarditis

Structural
Ruptured chordae tendineae
Spontaneous secondary to:
- Myocardial infarction
- Trauma
- Mitral valve prolapse
- Endocarditis
- Rupture or dysfunction of papillary muscle (ischemia or infarction)

Dilation of mitral valve annulus and left ventricular cavity
- Congestive cardiomyopathies
- Aneurysmal dilation of the left ventricle

Hypertrophic cardiomyopathy
Prosthetic paravalvular leak

Congenital Disorders
Mitral valve clefts or fenestrations
Parachute mitral valve abnormality in association with other congenital disorders

From Otto CM, Bonow RO. Valvular heart disease. In: Mann DL, Zipes DP, Libby P, et al., eds. Braunwald's Heart Disease; A Textbook of Cardiovascular Medicine. *10th ed. Philadelphia: Elsevier; 2015:1446–1523.*

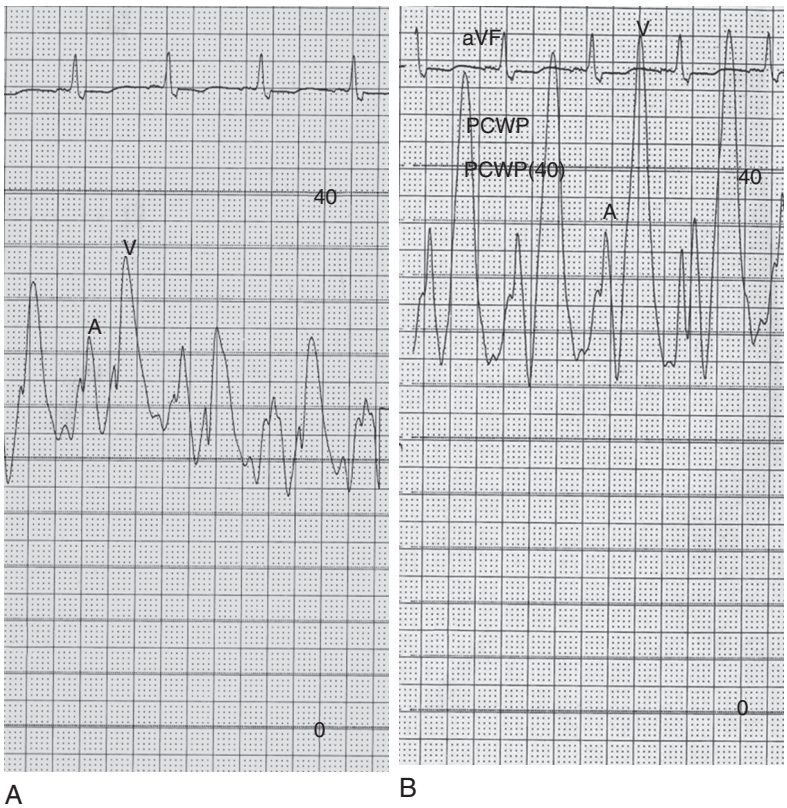
infarction (AMI), and infectious endocarditis, and should be considered in any patient who develops sudden hemodynamic decompensation in the peri-infarction period or who has known endocarditis. Chronic MR is secondary to a variety of structural, degenerative, connective tissue, inflammatory, and ischemic disorders, as well as congenital abnormalities outlined in Box 30.3.

The classic teaching has been that acute MR secondary to ischemia was caused by papillary muscle dysfunction, most likely secondary to ischemia of the posteromedial papillary muscle, which is dependent on a single blood supply from the right coronary artery. The anterolateral papillary muscle typically has dual circulation from the left anterior descending and circumflex coronary arteries, specifically from a diagonal branch and a circumflex marginal branch. The source of papillary muscle circulation is in fact variable, and on occasion the anterior papillary muscle also has a single blood supply.[143] The role of impaired circulation to the papillary muscle as the cause of ischemic MR has been revisited,[144] and evidence to date suggests that ischemic MR is secondary to alterations in ventricular geometry and leaflet tethering rather than dysfunction caused solely by impaired circulation to the papillary muscle during ischemia,[145] although alterations in papillary muscle geometry can be seen in chronic ischemic MR.[146] The hemodynamics of dynamic, ischemic MR are shown in Fig. 30.14.

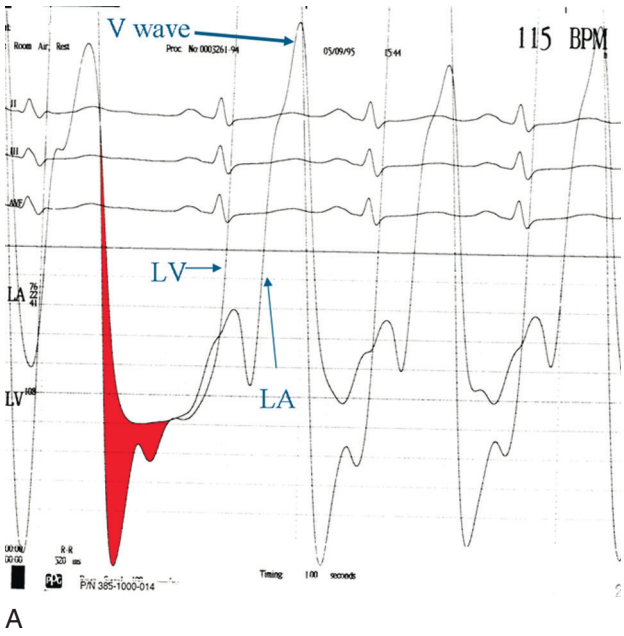
Analysis of thrombolysis in myocardial infarction (MI) data showed a 27% incidence of MR (most commonly in the setting of anterior rather than inferior MI), although these values vary widely by criteria and techniques used for screening, with the incidence ranging from 11% to 59%.[147] A Mayo Clinic review of more than 1300 patients with AMI found moderate to severe MR in 12% and found it to be an independent predictor of both heart failure and survival.[148] It is associated with multivessel CAD, as well as prior infarction.[149]

Papillary muscle rupture is a rare but potentially catastrophic cause of flail leaflets and represents a surgical emergency.[150] In addition to the typical AMI setting, it may be secondary to trauma and isolated other causes such as postpartum Ehlers-Danlos syndrome.[151] Other causes of acute MR to consider (see Box 30.3) include spontaneous chordal rupture, infectious endocarditis with distortion of the valve leaflets or chordal rupture, and prosthetic valve dysfunction including paravalvular prosthetic valve leak. In patients with sudden onset of acute MR, retrograde flow is typically into a normal-sized and relatively noncompliant left atrium unless preexisting atrial hypertension has been present. The sudden volume loading immediately places the left atrium on the steep portion of its pressure-volume curve, which commonly causes acute pulmonary edema. As is the case with acute AI, the left ventricle is unable to adapt acutely and effective forward stroke volume is decreased. In the setting of MI in particular, patients with acute MR may develop cardiogenic shock.

The classic hemodynamic response, a giant V wave, is shown in Fig. 30.15. Differentiating a giant V wave from a prominent pulmonary artery pressure waveform can be difficult in the critical



• **Fig. 30.14** Dynamic mitral insufficiency in a patient with transient left ventricular dysfunction after recent acute myocardial infarction. The panel on the left (A) demonstrates hemodynamics on a 40-mm Hg scale at baseline. Note elevated filling pressures at a mean of 24 mm Hg with V waves at average height of 32 mm Hg. The panel on the right (B) shows tracings recorded a few minutes later. Mean pulmonary capillary wedge pressure rose to 33 mm Hg with V waves to 48 mm Hg. *A,* A wave; *PCWP,* pulmonary capillary wedge pressure; *V,* V wave.



• **Fig. 30.15** Hemodynamics (A) of severe MR (40-mm Hg scale) with giant V wave (to 70 mm Hg) late in systole. As left atrium *(LA)* pressure rises in acute severe mitral regurgitation, the gradient between the left ventricle *(LV)* and LA pressure tracing is reduced and may result in a decrease in intensity of the murmur in late systole. The markedly thickened mitral valve (B) was excised from this patient after being torn *(arrow)* during balloon mitral commissurotomy. Elimination of mitral stenosis gradient *(area in A, filled in red)* is demonstrated. *BPM,* Beats/min.

care setting, and repeated attempts to obtain a wedge pressure when the catheter is already in the wedge position may result in iatrogenic pulmonary artery hemorrhage.

Diagnosis

Physical Examination

In acute MR the abrupt rise of left atrial pressure results from torrential retrograde flow, although the gradient between the left atrium and left ventricle may narrow substantially near the end of systole because of the substantial rise in left atrial pressure as shown in Fig. 30.15. Thus the systolic murmur may decrease in intensity before the onset of the aortic second heart sound. A systolic thrill may be noted. The sudden and severe left atrial hypertension typically results in pulmonary edema with accompanying physical findings, as well as an increase in the pulmonic second sound and paradoxical splitting of the second heart sound. Because the adaptive mechanisms are not yet in place, features of LV volume overload are not seen, although a prominent precordial impulse, reflecting increased (albeit retrograde) ejection, may be noted. Unlike AI, the pulse pressure is not increased and may be reduced to reflect the lower forward stroke volume.

In chronic MR, precordial features of volume overload include a displaced point of maximal impulse and prominent precordial pulsation. An S_3 gallop is heard, especially with marked dilation of the left ventricle,[110] and a diastolic flow murmur representing increased transvalvular flow (rather than MS) may be present. The first heart sound may be soft, reflecting lack of brisk apposition of the mitral valve leaflets. The murmur of MR commences immediately after the first heart sound, reflecting the observation that a significant amount of regurgitation takes place during what would otherwise be isovolumic systole (which normally commences immediately after mitral valve closure). The murmur of chronic MR is characteristically blowing; may be medium or high pitched; is best heard at the apex; radiates to the axilla and left scapula (when severe); and extends throughout systole, reflecting the presence of a relatively high gradient throughout LV ejection.

The location of radiation can provide a clue to the affected leaflet; anteriorly directed jets result from posterior leaflet dysfunction, and conversely, anterior leaflet prolapse results in a murmur best heard toward the patient's back. Because the Gallavardin phenomenon in AS mimics an MR murmur, it is important to differentiate these two when possible (AS and MR frequently occur concurrently, given the high LV systolic pressure with the former). The murmur of MR differs because it is holosystolic and increases rather than decreases with handgrip.

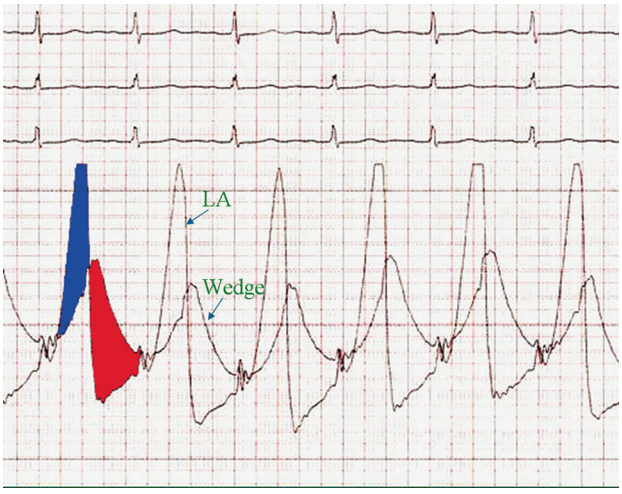
The intensity of the MR murmur reflects a number of phenomena relating to the size of the gradient, compliance of the left ventricle and left atrium, and contractility of the left ventricle but does not correlate well with extent of MR; thus the murmur may be difficult to hear or inaudible, especially in the critical care setting.[152]

Noninvasive Evaluation

Echocardiography provides visualization of the multiple structures responsible for causing MR, including the valve leaflets, annulus, chordae tendineae papillary muscles, and left ventricle (see Fig. 30.13). TEE provides superior imaging of the valve, including assessment for vegetations if endocarditis is suspected and better visualization of flail leaflets; it is particularly useful when the transthoracic views are incomplete or inadequate. In general, TEE is superior for fully assessing characteristics of the mitral regurgitant jet[153] and provides additional information in evaluating mitral valve morphology and motion. As with AI, Doppler methods allow assessment of the width of the regurgitant jet and size of the vena contracta, and semiquantitative measures of the regurgitant volume, regurgitant jet, and effective orifice area; these are discussed in detail in Chapter 8. In patients presenting with acute heart failure and a hyperdynamic left ventricle, acute MR should always be considered. Where TEE does not provide adequate information to assess severity of MR, cardiac MRI is indicated (class I).[154]

Cardiac Catheterization

Although the indications for cardiac catheterization (see Box 30.1) are similar to those for AS and AI, an additional consideration is included as a class I indication: to assess pulmonary artery pressures



• **Fig. 30.16** Underestimation of the left atrial V wave by pulmonary wedge pressure recording in the setting of severe mitral insufficiency (mitral regurgitation [MR]). The tracings show simultaneous left atrial and pulmonary artery wedge pressures in a patient with chronic severe MR because of paravalvular leak (40-mm Hg scale). The V wave on the wedge tracings is approximately 28 mm Hg, but on direct left atrial pressure the measurement obtained by transseptal puncture is 44 mm Hg. The gradients between the wedge pressure and left atrial pressure during systole *(area filled in blue)* and during diastole *(area filled in red)* represent artifact because of damping and phase delay of pressure waveforms reflected across the pulmonary vascular bed. The effect of this damping is gross underestimation of the severity of the V wave and overestimation of any gradient between the left atrium *(LA)* and left ventricle; these in turn result in underestimation of severity of MR and overestimation of the severity of mitral stenosis when pulmonary wedge pressures are used. The mean of the two pressures is exactly the same.

at rest and if necessary with exercise to evaluate appropriateness for surgery (see valve replacement indications later). The size of the V wave is not an accurate indicator of MR severity and is not used as a decision-making criterion for surgery because it may be unremarkable even in severe MR when there is high left atrial compliance. In addition, the size of the V wave is typically recorded by wedge rather than direct left atrial pressure, which can result in significant underestimation of the severity of MR (Fig. 30.16). Right heart catheterization and oxygen saturation sampling allow differentiation between two of the most common causes of abrupt mechanical deterioration in AMI: severe MR and ventricular septal defect. Both conditions can feature a large V wave because of sudden volume loading of a noncompliant left atrium—secondary to retrograde flow across the mitral valve in the case of acute MR and antegrade flow of shunted blood from the LV across the pulmonary circulation in the case of a ventricular septal defect.

Therapy

Medical Management

For acute, severe, symptomatic MR, the primary medical therapy consists of aggressive vasodilation with nitroprusside or nicardipine.[4] It provides improved aortic flow, diminishes MR, and decreases left-sided filling pressures. In the setting of acute MR with shock, nitroprusside alone is usually considered undesirable because of poor end-organ perfusion if further hypotension is caused by the drug. IABP is highly effective in this setting[155] (see Chapter 7) because it lowers aortic impedance, improves CO, and decreases regurgitant fraction at the same time as it restores blood pressure. A combination of an inotrope (typically dobutamine; a vasoconstrictor should be avoided) and nitroprusside can have similar salutary effects. When the acute MR is dynamic (i.e., occurs and resolves abruptly), the cause is frequently acute ischemia, and consideration should be given to evaluating the coronary circulation. In a small number of cases, acute coronary intervention has been documented to alleviate MR in the setting of acute ischemia.[156]

Medical therapy for chronic MR is more controversial. Because afterload is typically not increased, the benefits of afterload reduction are without clear physiologic foundation in normotensive patients with preserved LV function. As such, ACE inhibitors have consistently been shown not to be effective for chronic MR in this setting.[157–159] When concomitant systemic hypertension exists, physiologic benefits appear more convincing.[160] If patients have LV dysfunction superimposed on chronic MR, medical therapy with ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists may be beneficial, and several studies have observed functional improvement with resynchronization.[161,162] As with other valvular disorders, new-onset AF can result in abrupt hemodynamic deterioration and cardioversion should be considered with adjunctive pharmacotherapy to maintain sinus rhythm and rate control. Because of the sympathetic activation previously discussed, β-blockers appear to be beneficial[163,164] and may have additive benefit when used in combination with ACE inhibitors.[165] Both classes of drugs appear to be therapeutic when used after mitral valve repair.[166]

Mitral Valve Surgery

Three types of surgery are performed on the mitral valve: repair, replacement with preservation of the subvalvular apparatus and attachments, and replacement with transection of the chordae. In the setting of nonischemic MR, mitral valve repair has been consistently shown to improve outcomes compared with mitral valve replacement, both acutely and long term, with a fourfold lower operative mortality rate and a 30% improvement in 10-year survival rate.[167] With mitral valve replacement, patients who nevertheless have the chordal apparatus preserved have superior long-term outcomes compared with those who have the chords transected.[168] An additional benefit of repair is the potential avoidance of anticoagulation if patients are in sinus rhythm compared with replacement with a mechanical valve where anticoagulation is required.

In contrast, outcomes in the setting of ischemic MR have been much more muted. In a randomized trial of repair versus replacement, repair provided no survival or LV remodeling benefits at 2 years follow-up,[169] but there was a higher rate of recurrence of moderate or severe MR, with an associated increase in heart failure–related events. Similarly, random assignment of patients undergoing coronary artery bypass grafting (CABG) who had moderate ischemic MR to CABG alone or CABG plus mitral valve replacement did not demonstrate improvement in survival or LV remodeling in the latter group but was associated with more early neurologic events and supraventricular arrhythmias.[170]

In general, the timing of surgery for chronic MR should be before the onset of LV dysfunction. The most commonly used markers are symptoms and echocardiographic parameters, including LVEF less than 60%.[4] Patients who develop class III or IV symptoms, even transiently, have a nearly 10-fold increase in annual mortality rate,[171] with evidence that early surgery in the setting of severe MR improves overall survival. The 60% LVEF threshold for surgery has been shown to correlate with postoperative LV function[172] as well as survival.[173] The effective regurgitant orifice

has been shown to be strongly predictive of 5-year mortality risk; patients with an orifice size of 40 mm^2 or greater have an odds ratio of death greater than 5:1 compared with patients with orifice size of 20 mm^2 or less.[174] Preoperative end-systolic diameter of 40 mm or less has also been associated with superior outcomes. Patients with AF in general have a worse prognosis,[175] although in large part because of embolic events rather than LV dysfunction, as do patients with pulmonary hypertension or right-sided heart failure, or both.[176] Conventional wisdom has been that mitral valve surgery may result in postoperative return to normal function in patients with depressed EF.[177] However, patients with severe MR who reach the 60% EF threshold (or LV end-diastolic dimension ≥40 mm) have in fact already developed LV systolic function. As a result, the 2017 AHA/CCC Guidelines[84] have added a class IIa indication for mitral valve surgery for asymptomatic patients with severe primary MR and preserved LV function who have progressive increase in LV size or decreasing EF; this is based on evidence that waiting for patients to reach the thresholds described earlier, when the LV is dilating and systolic function is deteriorating, may result in irreversible LV dysfunction.[178] Comparison of long-term outcomes between operated and medically treated patients with asymptomatic MR has invariably favored the former,[174] although much of the data depend on nonrandomized registry data. The key to improved function and outcomes has generally included preserving the integrity of the submitral apparatus,[179] and comparison of successful repair versus replacement has indicated that high-volume institutions (>140 mitral operations/year) have the best results with nearly twice the rate of successful repair as low-volume institutions.[180]

A common teaching has been that repair or replacement of the mitral valve eliminates the "pop-off valve" represented by incompetent leaflets, resulting in dramatically increased afterload postoperatively. This has in turn led to concern that if significant preoperative LV dysfunction is present, the left ventricle will fail, with hemodynamic deterioration and subsequent death. In fact, careful investigation has demonstrated that when postoperative deterioration of LV function occurs, it has been secondary to disruption of chordal integrity[181] and elimination of the favorable effects of the submitral apparatus on valvular-ventricular interaction rather than the elimination of a low-pressure decompression pathway. Afterload following mitral valve surgery with chordal transection does in fact increase, whereas patients who undergo mitral valve surgery with preservation of the chordal apparatus have decreased LV chamber volume and, in keeping with the LaPlace equation, reduced afterload.[182] Thus the recommendations regarding LVEF for surgery have changed dramatically, and successful repair of mitral valves in a series of patients with EF less than 25% has been reported with operative risk of less than or equal to 5%.[183] The operative risk is in the 1% to 2% range for symptomatic patients with LV dysfunction but higher EF.[184] Similarly, the Society of Thoracic Surgeons database has reported mortality rates of approximately 5% with EF less than or equal to 30% but 3% with EF greater than 30%.[185] Propensity analysis of patients eligible for mitral valve repair who did or did not undergo the procedure has not shown a survival advantage in patients with mean EF less than 25%,[166] although a randomized trial has not been reported. Similarly, concomitant mitral valve surgery in patients with moderate or greater MR undergoing CABG procedures did not clearly improve short-term survival,[186] similar to the subsequent randomized trial of moderate ischemic MR already described.[170]

In symptomatic acute severe MR, mitral valve surgery is the primary treatment regardless of level of LV function.[4] With both infective endocarditis[131] and papillary muscle or chordal rupture, surgery is mandated to be performed with as little delay as possible.[187] However, the overall risk of mortality when MR accompanies AMI is substantially increased,[188] a phenomenon noted in patients undergoing emergent percutaneous intervention as well.[189] The management for chronic severe MR is complex as outlined in Fig. 30.17.

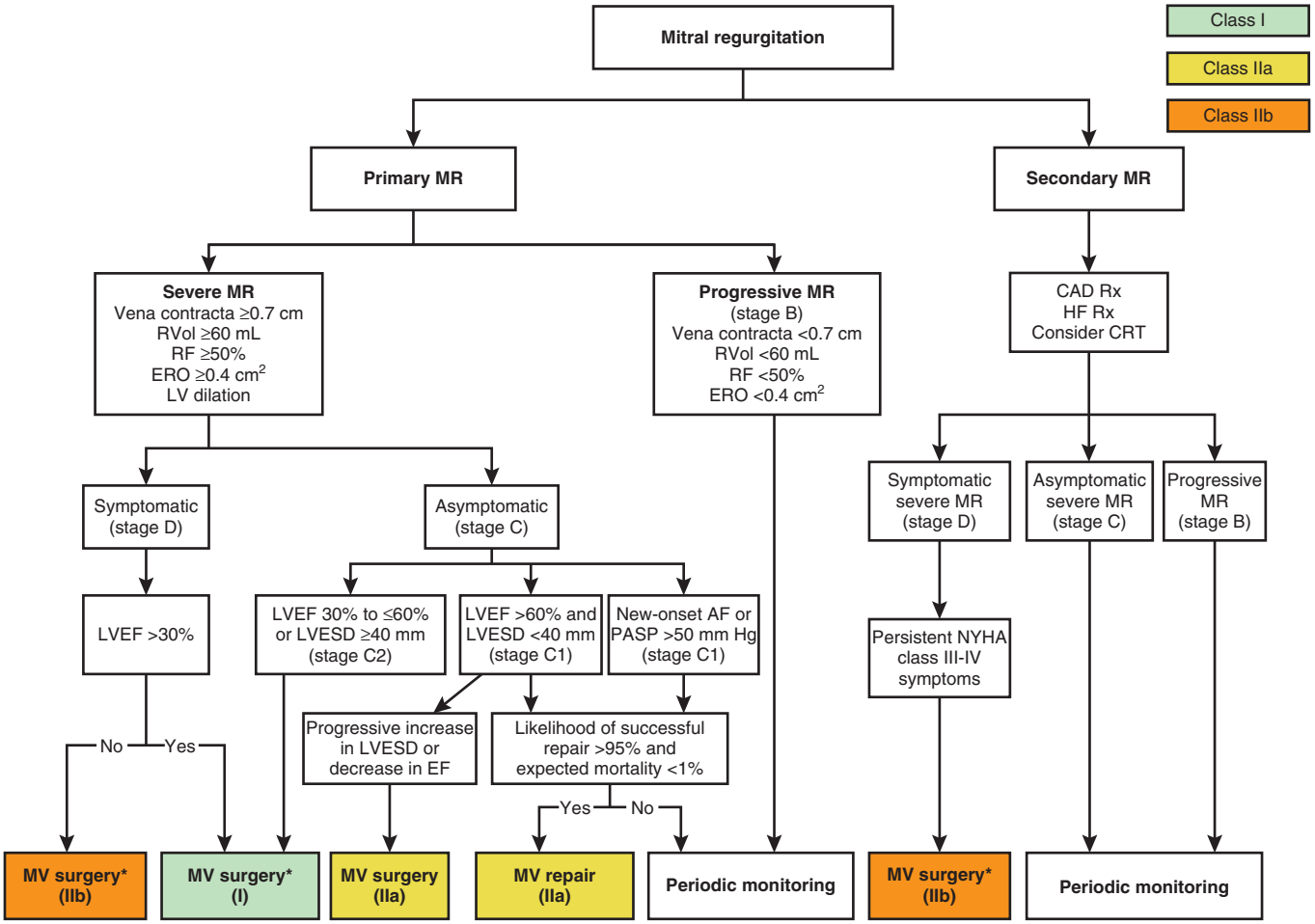
Percutaneous Mitral Valve Repair and Replacement

A number of innovative technologies are being developed for percutaneous treatment of MR (Fig. 30.18). The most extensively studied is based on catheter-based edge-to-edge repair of the mitral leaflets designed to mimic the surgical procedure developed by Alfieri and colleagues.[190] The EVEREST (Endovascular Valve Edge-to-edge REpair STudy) II trial[191] compared 184 patients randomly assigned to percutaneous repair (MitraClip; Abbott Vascular, Santa Clara, CA) versus 95 patients randomly assigned to surgical mitral valve repair and had promising though somewhat nuanced results. Although there was good safety profile and similar quality-of-life improvement, grade 2 or greater MR was present in nearly half the percutaneous repair patients at 1 year compared with only 17% of the surgical repair patients. The surgical patients did have more adverse events, primarily blood transfusions. The surgical approach appeared clearly superior for patients with degenerative (or primary) MR, with relative parity in outcomes in functional (or secondary) MR patients (those with structurally normal mitral valves, but typically dilatation of the mitral annulus). Although the difference between surgery and MitraClip persisted at 5-year follow-up, the majority of events that favored surgery were noted early. Follow-up after 6 months showed that the rates of worsening MR and surgery for mitral dysfunction were comparable; these findings point to durability of clip repair.[192] MitraClip is currently approved in the United States for severe primary MR in patients who are severely symptomatic (NYHA class III/IV) and are at prohibitive risk for surgery (a class IIB indication).[4] There is an ongoing Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial comparing MitraClip for functional MR versus guideline-directed medical therapy in patients who are very high risk to inoperable.

Transcatheter mitral valve replacement is being performed via a variety of access routes including transapical, transjugular, and transseptal. Most commonly the Sapien 3 valve (Edwards Lifesciences, Irvine, CA) is being placed in three settings when there is a suitable anchor: ViV replacement for prosthetic degenerative MR or MS (FDA approved), valve-in-ring when there is sufficient support from a previously placed annular prosthesis, and valve-in-calcium when there is severe mitral annular calcification (MAC). There are ongoing registries and moderate success, albeit with some important limitations, perhaps most importantly impingement on the LVOT, which requires careful preprocedure assessment and planning.[193]

Future Directions

The Alfieri procedure is an uncommonly performed type of surgical mitral valve repair, and as with most repair procedures typically involves placement of a prosthetic ring, an option not available with the percutaneous approach; this is a potential limitation of its long-term (>5-year) applicability as an isolated intervention.[194] In this context, it is worth noting that several other percutaneous technologies are under development[195] (see Fig. 30.18). They are broadly based on a few principles and techniques: (1) direct annuloplasty annular repair, (2) indirect annuloplasty by coronary



• **Fig. 30.17** Algorithm for management of patients with chronic mitral regurgitation. The asterisk denotes that mitral regurgitation *(MR).* MV repair is preferred over MV replacement when possible. *AF,* Atrial fibrillation; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *EF,* ejection fraction; *ERO,* effective regurgitant orifice; *HF,* heart failure; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic diameter; *MV,* mitral valve; *NYHA,* New York Heart Association; *PASP,* pulmonary artery systolic pressure; *RF,* regurgitant fraction; *RVol,* regurgitant volume; *Rx,* therapy. (From Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70:252–289.)

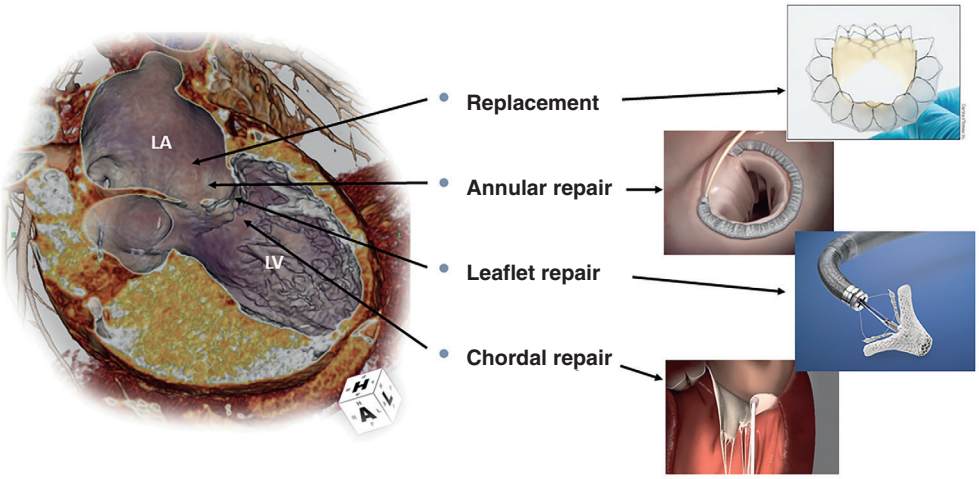
sinus cinching, (3) chordal repair, and (4) transcatheter mitral valve replacement technologies that can be delivered transapically or transseptally.

Hypertrophic Obstructive Cardiomyopathy

Although a disease of the heart muscle rather than a primary valvular disorder, HCM has important features of LV outflow obstruction and concomitant MR. The clinical presentation, physical examination, noninvasive and invasive findings, and overall management differ in general from AS or MR, and HCM represents an important consideration for patients in critical care units,[196] where patients with a systolic murmur and hypotension, syncope, or exercise-induced cardiac arrest in particular should have HCM included in the differential diagnosis. The disease has a wide variety of manifestations, including diastolic dysfunction and LV outflow obstruction, and may include coronary flow abnormalities resulting in ischemia, atrial and ventricular rhythm disorders, and LV systolic dysfunction. There is an associated risk of sudden death, heart failure, and cerebral and systemic embolism.[197] Approximately one-third of patients with HCM have a nonobstructive form of the disease, which in a minority of cases, predisposes patients to severe, sometimes refractory, heart failure.[198]

Pathophysiology

The hallmark of the obstructive form of HCM is dynamic obstruction of the LOVT with eccentric hypertrophy; many variations exist, and obstruction is not always at the subvalvular level. Only approximately one-fourth to one-third of patients with HCM have a resting gradient of 30 mm Hg or greater.[199] HCM is found in approximately 0.2% of the population[200] and is defined as hypertrophy of the left ventricle that is not secondary to hypertrophic stimuli such as systemic hypertension or AS. LV hypertrophy usually



• **Fig. 30.18** Novel therapeutic interventions for mitral insufficiency. All except the mitral valve clip used for leaflet repair are experimental in the United States. *LA,* Left atrium; *LV,* left ventricle.

develops during adolescence, although it can occur late.[201] Contrary to conventional wisdom, the majority of patients with HCM were found to have provocable gradients with exercise in a single large-volume center[202] (likely with some skewing owing to the nature of its referral population). The genetics of HCM have been studied extensively, and although complex, there is a familial association in a majority of patients. The degree of hypertrophy may be related to the underlying genetic abnormality. In familial HCM, autosomal dominant loci that encode one of the myocardial contractile proteins of the cardiac sarcomere are frequently present.[203] Cardiac myosin-binding protein C gene and cardiac β-myosin heavy chain gene mutations are most commonly noted. Although the clinical course may be generally benign in patients without risk factors for adverse events,[204] it is the most common cardiac cause of sudden death in young adults,[205] is associated with cardiac arrest in athletes,[206] and leads to heart failure, rhythm disturbances, and occasional sudden death in older patients. The patients at high risk for sudden death, comprising only about 10% to 20% of those within the HCM population, include those with prior cardiac arrest or sustained ventricular tachycardia, those with a family history of HCM and sudden death, hypotensive response to exercise, and severe LVH with wall thickness of 30 mm or greater.[201] A resting gradient across the outflow tract of more than 30 mm Hg alone predicts an increased risk of sudden death or development of moderate to severe congestive heart failure,[199] and there may be higher risk with very high gradients.[207] Because of impaired coronary flow reserve[208] and severe hypertrophy, myocardial ischemia is a potentially important factor in acute patient management; there is also an association between HCM and myocardial coronary bridging.[209]

Diagnosis

Physical Examination

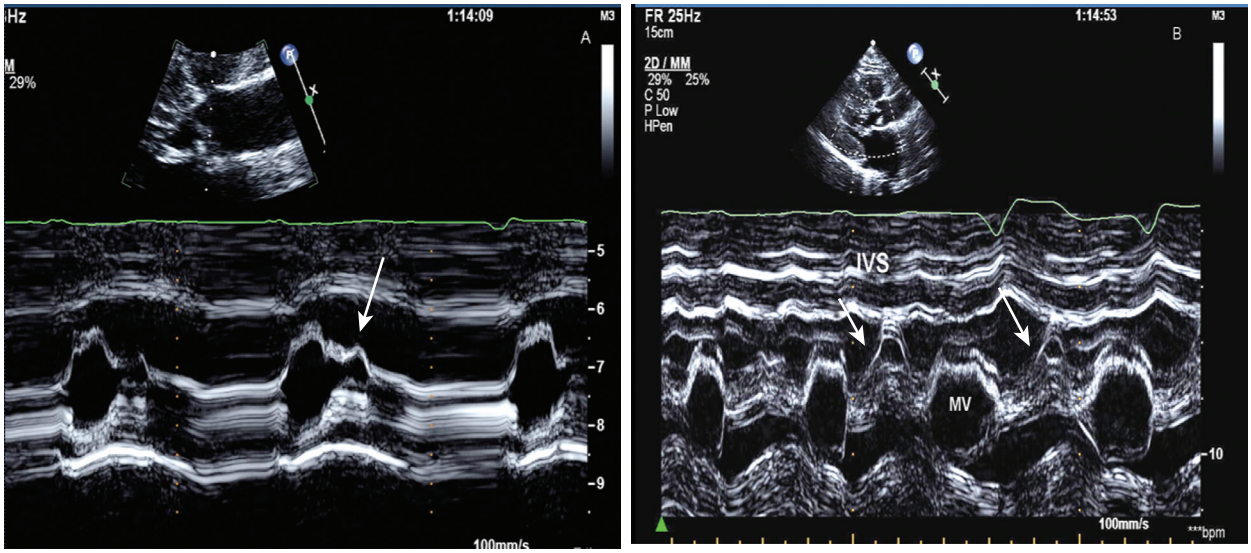
The physical examination in HCM features an abrupt early rise in systolic pressure followed by obstruction to LV outflow, resulting in a blunted pressure rise later in systole. This translates to the spike and dome pattern characteristic of obstructive HCM on palpation of the carotid pulse. The typically hypertrophic septum (1.3 to 1.5 times the thickness of the posterior wall and typically ≥18 mm in clinically significant HCM) obstructs the outflow tract after initial ejection as LV volume decreases. Physiologic maneuvers or clinical states that lower LV volume abruptly, such as standing, dehydration, or use of diuretics, can substantially exacerbate the gradient and increase the intensity of the systolic ejection murmur characteristic of HCM. Because the obstruction begins after the initial brisk ejection of blood from the ventricle, the onset of murmur is late after the first heart sound. It is best heard over the left base of the heart. In contrast to AS, the murmur typically does not radiate to the carotids, does not extend throughout systole, and decreases with squatting. The blunting of the carotid upstroke, so characteristic of AS, is not seen because of the vigorous early ejection.

Noninvasive Evaluation

Abnormalities of mitral valve function are common. Systolic anterior motion of the mitral valve is associated with further obstruction[210]; in addition, MR is a typical secondary finding in HCM. The ECG features LV hypertrophy, strain, and prominent Q waves in the inferior and precordial leads, with narrow QRS complexes being common. The echocardiogram is diagnostic for HCM, providing both an anatomic basis and physiologic evidence of the degree of obstruction (Fig. 30.19). Cardiac MRI is particularly valuable in assessing HCM, providing enhanced visualization of hypertrophied areas, the mitral valve leaflets, aberrant LV muscle bundles, and a variety of other features essential to understanding the many forms of the disease, and helpful in planning intervention.[211]

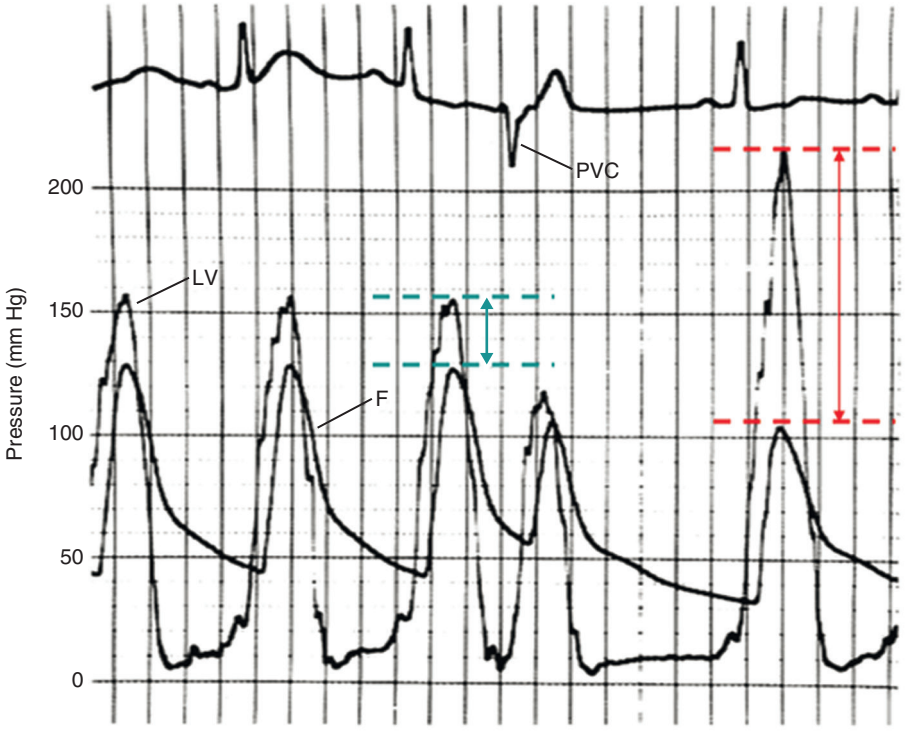
Cardiac Catheterization

Cardiac catheterization in HCM may reveal the standard triad of the Brockenbrough-Braunwald-Morrow sign in the postextrasystolic heartbeat: increase in the gradient between the left ventricle and the aorta, decrease in systemic blood pressure, and narrowing of the pulse pressure (Fig. 30.20). Access to the LV via transseptal puncture, although rarely necessary, affords the opportunity to record pressure gradients without the confounding issues of midcavitary obstruction or catheter entrapment.[212] Other stimuli that increase outflow obstruction and increase gradient are the Valsalva maneuver and amyl nitrite inhalation, in addition to postextrasystolic potentiation.



A B

• **Fig. 30.19** A, M-mode of hypertrophic obstructive cardiomyopathy with aortic valve opening showing the effect of midsystolic outflow obstruction; after initial normal opening, the aortic valve leaflets remain only partially separated because of diminished transvalvular flow *(arrow)*. B, Systolic anterior motion of the anterior mitral leaflet with apposition against outflow tract *(arrows)*. The severely hypertrophied septum on the two-dimensional view is shown at the top of each panel. *IVS,* interventricular septum; *MV,* mitral valve.



• **Fig. 30.20** The Brockenbrough-Braunwald-Morrow sign. Dramatic exaggeration of the resting gradient in the postextrasystolic beat, with lower systemic pressure, and narrowed pulse pressure (difference between femoral systolic and diastolic pressure) are demonstrated—all hallmarks of dynamic outflow obstruction. The *dashed lines* represent left ventricle *(LV)* and femoral *(F)* systolic pressures at rest *(green)* and after a premature ventricular contraction *(PVC) (red);* the gradient rises from a basal 30 mm Hg *(double-headed green arrow)* to approximately 130 mm Hg *(double-headed red arrow)*. (Modified from Pollock SG. Images in clinical medicine. Pressure tracings in obstructive cardiomyopathy. *N Engl J Med.* 1994;331:238.)

Therapy

Medical Management

The management of critically ill patients with HCM focuses on several core principles: optimizing LV volumes, specifically increasing preload while not decreasing afterload; decreasing contractility; and maintaining the patient in sinus rhythm. Thus the typical regimen of diuretics, vasodilators, and inotropes used in most patients presenting with congestive heart failure who do not have HCM can severely exacerbate the outflow gradient and lead to further decompensation or death[213] (as can IABP); somewhat counterintuitively in this setting, negative inotropes, particularly β-blockers, combined with volume loading can stabilize patients.[214,215] Other negative inotropes including verapamil and disopyramide appear to have favorable hemodynamic effects and may represent an alternative to β-blockade.[216] In the patient in shock, if vasopressors are required, agents such as phenylephrine that are primarily peripheral vasoconstrictors should be used rather than inotropic agents. Verapamil has negative inotropic benefits and some utility as an antiarrhythmic agent, as well as diastolic relaxation properties, and has been used successfully in both chronic therapy and acutely decompensated patients with HCM.[217] Verapamil does have some potentially undesirable vasodilator properties and can cause synergistic depression of conduction and contractility in combination with β-blockade; the effects of combined therapy, if used, should be monitored closely.[218] In HCM patients with ongoing chest pain despite medical therapy, ranolazine has been used as an alternative agent.[219]

Patients with hypertrophic heart disease are highly dependent on the atrial contribution to CO,[220] and patients with obstruction in particular depend on the additional LV filling from atrial contraction. AF is a cause of acute decompensation in HCM patients, and cardioversion should be considered acutely. AF occurred in approximately one-fourth of patients with HCM at 9-year follow-up and is predictive of heart failure–related death and stroke.[221] In terms of the latter, patients with HCM and AF appear particularly predisposed to thromboembolic events[222]; anticoagulation has been shown to reduce the incidence significantly.[223] Left atrial size and function predict the onset of AF.[224] The Maze procedure and catheter ablation of left atrial pathways have been used successfully to prevent recurrent AF.[225,226] Amiodarone has been particularly effective for the maintenance of sinus rhythm in the population with AF and HCM[227] and may also have additional efficacy in preventing sudden death in patients with episodes of nonsustained ventricular tachycardia.[228,229] Ventricular fibrillation appears to be the primary cause of sudden death and can be prevented with implantable defibrillators for either primary or secondary prevention, with activation of the devices in 5% to 11% of patients annually depending on indications for placement[230]; episodes of sustained ventricular tachycardia and a history of prior sudden death place patients in the highest risk category.

Percutaneous Intervention or Surgery

Once patients develop refractory symptoms despite pharmacologic management and have significant obstruction to LV outflow (outflow gradient >50 mm Hg at rest or with physiologic provocation), surgical myomectomy or alcohol septal ablation must be considered. The choice is controversial, but in general surgical septal myectomy achieves sustained relief of LVOT obstruction with lower incidence of need for permanent pacemaker and without the potential adverse consequences of the iatrogenic infarction caused by alcohol.[231] Ultimately, the decision depends on LV and coronary anatomy, comorbid conditions, severity of coexistent mitral valve or other potentially surgical heart disease, and a variety of other clinical issues; equivalence of outcomes with the less invasive percutaneous approach has not been demonstrated.[232] Although alcohol ablation does reduce the outflow gradient, it creates a septal infarct and intramyocardial scarring, but it represents an alternative for older patients and those with major comorbidities who are reluctant to have surgery or are poor candidates for surgery.[233] Complications of alcohol septal ablation include the need for permanent pacemaker implantation in 10% to 20% of cases, risk of ventricular tachyarrhythmias, periprocedural mortality (2%), and sudden death. Typical thresholds for intervention are a resting peak instantaneous gradient of 50 mm Hg or more, although depending on degree of symptoms and provocability, a variety of other thresholds have been applied.[201] Mitral valve replacement can frequently be avoided, especially in patients without intrinsic mitral disease in whom MR is largely abolished by myomectomy and relief of the outflow gradient.[234] In patients with intrinsic mitral valve disease or for a variety of other anatomic considerations, mitral valve surgery including use of low-profile prostheses is used.[201] Dual-chamber pacing, once considered therapeutically effective,[235] with theoretical benefit from asynchronous septal contraction and secondary reduction in outflow tract gradient, has not been shown to have clear therapeutic benefit in randomized clinical trials, with functional benefits occurring in a limited subset of elderly patients.[236]

Mitral Valve Stenosis

Mitral valve stenosis (MS) is primarily a rheumatic disorder and, as such, has become increasingly uncommon in industrialized nations. Nevertheless, the disease remains prevalent in developing countries and a small but significant number of patients continue to present in the critical care setting throughout the world. Rheumatic MS involves disease of both the valve leaflets and submitral apparatus and may involve the valve ring as well (Fig. 30.21). Although MS is primarily caused by rheumatic deformity and scarring of the valve leaflets and subvalve with fusion of the commissures, a variety of disorders result in leaflet and annular calcification that also create obstruction between the left atrium and left ventricle. Most notably, MAC, present in 6% of patients undergoing routine echocardiography,[237] is more prevalent in the elderly, women, smokers, and patients receiving dialysis (who have high parathyroid hormone levels). It may present with severe nonrheumatic MS, although MR is a more common association.[238,239] A variety of uncommon other causes account for less than 1% of cases of MS.[240]

Pathophysiology

The physiologic hallmark of MS is obstruction to left atrial outflow resulting in rising left atrial and pulmonary pressures (the extent of the latter depends to a significant degree on left atrial compliance). The normal mitral valve is in the range of 4 to 6 cm^2, and patients typically do not become symptomatic until valve areas decrease significantly below 2 cm^2. As valve area decreases, an additional pressure gradient is required to maintain transvalvular flow (see Fig. 30.8). Because antegrade flow occurs entirely during diastole, and the diastolic filling period shortens or lengthens disproportionately with increase or decrease in HR, respectively, the gradient is highly flow dependent. In MS, as with virtually all valvulopathies, CO is potentially highly dependent on maintenance of sinus rhythm; because the influence on CO is exaggerated by the need for active

• **Fig. 30.21** Long-axis view during diastole of the mitral apparatus, left atrium, and left ventricle in a normal patient (A) and a patient with mitral stenosis (B). Cross-sectional views of the left atrial surface of the valve are shown in the inset. With mitral stenosis, the valve opening is restricted with a characteristic doming appearance, the commissures are fused, the leaflets are thickened, the subvalvular apparatus is deformed, and some calcification is noted. The left atrium is enlarged. (From Turi ZG. Cardiology patient page. Mitral valve disease. *Circulation.* 2004;109:e38–e41.)

left atrial pumping across a stenotic orifice, atrial contraction is particularly important in MS. A frequent mode of presentation is acute congestive heart failure in a patient with MS who suddenly develops AF; the concomitant loss of atrial contraction and high ventricular rate with short diastolic filling period frequently results in pulmonary edema.

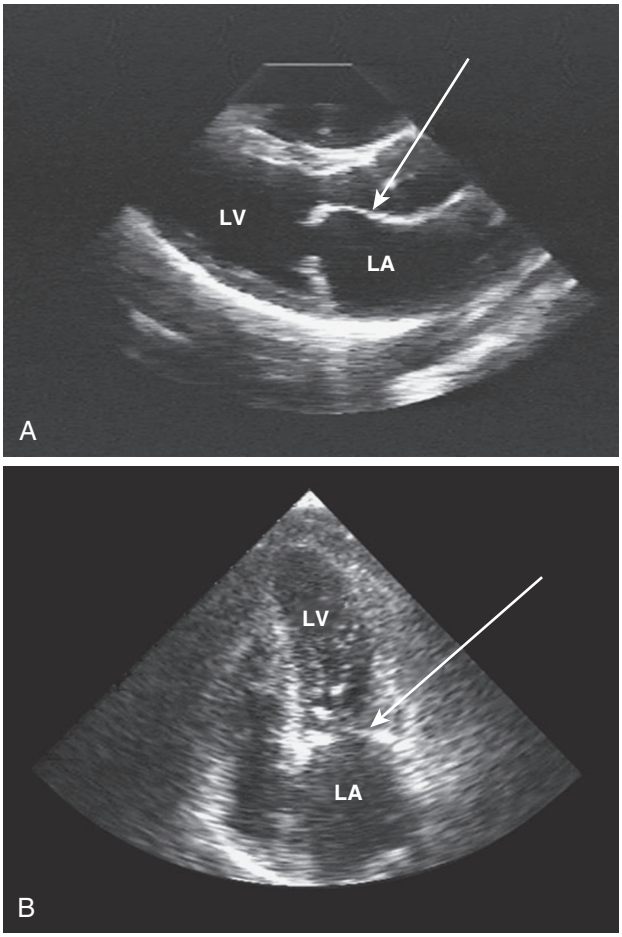
Diagnosis

Physical Examination

The diagnosis of MS on physical examination is frequently missed, in part because it is uncommonly seen by most practitioners outside developing countries. Besides findings suggestive of congestive heart failure with a low output in the critical care setting, several findings correlate strongly with MS. A right ventricular lift may occur in patients with advanced and chronic pulmonary hypertension, and occasionally a palpable pulmonic second sound is felt. Both S1 and P2 are increased early in the course of the disease; with progressive deformity of the subvalvular apparatus, S1 may become quite soft as mitral valve closure velocity decreases. The opening snap is preserved until the end stages of MS, and the severity of the disease correlates inversely with the length of time between S2 and the opening snap. The diastolic rumble may not be heard if the patient is not placed in the lateral decubitus position and is difficult to hear in the critical care setting. Presystolic accentuation is the result of increased flow in late diastole caused by atrial contraction in patients in sinus rhythm. The diagnosis is often elusive in both the outpatient and critical care settings,[224] and patients are sometimes treated for years for bronchitis, pneumonia, or asthma when in fact the presentation is congestive heart failure with the underlying disease process being MS.

Noninvasive Evaluation

The echocardiogram is the primary tool for diagnosis of MS. The typical hockey-stick appearance of the rheumatic anterior mitral leaflet is caused by partial restriction of mobility (Fig. 30.22). Other important characteristics of the mitral leaflets are degree of thickening, mobility, and calcification, all of which, along with extent of subvalvular disease, help to address suitability for balloon dilation or commissurotomy rather than valve replacement.[241] It is important to differentiate rheumatic MS from severe nonrheumatic MS, as shown in Fig. 30.22. TEE provides the requisite sensitivity to detect left atrial thrombus before balloon commissurotomy or cardioversion. Severity of MS is graded by physiologic and anatomic criteria: The former depends on Doppler interrogation of transvalvular flow, with peak velocity used to estimate the gradient; the rate of decompression of the left atrial pressure, or pressure half-time, correlates inversely with valve area. The valve area is frequently directly measured using planimetry of a cross-sectional view. Because these methods have potential for error, a number of alternative methodologies have been proposed,[242–244] although there is no agreement on a gold standard.[245] As with AS, a dramatic increase in gradient accompanies increased flow related to exercise or dobutamine infusion[246] (Figs. 30.23 and 30.24). Cardiac catheterization may be required if the noninvasive data are inconclusive; there is a tendency for the pulmonary wedge pressure/LV gradient to overestimate the severity of MS compared with left atrial/LV gradient measurement[247] (Fig. 30.25). Cardiac catheterization can also be used to assess pulmonary artery pressures and response to exercise if the clinical and noninvasive pictures are discordant.[4]



• **Fig. 30.22** Two appearances of stenotic mitral valves. A, The parasternal long-axis view shows typical rheumatic deformity with a hockey-stick appearance of the anterior mitral leaflet *(arrow)*. B, The four-chamber view is from a patient with a significant gradient across the mitral orifice; this patient was treated with dialysis, did not have rheumatic heart disease, and demonstrated significant calcification of the mitral leaflets and annulus *(arrow)*. *LA,* Left atrium; *LV,* left ventricle.

Therapy

Medical Therapy

Medical therapy specifically aimed at improving hemodynamics and preventing stroke in MS is basically twofold: slowing the HR and anticoagulation. In sinus rhythm, β-blockade is the preferred therapy; patients with significant bronchospasm or with coexistent, usually secondary, severe pulmonary hypertension with or without right-sided heart failure may not tolerate β-blockers. Diltiazem or low doses of β-blocker combined with diltiazem or verapamil are sometimes used in this setting. With combined therapy, care should be exercised that severe HR slowing or atrioventricular block does not occur, and verapamil may not be tolerated in right-sided heart failure. For the acutely decompensated patient with MS, diuretics, nitrates, inotropes (preferably agents that do not raise HR) and, to a lesser degree, arterial vasodilator therapy may all be beneficial.

Approximately 30% of patients with MS are thought to develop AF, with the risk increased by progressive left atrial dilatation. The risk of embolic events, especially stroke, is substantially higher than in AF patients without MS[248] (up to 15% in unanticoagulated patients), possibly in part because of a hypercoagulopathy and increased platelet activation associated with MS,[249] making the use of anticoagulation essential. It is not uncommon for the presenting finding to be an embolic event in a patient with previously undiagnosed MS. Even in the setting of sinus rhythm,[4] if spontaneous echocardiographic contrast is seen in the MS patient or left atrial size is greater than 55 mm, anticoagulation may decrease the risk of stroke[249] and it should also be used in the sinus rhythm patient with prior embolic event or with left atrial thrombus detected by TEE.

In the setting of new-onset AF and acute decompensation, cardioversion should be considered. Regardless of chronicity, HR slowing is essential; digoxin, β-blockers, diltiazem, or verapamil alone or in combination may be beneficial. Rate control only at rest is inadequate; many patients with low resting HRs become tachycardic with minimal exercise. This is a vicious circle because the tachycardia may be a response to inadequate stroke volume; the tachycardia then lowers the diastolic filling period and further exacerbates the gradient. Control of tachycardia is important beyond its hemodynamic benefit; it also helps avoid tachycardia-induced cardiomyopathy.[250]

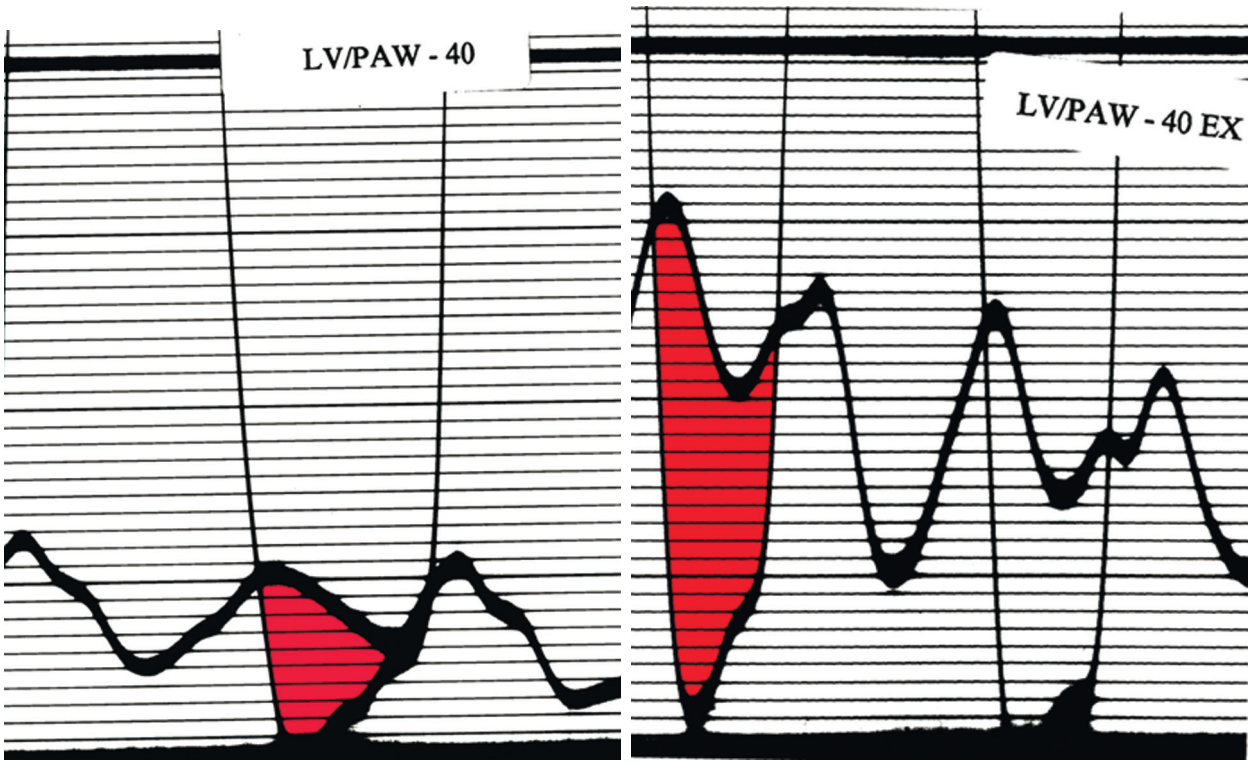
Percutaneous Intervention or Surgery

Percutaneous balloon mitral valvuloplasty (PBMV) is equivalent or superior to surgery in patients with favorable valve anatomy,[251,252] characterized by mild to moderate impairment of leaflet mobility, valve thickness, valve calcification, and subvalvular disease, the components of the Wilkins-Weyman echocardiography score.[253] The scoring system has been shown to correlate with long-term outcomes.[254] Surgery should be reserved for patients with unfavorable anatomy, more than mild MR, or persistent thrombus in the left atrium despite anticoagulation.[4] The threshold for percutaneous or surgical intervention is a mitral valve area of 1.5 cm^2 or less. If patients are symptomatic and have favorable anatomy or if they are asymptomatic but have very severe MS (valve area ≤1.0 cm^2) or new-onset AF, PBMV is indicated. Patients who have unfavorable anatomy and are functional class III or IV are considered to have a class IIb indication for PBMV if they are poor candidates for surgery. Symptomatic patients with progressive but less than severe MS (valve area >1.5 cm^2) who have wedge pressure greater than 25 mm Hg with exercise are also considered class IIb candidates.[4]

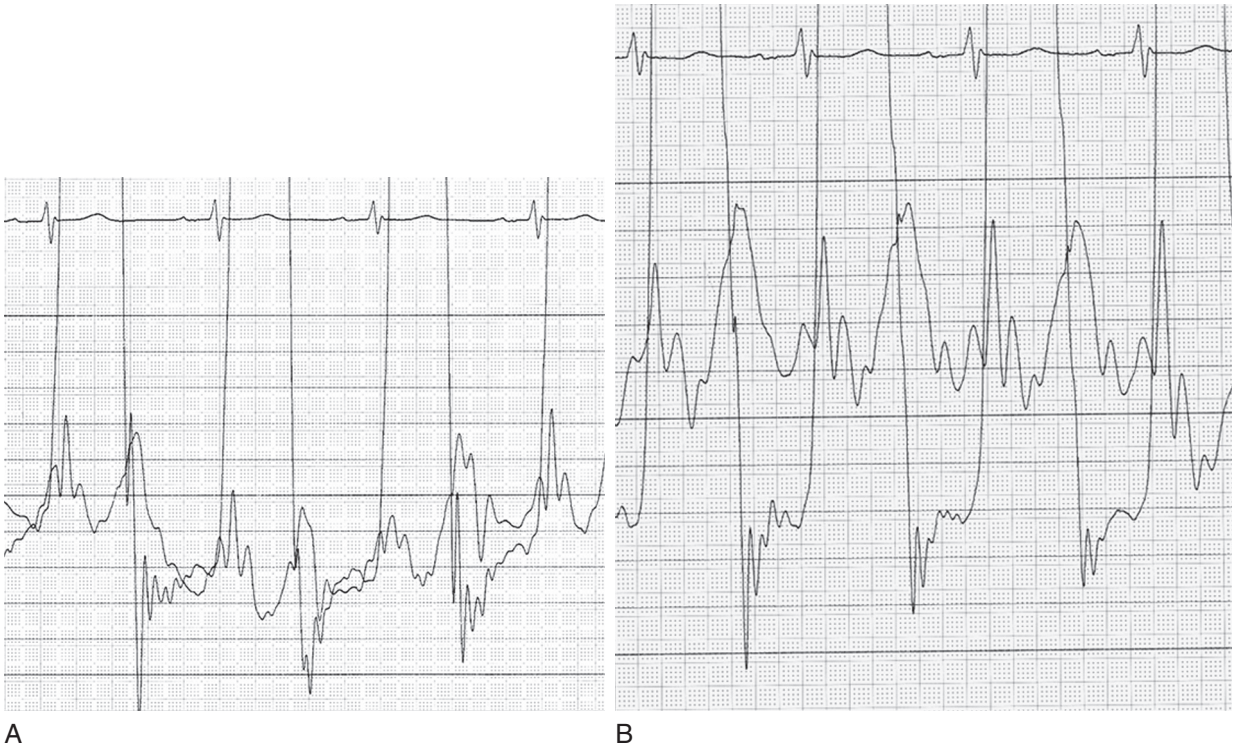
For severely symptomatic patients with severe MAC who are not candidates for surgery, an increasing number of percutaneous balloon expanding TAVR valves have been placed on a compassionate use basis.[255] However, 30-day postprocedure mortality has been as high as 30%. LV obstruction with the newly implanted valve can be catastrophic; hence, imaging algorithms for preprocedure assessment are important. If the patient is at high risk of LVOT obstruction, an alcohol septal ablation or percutaneous laceration of the anterior mitral leaflet has been performed in a limited number of cases to expand the outflow tract.

Prosthetic Heart Valves

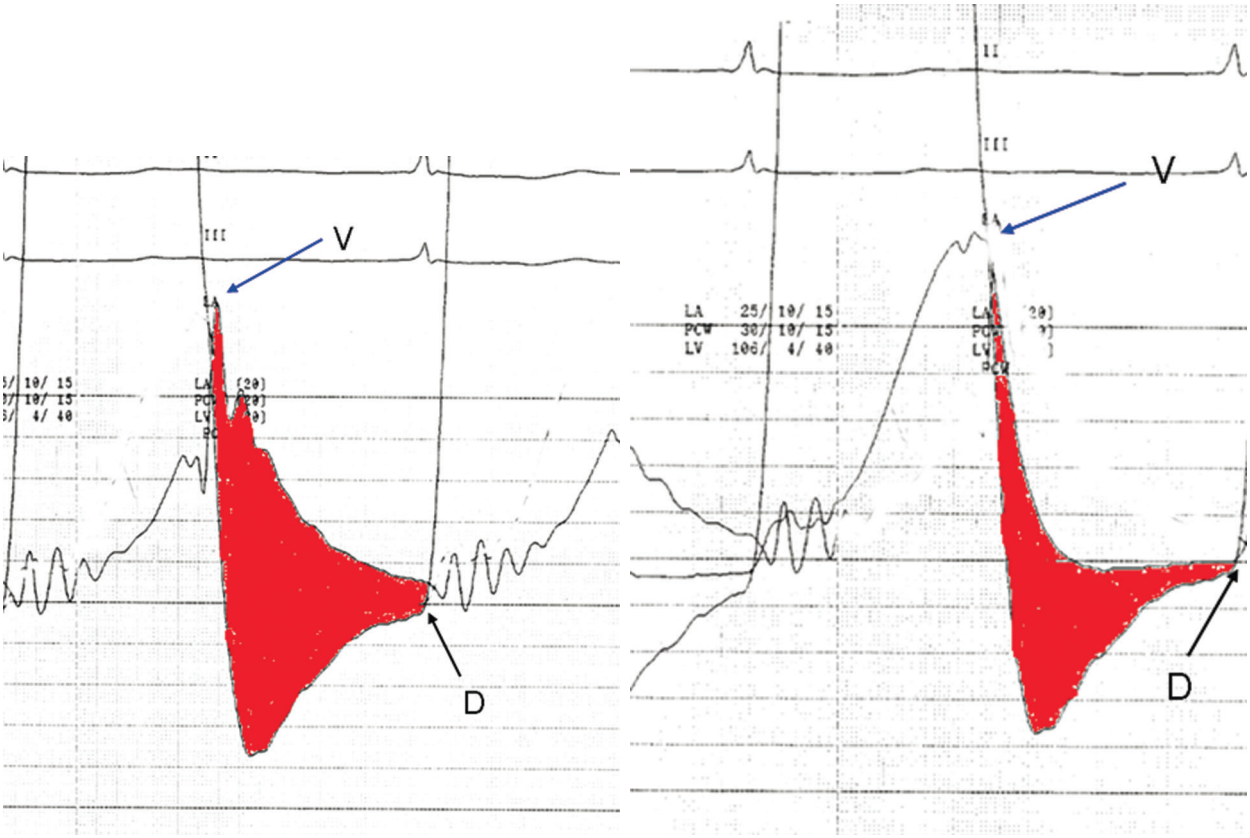
With the increasing number of patients undergoing valve replacement, prosthetic valves are of increasing importance in critical care management. Prosthetic heart valves (PHVs) are broadly categorized into biologic (stented, stentless, and more recently percutaneous) and mechanical (almost exclusively bileaflet in the modern era) valves. The management of normally functioning prosthetic valves (particularly anticoagulation) can add to the complexity of critical



• **Fig. 30.23** Effect of exercise and increased heart rate on mitral valve gradient *(red)* in a patient with mitral valve stenosis (40-mm Hg scale). The left tracing (A) shows a mean gradient of approximately 5 mm Hg with diastasis late in diastole; with increased heart rate and cardiac output (B), the gradient rose to a mean of approximately 20 mm Hg, a fourfold increase. *LV,* Left ventricle; *PAW,* pulmonary artery wedge.



• **Fig. 30.24** Effect of dobutamine infusion on transmitral valve gradient (40-mm Hg scale). Effect in a patient whose gradient was nearly abolished at rest (A) and was augmented dramatically with infusion of dobutamine (B).



• **Fig. 30.25** Effect of using pulmonary wedge pressure (A) or direct left atrial pressure (B) to assess gradient *(in red)* between the left atrium and left ventricle in mitral stenosis (40-mm Hg scale). Using the wedge pressure, the gradient appears to be approximately twice as great as when left atrial pressure is used. Rapid decompression of left atrial pressure is shown in the tracing on the right. The findings are consistent with mixed mitral stenosis and regurgitation, with the dominant physiology secondary to mitral insufficiency. In both tracings, diastasis *(D)* is noted by end diastole, a feature not consistent with severe mitral stenosis except in marked bradycardia. The V-wave height is similar in both tracings, unlike in Fig. 30.16. The two tracings shown here were recorded a few seconds apart.

care, and dysfunctional valves lead to a variety of symptoms, including dyspnea and precordial pain, as well as syncope, stroke, systemic embolism, and infection including endocarditis. Management of anticoagulation and antiplatelet therapy in patients with PHVs is complex and can result in a variety of hemorrhagic and thrombotic complications. The incidences of various complications related to PHVs[256–259] are noted in Table 30.3.

Pathophysiology

Thrombus formation occurs most commonly in mechanical valves. The mitral valve is more likely to be affected, in part because of lower pressure, slower flow, and more stagnation of blood in the left atrium, particularly in the setting of AF.[260] With aortic PHVs, the rate of thromboembolic events is highest in the first 3 months after AVR.[261] Although mechanical valves have a higher incidence of thromboembolic events without anticoagulation, the rates become comparable to bioprosthetic valves when patients are anticoagulated. Recently subclinical leaflet thrombosis has been described in both TAVR as well as surgical bioprosthetic PHV, resulting in reduced motion of one or more leaflets; this is mainly noted on four-dimensional (4D) volume-rendered cardiac CTA scans.[91] Clinical

TABLE 30.3 Incidence of Complications Associated With Prosthetic Heart Valves

Complications of Prosthetic Heart Valves	Incidence/Prevalence
Bioprosthetic valve failure	25%–40% at 15 years (porcine valves)
Prosthetic valve thrombosis	0.01%–6% per year
Thromboembolic complications	2.5%–3.7% per year (mechanical valve)
Mechanical valve obstruction	0.5%–0.6% per year
Pannus formation	0.2%–4.5% per patient-year
Severe prosthesis-patient mismatch	2%–11%
Severe hemolysis	3%
Paravalvular leak	5%–18%
Infective endocarditis	1%–6%

presentation can include stroke as well as hemodynamic abnormalities, but overall clinical implications of this finding require further investigation.

Prosthetic valve obstruction as reflected by elevated velocities/gradient across the prosthetic valve can be the cause of congestive heart failure and hemodynamic decompensation. The obstruction can be caused by thrombus or pannus formation, prosthesis-patient mismatch (P-PM), or degeneration of the bioprosthesis including calcification and valve leaflet fibrosis. Abrupt mechanical obstruction of the leaflets is more likely due to thrombus than pannus. P-PM is present when the effective orifice area (EOA) of the implanted prosthetic valve is too small in relation to the patient's size (BSA).[262] Typically the valve itself functions normally, but high transvalvular gradients are noted, caused by the small orifice of the implanted PHV. P-PM is now recognized to be an independent predictor of both congestive heart failure as well as mortality. It is best prevented by careful choice of valve size at time of AVR as well as expansion of the aortic root at the time of surgery when needed.[263]

Prosthetic valve regurgitation can occur secondary to leaflet degeneration, calcification, thrombus or pannus formation, and endocarditis. Mechanical prosthetic valves usually have small regurgitant jets called "washing jets" that help prevent thrombus formation. Structural failure of a mechanical prosthesis is rare (although it was a major concern with mechanical PHVs placed before the mid-1980s). Bioprosthetic valves may have severe regurgitation owing to a tear or rupture of one or more of the valve cusps that have become rigid and calcified, chronic degeneration of the leaflets, or in the setting of endocarditis where a variety of mechanisms for severe regurgitation include leaflet perforation.

Besides valvular regurgitation, PVL is a significant and highly morbid clinical entity. The risk factors for PVL include severe calcification of the annulus to which the valve is sewn, surgical technique (continuous sutures have higher risk), multiple valve replacements, inflammation, endocarditis, or steroid use.[258] Implantation of TAVR valves either too shallow or too deep can cause severe PVL. The cardinal hallmarks of significant PVL are heart failure owing to the volume loading caused by regurgitation and hemolytic anemia owing to the high velocity of regurgitant blood flow through the typically narrow PVL orifice, which results in high shear forces and hemolysis of red blood cells.[258] There is occasional hemolysis associated primarily with older-generation mechanical valves.[264]

Infective endocarditis is caused by contamination at the time of surgery or by direct contact of organisms to the prosthetic valve and surrounding structures early after implantation. After endothelialization of the prosthetic valve, as with native valve endocarditis, pathogenic mechanisms include adherence of bacteria to injured or inflamed valve structure, persistence of bacteria and proliferation, and dissemination into the blood stream.[265] Highly virulent organisms such as *S. aureus* can affect adjacent structures and cause perivalvular abscess, fistula, and valve dehiscence.

Diagnosis

Physical Examination

Patients can present with signs of heart failure, stroke, or endocarditis; diagnostic clues may not be apparent. The presence of a new murmur should raise suspicion of prosthetic valve dysfunction. In the case of mechanical valves, the absence or blunting of opening and closing sounds suggests thrombus or pannus formation. The normal auscultatory findings of prosthetic valves and abnormal findings have been described[266]; it is important to appreciate the significance of a variety of murmurs as well as diminished prosthetic valve closing sounds in particular.

Noninvasive Evaluation

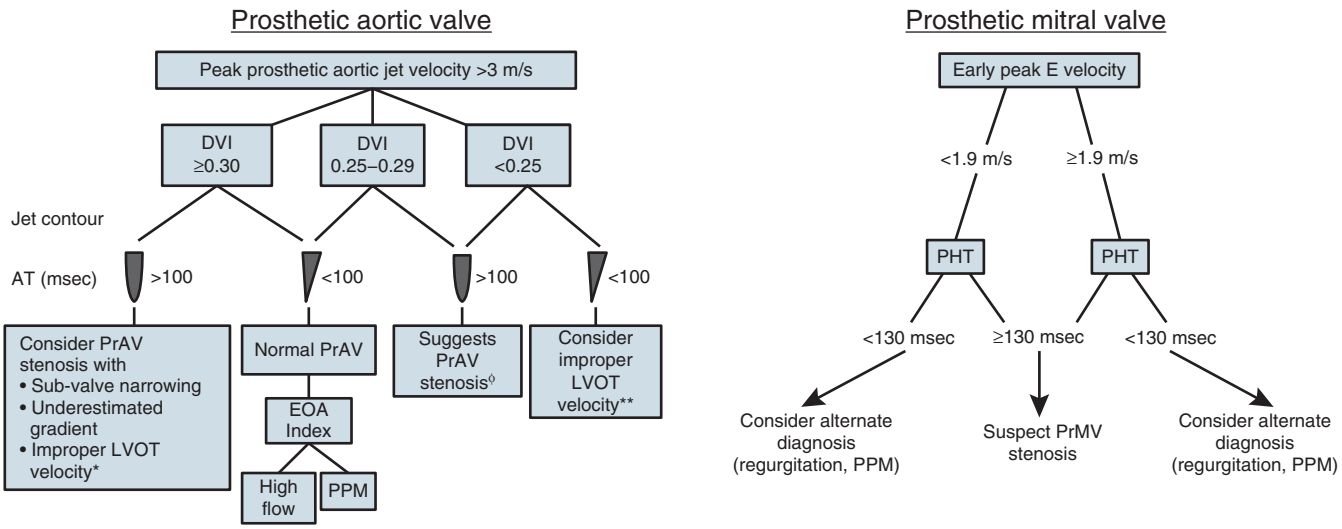
Transthoracic echocardiography remains the first-line modality for evaluating prosthetic valve structure and function. TEE has substantially higher sensitivity to assess for endocarditis and regurgitation, especially with mitral valves. PHV evaluation should include stability of the PHV, leaflet morphology and mobility, thrombus or pannus formation of the prosthesis on two-dimensional (2D) and 3D echocardiography, flow dynamics by color Doppler, valve hemodynamics and quantification by Doppler, size and function of cardiac chambers, assessment for any vegetations, as well as pulmonary artery pressure. Apart from transprosthetic velocity and gradients, the key parameters used are EOA, Doppler velocity index, acceleration time, and pressure half-time in the case of mitral prosthetic valves. Doppler flow parameters like vena contracta, jet width, circumferential extent, regurgitant fraction, and volume can be calculated to assess valvular and paravalvular regurgitation.[257,267] Higher than expected gradients from baseline echocardiography (recommended at 6 weeks to 3 months after surgery) may be present owing to high-output states, P-PM, or PVL and should be differentiated from true prosthetic valve obstruction (Fig. 30.26). An indexed EOA less than 0.65 cm^2/m^2 (in obese patients with body mass index ≥30 kg/m^2; cutoff <0.60) is the criterion to determine the presence of P-PM. Peak velocity greater than 4 m/s, mean gradient greater than 35 mm Hg, Doppler velocity index less than 0.25, EOA less than 0.8 cm^2, rounded, symmetric contour of the jet velocity, and acceleration time longer than 100 msec suggest significant aortic prosthetic stenosis. Similarly, peak velocity of 2.5 m/s or higher, mean gradient greater than 10 mm Hg, EOA less than 1 cm^2, and pressure half-time greater than 200 msec is consistent with severe mitral prosthetic stenosis.[267] Often restricted valve leaflet mobility, thrombus, calcification, or pannus formation is seen in prosthetic stenosis.

Other imaging modalities can be used for specific purposes. In addition to echocardiography (bioprosthetic PVL seen in Fig. 30.27A), cinefluoroscopy or multiphase CT can be used to evaluate leaflet mobility in mechanical valves; these can be excellent tools for assessing PVL (Fig. 30.27B and C). CT offers excellent spatial imaging and is highly sensitive to detect calcification. 4D CT can be used to assess prosthetic valve mobility in addition to the detection of leaflet thrombosis on bioprosthetic valves.[91] Cardiac MRI, especially with steady-state free precession sequences (discriminates blood from tissue) and phase-contrast velocity mapping, can detect turbulent flow, velocity, and regurgitant volume through the regurgitant orifice.[268,269] Radiolabeled white blood cell single-photon emission CT (WBC SPECT/CT) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (F-FDG PET/CT) are showing promise in diagnosing prosthetic valve endocarditis.[270]

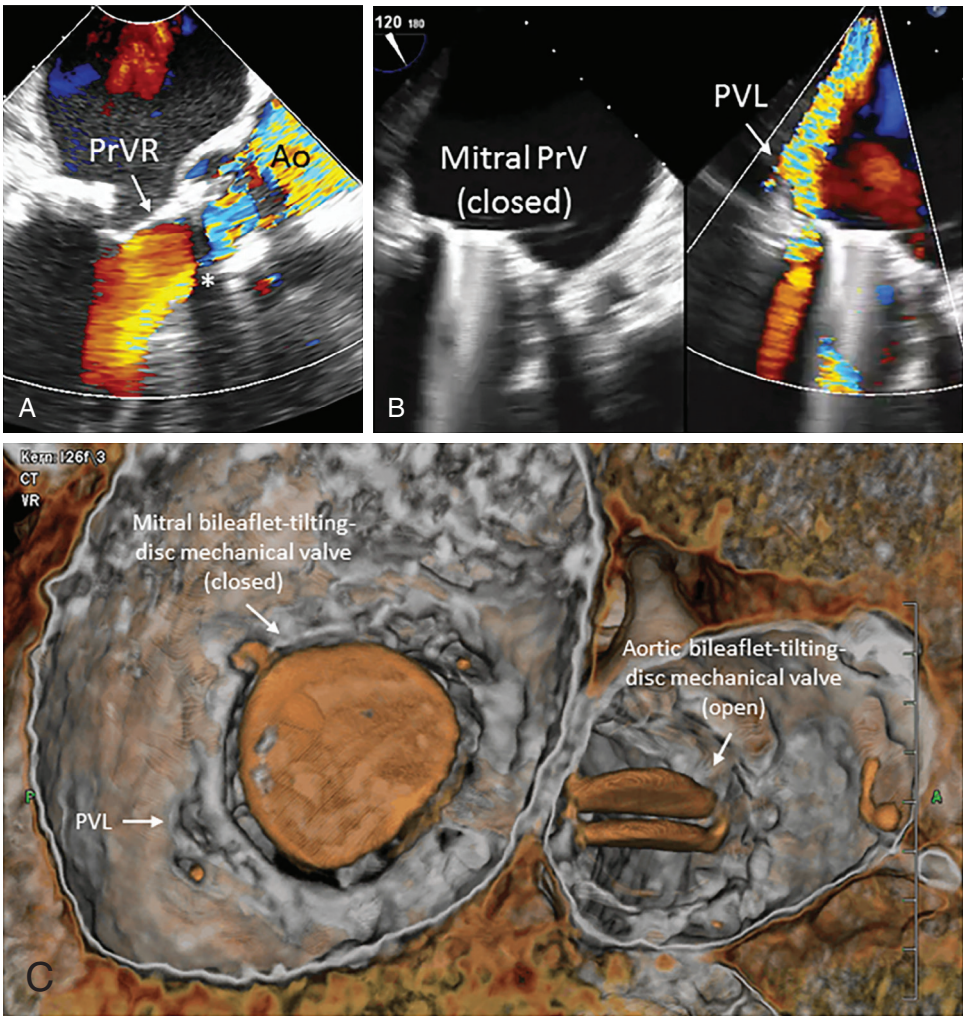
Therapy

Medical Therapy

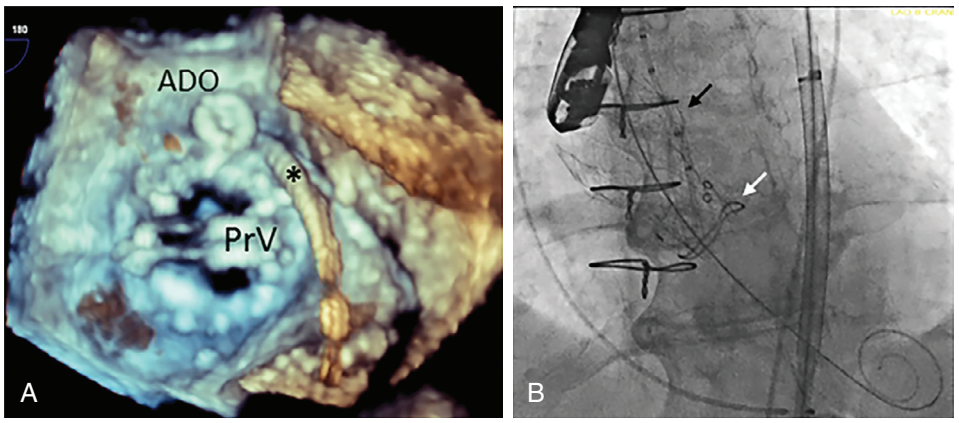
The AHA and ACC recommend antithrombotic therapy with vitamin K antagonists (VKAs) for mechanical valves with an international normalized ratio (INR) range of 2.5 to 3.0. Additionally, aspirin 75 to 100 mg daily is recommended for mechanical valves.[4,84] Anticoagulation with VKA (INR target 2.5) for surgical bioprosthetic valves for 3 to 6 months is recommended (class IIa) as there is an increased risk of stroke early after surgery.[271] Temporary interruption of VKA without a bridging agent (heparin) can be carried out with bileaflet mechanical aortic valves if no other risk



• **Fig. 30.26** Algorithm for evaluation of elevated peak velocities across aortic and mitral prosthetic valves on echocardiography. *AT,* acceleration time; *DVI,* Doppler velocity index; *EOA,* effective orifice area; *LVOT,* left ventricular outflow tract; *PHT,* pressure half-time; *PPM,* prosthesis patient mismatch; *PrAV,* prosthetic aortic valve; *PrMV,* prosthetic mitral valve. (Adapted from Zoghbi WA, Chambers JB, Dumesnil, JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. *J Am Soc Echocardiogr.* 2009;22:975–1014.)



• **Fig. 30.27** A, A 15-year-old aortic Hancock II (Medtronic, Inc., Minneapolis, MN) valve showing severe prosthetic valve regurgitation *(PrVR)*. There is shadowing and masking *(asterisk)* of the regurgitant jet owing to the sewing ring of the bioprosthetic valve. B, A mitral mechanical prosthetic valve *(PrV)* is seen in the closed position. There is a paravalvular leak *(PVL)* noted on color Doppler. C, Computed tomographic reconstruction of the aortic and mitral bileaflet tilting-disk valves. PVL is seen at the 5-o'clock position. *Ao,* Aorta.



• **Fig. 30.28** A, Three-dimensional transesophageal echocardiography showing closure of a mitral prosthetic valve *(PrV)* paravalvular leak (PVL). A delivery catheter *(asterisk)* is seen going through the PVL beside a previously placed Amplatzer Duct Occluder *(ADO)* device (St. Jude Medical/Abbott, St. Paul, MN). Two Amplatzer Vascular Plug II devices were placed through the catheter, eliminating PVL. B, The patient from figure A underwent valve-in-valve transcatheter aortic valve replacement (TAVR). The fluoroscopic image shows Hancock II bioprosthetic valve *(white arrow)* in which an Evolut R (Medtronic, Inc., Minneapolis, MN) TAVR valve *(black arrow)* was placed. There was no residual regurgitation noted after the procedure and the patient's condition improved significantly.

factors for thrombosis are present. Otherwise, bridging should be considered, keeping in mind the enhanced risk of bleeding for patients with mechanical AVRs and thromboembolic risk (including older-generation valves) and patients with mechanical mitral valves.[84,272] Administration of fresh frozen plasma is reasonable with mechanical valves for patients receiving VKAs who require emergency noncardiac surgery or invasive procedures.[4] In patients presenting with left-sided mechanical valve obstruction caused by thrombosis, urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy (echocardiography-guided) or surgery is recommended. A large clot (>0.8 cm^2), recurrent thrombosis, readily available surgical expertise, and low surgical risk should sway the treatment toward surgery rather than thrombolysis. In bioprosthetic valves with suspected or confirmed thrombosis in patients who are hemodynamically stable with no contraindications for anticoagulation, initial treatment with VKAs is reasonable and repeat imaging is usually performed to document resolution. Unfortunately, there is as yet no evidence-based medical therapy to prevent or treat bioprosthetic degeneration.

Prosthetic valve endocarditis (PVE) requires aggressive management and often early surgery, with management guided by identification of the causative organism and infectious disease consultation. Revised guidelines for the management of infective endocarditis can be found in a 2015 Scientific Statement from the AHA.[112]

Percutaneous Intervention or Surgery

Redo surgery remains the mainstay of treatment in operable patients with prosthetic stenosis, dysfunction, prosthetic or paravalvular regurgitation, dehiscence, and PVE; however, it is associated with significant morbidity and mortality. Surgery should be considered early (during initial hospitalization before completion of a full therapeutic course of antibiotics) for PVE in patients with valve dysfunction resulting in heart failure; left-sided PVE caused by *S. aureus*, fungal or highly resistant organisms; PVE complicated by heart block or abscess; or persistent infection lasting longer than 7 days.[4,84] Redo surgery with aortic root enlargement is an option for P-PM, whereas balloon rupture of the PHV followed by ViV TAVR has been performed successfully in a small series of patients with bioprosthetic P-PM.[273]

With the advent of catheter-based therapies, percutaneous ViV replacement for stenotic or regurgitant bioprosthetic valves with TAVR valves has become FDA approved. Examples of PVL closure and ViV replacement in a patient at high risk for reoperation are seen in Fig. 30.28. Transcatheter ViV procedures are being performed off-label in other prosthetic valves as well. The current indications for percutaneous PVL closure (still off-label in the United States) are PVL-related heart failure or hemolysis in patients who are at high risk for surgery and have anatomic features suitable for catheter-based therapy.[258]

Key Points

- Valvular heart disease in the critical care setting ranges from the primary cause of acute decompensation to a comorbidity of varying degrees of clinical significance.
- Valvulopathy affects not only valve anatomy but also cardiac structure and function and overall hemodynamics; it is essential to consider all four elements in diagnosis and management.
- AS in the critical care setting requires careful titration of need to maintain cardiac output, avoid hypotension, and replace the aortic valve early if AS is the primary cause of symptoms.
- Low-gradient, low-output AS requires increasing cardiac contractility or transvalvular flow, or both, to differentiate severe AS from primary myocardial dysfunction.

- Acute aortic and mitral insufficiency in the decompensated patient benefit from vasodilator therapy with or without inotropic support; routine vasodilator treatment of chronic aortic and mitral insufficiency in asymptomatic patients does not have the benefit of a compelling evidence base.
- Intraaortic balloon counterpulsation is useful in hemodynamically decompensated patients with MR, of some benefit in severely ill patients with AS, but contraindicated in those with HCM and especially in patients with AI.
- AF exacerbates hemodynamic deterioration in valvulopathies; if left atrial size is less than 6 cm and thrombus is not present, cardioversion and maintenance of sinus rhythm may be highly beneficial.
- Prosthetic valves are a source of significant pathology, including prosthesis-patient mismatch, thrombosis, degeneration, endocarditis, and paravalvular leak among others.

Acknowledgment

The authors than Priscilla Peters for kindly providing Figs. 30.12, 30.19, and 30.22.

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Review Questions

1. An 80-year-old male is hospitalized with congestive heart failure. The patient does not have coronary artery disease. The aortic valve is severely calcified. Aortic valve intervention might be recommended in which (one or more) of the following patient scenarios?

a. Maximum aortic velocity (V_{max}) is 3.2 m/s, mean gradient 25 mm Hg, ejection fraction (EF) 30%, aortic valve area (AVA) 0.8 cm^2. Dobutamine infusion results in a mean gradient rising to 32 mm Hg, EF to 40%, and valve area increasing to 1.1 cm^2.

b. V_{max} is 3.2 m/s, mean gradient 25 mm Hg, EF 55%, AVA 0.8 cm^2, stroke volume index (SVI) 45 mL/min per m^2.

c. V_{max} is 3.2 m/s, mean gradient 25 mm Hg, EF 30%, AVA 0.8 cm^2. Dobutamine infusion results in a mean gradient of 45 mm Hg, EF to 40%, and valve area remaining at 0.8 cm^2.

d. V_{max} is 3.2 m/s, mean gradient 25 mm Hg, EF 55%, aortic valve area 0.8 cm^2, SVI 30 mL/min per m^2.

Answer: c and d. In low-gradient aortic stenosis (AS) where mean gradient is less than 40 mm Hg, it is important to ensure that patients have true severe AS as the cause of heart failure. The patient in scenario a. has pseudo-severe AS, where the low EF is secondary to left ventricular (LV) dysfunction rather than severe AS. Thus with dobutamine infusion, LV function improves, and although there is a slight rise in gradient, the valve opens better, resulting in a higher valve area. The patient in scenario b. has preserved EF with a low gradient; this is a possible presentation of severe AS for patients with small hypertrophic ventricles who simply cannot generate enough flow across the aortic valve to generate a gradient of 40 mm Hg. However, this patient has normal stroke volume (SV). The patient in scenario c. has a "classical" low-gradient, low-flow stage D2-type AS. As such, dobutamine infusion results in an increase in cardiac output and gradient, but the valve area remains the same or rises only slightly, implying a true fixed obstruction of the valve orifice. The patient in scenario d. has classic stage D3-type aortic stenosis with preserved LV function and low gradient owing to low SV volume, typically defined as less than 35 mL/min per m^2.

2. A 68-year-old male patient with symptomatic chronic severe mitral insufficiency and mitral valve prolapse is referred for percutaneous mitral valve repair. His LV ejection fraction is 40%. He is a diabetic receiving dialysis with prior bypass surgery who had mantle radiation for lymphoma 25 years ago. You perform a workup for possible transcatheter mitral clip placement, note him to be suitable on an anatomic basis, and explain to him that which of the following applies to him?

a. He does not meet ACC/AHA criteria for mitral valve repair at present.

b. He does meet American College of Cardiology/American Heart Association (ACC/AHA) criteria but should have surgical mitral valve repair instead.

c. Based on a randomized trial of patients like him, percutaneous mitral valve repair is a suitable alternative to surgery.

d. The likelihood of moderate or greater mitral insufficiency after percutaneous mitral valve repair will be slightly worse than if he were to undergo surgery.

e. When compared with surgical mitral valve repair, the overall outcomes for percutaneous repair of functional mitral regurgitation (MR) have been similar, whereas the outcomes for degenerative MR (like he has) have been inferior to surgery.

Answer: e. By ACC/AHA criteria, patients with symptomatic chronic severe MR and EF greater than 30% meet class I criteria for mitral valve repair; this recommendation is unchanged in the 2017 amended guidelines. As a diabetic patient receiving dialysis with a likely hostile chest (prior coronary artery bypass grafting plus mantle radiation), he would make a prohibitive risk for surgical repair of the mitral valve. The EVEREST II Trial compared patients with well-preserved EF and low risk for surgery; the high-risk study was not a randomized trial. Both studies enrolled patients with preserved EF. The evidence base therefore does not warrant answer c. Moderate or greater mitral insufficiency in EVEREST II was almost 3 times as likely at 1 year (46% vs. 17%) with percutaneous rather than surgical mitral valve repair. In subgroup analyses, outcomes after mitral valve clip were similar for functional MR compared to surgery, whereas surgery was superior to clipping for degenerative MR. This patient is a potential candidate for U.S. Food and Drug Administration (FDA)-approved mitral clip implantation in patients with degenerative MR.

3. A 50-year-old female presents to the emergency department with dyspnea on exertion with NYHA class III-IV symptoms. Her past medical history includes known hypertrophic cardiomyopathy and coronary artery disease with a stent to the left anterior descending artery (LAD) a year ago. She is currently taking Toprol XL 50 mg daily. Her blood pressure is 140/80 and her heart rate is 65 beats/min. Her echocardiogram shows normal LV function and septal hypertrophy with a septal width of 2.2 cm. The left ventricular outflow tract (LVOT) gradient at rest was 55 mm Hg. There is systolic anterior movement of the anterior mitral valve leaflet. The mitral valve leaflet is abnormally long, and moderate to severe MR is seen. She underwent coronary angiography that shows a patent LAD stent and nonobstructive disease in the rest of the vessels. Which of the following is the best management strategy?

a. Increase Toprol XL to 100 mg daily to decrease the heart rate even further.

b. Refer to an interventional cardiologist for alcohol septal ablation and reassess the mitral regurgitation later.

c. Perform stress echocardiogram to determine if the LVOT gradient increases with exercise.

d. Refer to cardiac surgery for myomectomy and mitral valve repair.

Answer: d. Patients who have an LVOT gradient greater than 50 mm Hg at rest or with physiologic provocation despite reasonable pharmacologic management can be considered for intervention with surgical myomectomy or alcohol septal ablation. Generally speaking, the latter should be reserved for patients who have major comorbidities and are poor candidates for surgery. Surgical myomectomy with mitral valve repair in patients with coexisting mitral valve pathology is a better option for sustained relief of LVOT obstruction and has a lower incidence of permanent pacemaker placement, avoids myocardial necrosis with its attendant risks, and addresses the mitral valve pathology. Performing a stress echocardiogram is not necessary as this patient already qualifies for intervention based on her resting LVOT gradient.

31

Cardiac Arrhythmias

JOHN M. ZIMMERMAN, TAYA V. GLOTZER, AND RICHARD G. TROHMAN

CHAPTER OUTLINE

Bradycardias
- Sinus Bradycardia and Sinus Node Dysfunction
- AV Block
- Junctional Rhythm
- Vagally Mediated Sinus Arrest, Bradycardia, and Heart Block

Supraventricular Tachycardia
- Overview
- Premature Atrial Contractions, Junctional Premature Contractions
- Paroxysmal Supraventricular Tachycardia
- AV Nodal Reentrant Tachycardia
- AV Reentrant Tachycardia and Wolff-Parkinson-White Syndrome
- Atrial Tachycardia
- Atrial Flutter
- Multifocal Atrial Tachycardia
- Nonparoxysmal AV Junctional Tachycardia, and Junctional Ectopic Tachycardia
- Sinus Tachycardia

Management of SVT
- Management of Regular Narrow Complex Supraventricular Tachycardia
- Management of Irregular Narrow Complex Supraventricular Tachycardia
- Management of Regular and Irregular Wide Complex Supraventricular Tachycardia
- Chronic Treatment of Supraventricular Tachycardia
- Atrial Fibrillation

Ventricular Arrhythmias
- Mechanisms of Ventricular Arrhythmias
- Approach to Ventricular Arrhythmias in the Critically Ill
- Premature Ventricular Contractions
- Nonsustained Ventricular Tachycardia
- Sustained Ventricular Tachycardia
- Ischemic Sustained Ventricular Tachycardia
- Sustained Polymorphic VT/VF
- VT/VF Storm
- Ventricular Arrhythmias in Patients With LV Assist Devices
- Ventricular Arrhythmias Associated With an Acute Myocardial Infarction
- Less Common Substrates
- Brugada Syndrome
- Catecholaminergic Polymorphic VT
- Short QT Syndrome
- Short-Coupled Torsades de Pointes
- Electrical Shocks
- Electrolyte, Endocrine, and Metabolic Abnormalities
- Acquired QT Prolongation

Metabolic Derangements

Conclusions

Cardiac arrhythmias occur in up to 30% of patients admitted to the intensive care unit (ICU).[1] Arrhythmias are associated with an increased morbidity and prolongation of the hospital stay. Management of serious cardiac arrhythmias is the shared responsibility of emergency specialists: critical care physicians, cardiologists, and electrophysiologists. Antiarrhythmic drugs are the mainstay of acute therapy for supraventricular arrhythmias and hemodynamically stable ventricular tachycardia (VT), but we also have the option of catheter ablation for refractory supraventricular arrhythmias and VT. Temporary pacing remains the "gold standard" for urgent/emergent therapy of symptomatic bradyarrhythmias. Permanent pacing is the only option for treatment of chronic bradycardias. Patients with structural heart disease at risk for sudden cardiac death (SCD), and those resuscitated from hemodynamically unstable ventricular tachyarrhythmias are usually managed with implantable defibrillators that can have adjunctive biventricular pacing for treatment of congestive heart failure (CHF) in patients with native conduction disturbances.

Critical care physicians deal with a plethora of medical and surgical problems in their patients. Arrhythmias may be the primary abnormality or may be secondary to myocardial ischemia, electrolyte imbalance, or toxic/metabolic disturbances. Optimal management of arrhythmias requires expertise in electrocardiography and clinical pharmacology as well as knowledge of arrhythmia precipitants, including proarrhythmia caused by antiarrhythmic medication or other drugs.[2] The responsibility of the critical care physician is to facilitate the transition from acute to chronic care by referring the patient with an arrhythmia to a cardiologist or an electrophysiologist.

Therefore the major emphasis of this chapter is on acute care of the patients with arrhythmias.

Bradycardias

Bradyarrhythmias usually present as either sinus node dysfunction or atrioventricular blockade (AV block). Bradyarrhythmias and indications and techniques for temporary cardiac pacing are reviewed extensively in Chapter 5. A brief overview is included here to highlight important issues for the intensivist.

Sinus Bradycardia and Sinus Node Dysfunction

Sinus bradycardia is defined as periods when the impulse from the sinoatrial (SA) node is less than 60 beats/min. Normal resting heart rates vary with age and physical conditioning and are affected by multiple factors, including medications, emotions, fever, and the interplay between the parasympathetic and sympathetic nervous systems. In the absence of symptoms, sinus bradycardia is usually benign and requires no treatment. In healthy adults sinus bradycardia is a frequent finding, especially during sleep when rates of 30 beats/min and pauses up to 2 seconds are not uncommon and are usually benign.[3–6]

Without overt heart disease physiologic bradycardia can be due to enhanced vagal tone as is seen in well-conditioned athletes.[7–10] In the elderly, sinus bradycardia may be a prelude to the development of sick sinus syndrome, a condition in which the sinus node is no longer functioning appropriately.[11] Finally, bradycardia in a normal heart can be due to a rare familial disorder in which asymptomatic sinus bradycardia results from a mutation in the *HCN4* and *SCN5A* ion channel genes.

Vasovagal episodes may be associated with severe bradycardia owing to heightened parasympathetic activity and sympathetic withdrawal.[12] Stimuli that cause vagal activation, include carotid sinus stimulation, vomiting, the Valsalva maneuver, as well as many other external events that can precipitate activation of the neurohormonal axis, causing heightened parasympathetic activity and sympathetic withdrawal and resulting syncope.

Pathologic Conditions Causing Sinus Bradycardia

Sinus bradycardia may be the first manifestation of sinus node dysfunction and sick sinus syndrome, which is a condition in which the sinus node can no longer provide adequate heart rates for normal physical activities. This results in patient complaints of fatigue and exercise intolerance.[13] Sinus bradycardia is a complication of acute myocardial infarction (AMI) in 10% to 15% of cases, particularly those involving the right coronary artery, as it supplies the SA node in approximately 60% of people. Patients with obstructive sleep apnea frequently have sinus bradycardia, which can be severe, with rates less than 30 beats/min during apneic episodes.[14] Sinus bradycardia can be caused by increased intracranial pressure, which should be suspected when bradycardia occurs in patients with neurologic disorders. Other neurologic conditions that can cause sinus bradycardia include stroke or trauma to the cervical or thoracic spine that causes sympathetic denervation of the heart leaving unopposed parasympathetic tone.[15] Infectious agents that cause bradycardia include Lyme disease, Chagas disease, *Legionella,* psittacosis, Q fever, typhoid fever, typhus, babesiosis, malaria, leptospirosis, yellow fever, dengue fever, viral hemorrhagic fevers, trichinosis, Rocky Mountain spotted fever, and gram-negative sepsis.[11,16] Miscellaneous pathologic causes of bradycardia include hypothyroidism, anorexia nervosa, hypothermia, and severe hypoxia.

Several medications are associated with sinus bradycardia either as an expected response or associated with toxicity.

- Nondihydropyridine calcium channel blockers: verapamil and diltiazem
- Opioids and sedatives
- Cimetidine
- Ivabradine
- Amiodarone and other antiarrhythmic medications
- Hepatitis C drugs sofosbuvir and daclatasvir in patients receiving amiodarone
- Chemotherapeutic agents including thalidomide, lenalidomide, paclitaxel
- Organophosphate compounds

Of note, digoxin, in therapeutic doses, does not significantly affect the sinus node.[13]

Types of SA Nodal Dysfunction

Sinus pause or arrest is defined as the absence of sinus P waves on the ECG that can last from 2 seconds to several minutes. This is caused by a failure of discharge from the sinus node and thus has no arithmetic relationship to the basic sinus rate (Fig. 31.1).

SA nodal exit block occurs as a result of interference with the delivery of impulses from the SA node to the neighboring atrial tissue. First-degree SA exit block results from intra–SA node conduction delay and is not manifest on the surface ECG. Second-degree SA exit block has two types. Type I second-degree SA exit block is characterized by progressive PP interval shortening before a pause caused by a dropped P wave. This is analogous to the Wenckebach phenomenon that occurs in the AV node. The pause has a duration that is less than two PP cycles in duration. In type II second-degree SA exit block, pauses are exact multiples of the basic PP interval, analogous to second-degree type 2 block that occurs in the AV node (Fig. 31.2). Third-degree SA nodal exit block prevents sinus node impulse to reach the right atrium. It cannot be distinguished from sinus arrest.

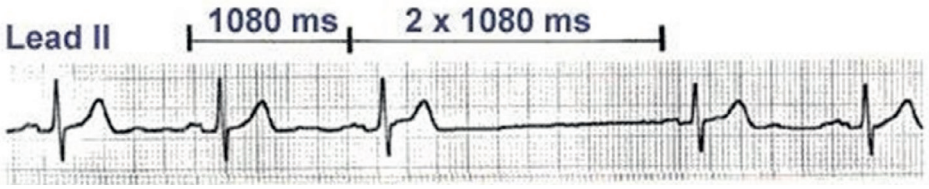
Sinus arrhythmia (Fig. 31.3) is a normal variant in which there are respirophasic changes in the PP intervals on ECG (usually prolongation of PP intervals during expiration). Rarely sinus arrhythmia can be seen secondary to digoxin toxicity. Sinus arrhythmia, except when caused by digoxin toxicity, is not considered abnormal, rarely causes symptoms, and requires no treatment.

Wandering atrial pacemaker is present when there are three or more ectopic atrial foci within the atrial myocardium that serve as the dominant pacemaker for atrial rhythm (Fig. 31.4). Because the location of the pacemaker changes, the PR interval can change as well. This can be seen in young, healthy individuals, especially in athletes; symptoms are rare and no treatment is required.

Treatment of Sinus Bradycardia

When severe symptomatic sinus bradycardia occurs, the patient should be treated per the standard Advanced Cardiovascular Life

• **Fig. 31.1** Sinus pause.



• **Fig. 31.2** Sinoatrial exit block (type II).

• **Fig. 31.3** Sinus arrhythmia, a normal variant of sinus rhythm. Here there are respirophasic changes in the RR interval on electrocardiogram (gradual prolongation of RR intervals during expiration).

• **Fig. 31.4** Wandering atrial pacemaker.

Support (ACLS) guidelines[17] (Fig. 31.5). Atropine is the initial treatment: 0.5 mg intravenous (IV) push to repeat every 3 to 5 minutes, if needed, up to a dose of 3 mg IV. If atropine is not effective, IV dopamine or IV epinephrine can be used. If the patient does not respond to atropine, dopamine, or epinephrine, transcutaneous pacing can be effective in the acute management of these patients. In large patients, high transcutaneous pacing outputs are required to achieve capture and this can cause significant discomfort to the patient. It is important to assess either the radial or femoral pulse during transcutaneous pacing to confirm capture, as telemetry readings often give a false indication of capture owing to the large pacing artifact seen on the monitor; 30% to 40% of patients have either no or inconsistent capture with transcutaneous pacing. Any patient with symptomatic sinus node dysfunction that is not acutely reversible with medications or transcutaneous pacing requires placement of a temporary transvenous pacemaker. If no reversible cause of the bradycardia is found, permanent pacing is required.

AV Block

AV block is the delay or interruption of conduction between the atrium and ventricle because of anatomic or functional impairment. AV block can be intermittent or permanent. We describe the various types of AV block in the following text.

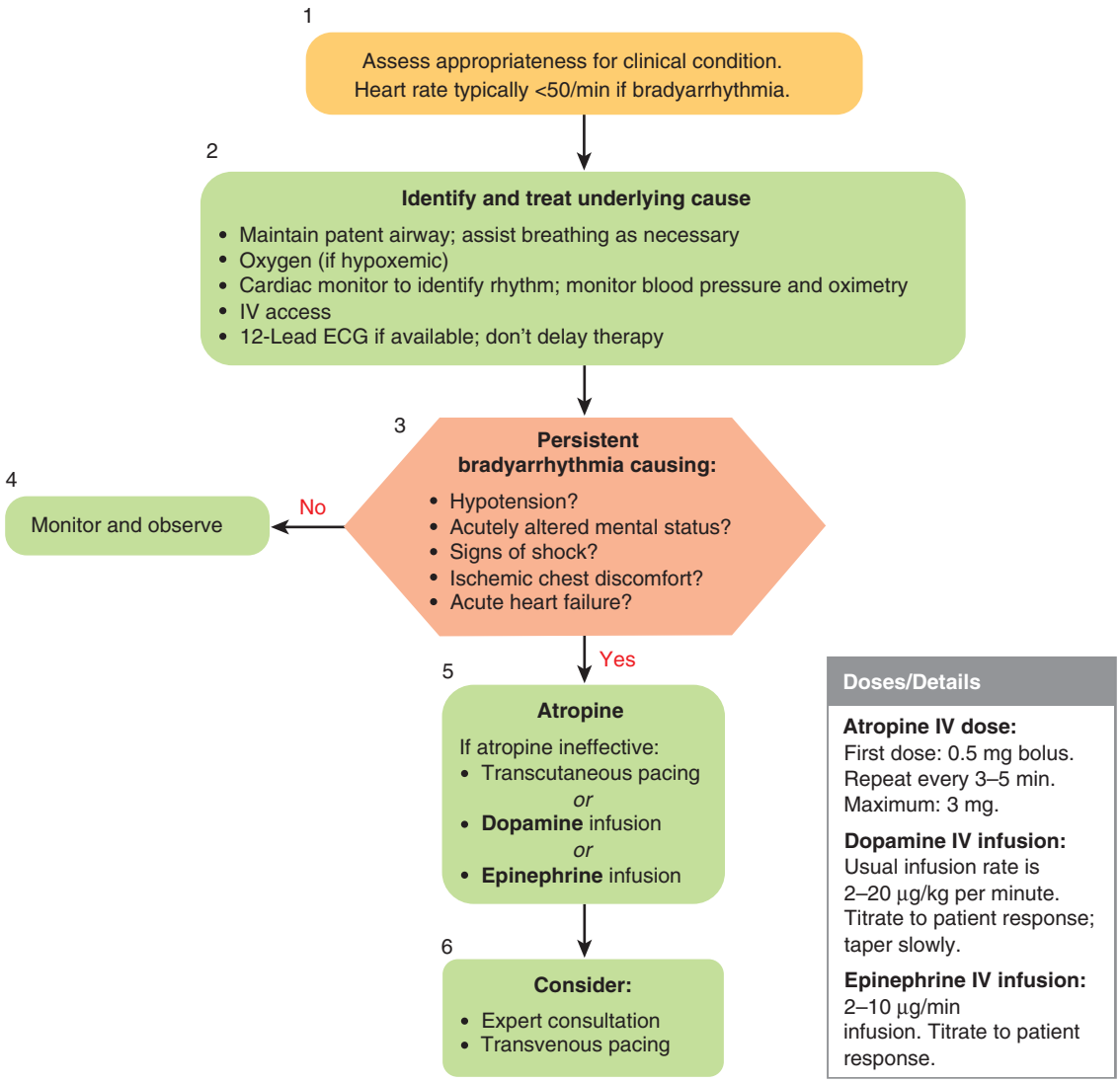
First-degree AV block is simply delayed conduction from the atria to the ventricles. Every atrial impulse is conducted to the ventricles in a delayed fashion such that the PR interval is greater than 200 msec. If the QRS complex on the surface ECG is narrow, the delay is almost always in the AV node. In the presence of a wide QRS complex, the delay may be in either the AV node or the His-Purkinje system.

Second-degree AV block occurs when not every atrial impulse is conducted to the ventricles. Second-degree AV block is classified as Mobitz type I (Wenckebach); Mobitz type II is 2:1 AV block or high-degree AV block. In *Mobitz I (Wenckebach) block,* PP intervals are constant, with gradual PR prolongation before failure of impulse conduction to the ventricle (nonconducted P wave) (Fig. 31.6). Although classic Wenckebach block involves simultaneous shortening of successive RR intervals before AV block, variable RR intervals are actually more common. In younger people, Mobitz I AV block with narrow QRS complexes is benign and does not progress to more advanced AV conduction disturbances. In older patients, however, the prognosis may be worse and similar to that of Mobitz II block (see following text). Mobitz type I AV block with a narrow QRS complex almost always occurs at the AV node. Rarely, Mobitz I second-degree AV block may have an intra-His location. Mobitz I AV block with wide QRS complexes may occur in either the AV node or the His-Purkinje system. Mobitz I second-degree AV block may accompany an inferior myocardial infarction (MI). That condition is benign, with a favorable prognosis in the absence of hemodynamic compromise. The conduction disturbance usually is transient, and permanent pacing is not required.

Mobitz II AV block is characterized by sudden failure of atrial impulse conduction to the ventricle without prior PR prolongation (Fig. 31.7). This form of AV block can herald development of complete AV block and possible syncope. Mobitz II AV block usually occurs in the setting of wide QRS complexes, and usually is a sign of infranodal, His-Purkinje system conduction system disease. Escape rhythms are unreliable below the AV node; therefore Mobitz II second-degree AV block is often an indication for permanent pacing. Mobitz II second-degree AV block in the setting of anterior infarction is associated with pump failure and high mortality rates. Survivors should receive permanent pacemakers.

Complete AV block is diagnosed by the presence of independent atrial and ventricular activity on the ECG, with the atrial rate being faster than the ventricular rate. The PP interval is constant and the RR intervals are constant. The PR interval is variable in a random, nonrecurring pattern (Fig. 31.8). Complete AV block can also be present during all varieties of atrial tachycardias (ATs) including atrial fibrillation (AF).

Complete AV block proximal to the His bundle results in a narrow QRS complex escape rhythm with rates of 50 to 60 beats/min. Complete intra-His block may also result in a narrow QRS escape rhythm with ventricular rates less than or equal to 45 beats/min. Complete AV block below the His bundle results in a wide



• **Fig. 31.5** Management of adult bradycardia. *ECG,* Electrocardiogram. (From Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(18 suppl 2):S444–S464.)

• **Fig. 31.6** Second-degree atrioventricular block, Mobitz type I (Wenckebach). The PR interval progressively lengthens until a P wave is not conducted. The intervals may be fixed or variable. In this example, there are four P waves for every three QRS complexes.

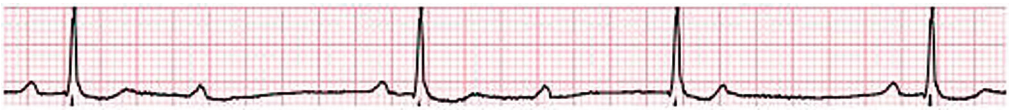
QRS complex escape, usually less than 40 beats/min, and is an indication for immediate pacing because the escape rhythm in this case is very unreliable and could terminate at any time.

In the setting of inferior infarction, complete (narrow QRS) AV nodal block can occur and is expected to recover in more than 90% of patients (time to recovery 30 minutes to 16 days).[18] In general, atropine improves AV nodal conduction and carotid massage worsens it. These interventions have the opposite effect when the AV block is in the His-Purkinje system. Exercise, by increasing endogenous catecholamines, may reduce the extent of block at the AV node but may worsen block below the AV node. Precipitation of second-degree, high-grade, or complete AV block during exercise strongly suggests an infranodal site of block and is an indication for permanent pacing.[19]

The surface ECG allows the clinician to localize the site of AV block without the use of invasive electrophysiologic testing. It is important to remember a few general rules to avoid common ECG misinterpretations of second-degree AV block. First, 2:1 AV block

• **Fig. 31.7** Second-degree atrioventricular block, Mobitz type II. There is a constant PR interval until a P wave is suddenly not conducted. Note the QRS is prolonged to approximately 120 msec.

• **Fig. 31.8** Complete heart block. The P waves and QRS complexes are regular, but they are not associated with one another.



• **Fig. 31.9** 2:1 Atrioventricular (AV) block. In the setting of AV block with a 2:1 interval, it is not possible to determine by surface electrocardiogram if the block is Mobitz type I or Mobitz type II. Narrow QRS complexes generally result from AV nodal block. Wide QRS complexes are compatible with block in either the AV node or His-Purkinje system.

• **Fig. 31.10** High-grade atrioventricular (AV) block. Two or more P waves are not followed by a QRS complex. In this example, there are three P waves for each QRS complex, an example of 3:1 high-grade AV block.

can be nodal or infranodal and, second, 2:1 block associated with narrow QRS complexes generally results from AV nodal block (Fig. 31.9). Wide QRS complexes are consistent with block in either the AV node or His-Purkinje system. If more than one P wave is not conducted to the ventricle, the term *high-grade AV block* is used (Fig. 31.10).

Pathophysiologic Causes of AV Block

- *Idiopathic cause.* This is the most common cause of AV block; it accounts for 50% of cases and is caused by progressive impairment of the conduction system over decades. Lev disease refers to progressive fibrotic infiltration of the conduction system in patients younger than 60 years. Lenegre disease occurs in older patients (>70 years) and is caused by fibrosis or calcification extending from any of the fibrous structures adjacent to the conduction system into the conduction system.[20,21]
- *Causes associated with other cardiac disease.* Ischemic heart disease accounts for approximately 40% of cases of AV block.[22] AV block is seen with either chronic ischemic heart disease or during AMIs. Up to 20% of patients with AMIs develop some form of AV block.[23,24] The larger the infarct, the more likely and more severe the heart block is. Restoring perfusion in the setting of an AMI often improves AV conduction. Myocarditis can cause AV block from a variety of causes, including rheumatic fever, Lyme disease, diphtheria, viruses, toxoplasmosis, and syphilis.[25–34] Infiltrative cardiomyopathies such as amyloidosis and sarcoidosis can also lead to AV block
- *Cardiac procedures.* Transient AV block can occur from catheter manipulations in the right heart across the tricuspid valve—for example, Swan-Ganz catheter placement or pacing wires of any type. This "traumatic" AV block usually recovers within several minutes to hours. AV conduction abnormalities may also result from other cardiac procedures, including coronary artery bypass grafting, valve replacement surgery, transcatheter aortic valve implantation, catheter ablation of arrhythmias, transcatheter closure of ventricular septal defect, and alcohol (ethanol) septal ablation.[35–37]
- *Congenital causes.* AV block can be seen in a variety of congenital heart defects that result in structural abnormalities, such as congenitally corrected transposition of the great arteries, large primum atrial septal defects, and large AV septal defects. Congenital AV block can also be seen without structural heart disease, most commonly in neonatal lupus where anti-Ro/SSA or anti-LA/SSB antibodies pass via the placental from the mother

to the baby.[38,39] The mortality rate in this condition is highest in neonates, diminishes during childhood and adolescence, and then increases later in life. Persistent ventricular rates less than 50 beats/min correlate with the development of symptoms and syncope. Symptomatic patients and those patients with left ventricular (LV) dilatation should receive permanent pacemakers.

Medications Causing AV Block

Multiple medications can impair AV conduction. The most common are β-blockers, nondihydropyridine calcium channel blockers (verapamil and cardizem), digoxin, adenosine, amiodarone, and other antiarrhythmic medications. Most patients with drug-induced AV block have preexisting underlying conduction disease. In a study of 169 patients with second- or third-degree AV block not related to digitalis toxicity, AMI, or vasovagal syncope, 54% were receiving β-blockers, verapamil, or diltiazem.[40] Drug discontinuation resulted in resolution of AV block in 32 of 79 cases, but AV block later recurred without medication in 18 of these patients.

Miscellaneous Causes of AV Block

Hyperkalemia with plasma potassium concentrations above 6.3 mmol/L, hyperthyroidism, hypothyroidism, myxedema, and thyrotoxic periodic paralysis can all cause degrees of AV block.[41–43]

Treatment of AV Block

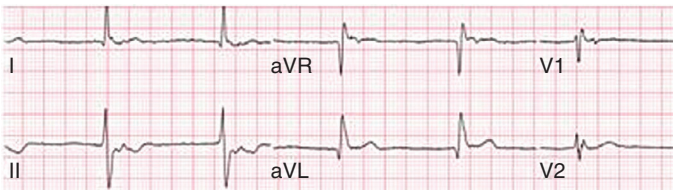
Often there are medications that can be withdrawn to improve AV conduction, but there are no medications that can be administered to permanently improve AV conduction. Transient AV nodal block may be managed with atropine. Infranodal block may be managed with (carefully titrated) isoproterenol until temporary or permanent pacing is established.

Junctional Rhythm

When the sinus node does not depolarize the atrium for any reason (high vagal tone, sinus node dysfunction), the cells near the AV junction (AV node, His bundle) may take over as the active pacemaker. Retrograde activation of the atrium, manifest as negative P waves in the inferior leads (II, III, aVF), may be seen (Fig. 31.11). If the junctional rhythm goes faster than 60 beats/min, it is termed an *accelerated junctional rhythm*. This is a common manifestation of digitalis toxicity or can be seen with any type of cardiac injury (myocarditis, after coronary artery bypass grafting, and after valve replacement surgery).[44]

Vagally Mediated Sinus Arrest, Bradycardia, and Heart Block

The most common cause of nonconducted P waves on telemetry or Holter recordings is bradycardia-associated AV block caused by increased vagal tone. This manifests as sudden (usually nocturnal) block of one or more P waves with or without antecedent PR prolongation. This phenomenon is characterized by PP prolongation before AV block. Vagally mediated sinus arrest, bradycardia, and heart block often occur in the ICU setting as a result of suctioning, gagging, femoral vessel compression (for hemostasis), and a variety of other triggers (Box 31.1). Vagal stimulation may lower blood pressure with or without significant bradycardia. Bradyarrhythmias and hypotension usually resolve when vagal stimulation ceases. Persistent bradycardia or hypotension mediated by vagal tone may require placing the patient in the Trendelenburg position, temporary saline solution infusion, or IV administration of atropine to fully resolve the transient episode.



• **Fig. 31.11** Junctional rhythm with retrograde P waves that are negative in the inferior leads.

• BOX 31.1 Triggers for Vagally Mediated Heart Block

Gagging reflexes such as with intubation or placement of a nasogastric tube
Endotracheal suctioning and irrigation of the carina
Distention of a visceral organ such as during colonoscopy or bladder irrigation
Increased intrathoracic pressure as may occur with coughing or excessive tidal volumes on the ventilator
Direct stimulation of the carotid body, which may occur with vascular surgery in this area
Increased intracranial pressure and certain neurologic procedures
Manual compression during femoral artery line removal
Seizure-related
Neurocardiogenic syncope or simple fainting in patients undergoing painful procedures or possibly in visitors to the intensive care unit

Supraventricular Tachycardia

Overview

Supraventricular tachyarrhythmias occur frequently in critically ill patients. Conditions such as hypoxemia, electrolyte imbalance, catecholamine excess (endogenous and exogenous), and other metabolic disturbances predispose ill patients (with or without preexisting arrhythmic substrates) to tachyarrhythmias. Intensivists must be prepared for acute management of supraventricular tachycardia (SVT). Knowledge of arrhythmia mechanisms, appropriate choices for acute pharmacotherapy, and indications for urgent or emergent direct current cardioversion are requisite.[45] We discuss the mechanisms of SVTs, provide an ECG-guided approach to their diagnosis, and cover specific treatments for these dysrhythmias. The substrate for some SVTs is present before ICU admission, but the most common SVTs—AF (and flutter) and multifocal AT (which may be transient, requiring no chronic therapy)—do not necessarily have a prior substrate.

Premature Atrial Contractions, Junctional Premature Contractions

Premature atrial, junctional, or ventricular beats are common in patients with or without structural heart disease and rarely result in significant alteration of cardiac output. They may occur as a result of enhanced sympathetic tone, metabolic stress, pericarditis, or direct mechanical irritation (as occurs with intracardiac catheters). They can also be due to the stimulant effects of caffeine, alcohol, intravenous inotropic support, or illicit drugs (such as cocaine).

Atrial premature beats may be conducted aberrantly to the ventricle and can be confused with premature ventricular beats, or they may block in the AV node, creating a pause that may be confused with sinus arrest or SA exit block. Atrial premature beats may initiate reentrant SVTs or AF. Premature atrial contractions rarely require treatment, unless they trigger sustained SVTs. β-Blockers or calcium blockers would be the first-line therapy for premature beats if treatment is required.

Paroxysmal Supraventricular Tachycardia

The prevalence of paroxysmal SVT (PSVT) in the general population is 2.25 per 1000 persons.[45] Compared with patients with PSVT and other cardiovascular diseases, patients with PSVT and structurally normal hearts are younger (37 years vs. 69 years, $P = 0.0002$) and have faster PSVT (186 beats/min vs. 155 beats/min, $P = 0.0006$). Women have twice the risk of men of developing PSVT.[45] Individuals older than 65 years have more than 5 times the risk of younger persons of developing PSVT.[46]

Among women with SVT and no other cardiovascular disease, the onset of symptoms begins during childbearing years (e.g., 15–50 years) in 58%.[46] The first onset of SVT can occur during pregnancy (in 3.9% of women), but among women with an established history of SVT, pregnancy exacerbates arrhythmia occurrences and makes them more difficult to treat because of the potential side effects of treatments (medications or catheter ablation) to the fetus.[47]

It is important to record a 12-lead ECG of any SVT to differentiate tachycardia mechanisms. If the AV node is *not* an obligate component, treatment that targets the AV node does not reliably terminate those arrhythmias. Also, if the QRS duration is longer than 120 msec, it is crucial to distinguish VT from SVT with aberrant conduction, preexisting bundle branch block, or preexcitation. The presence of AV dissociation (with ventricular rate faster than atrial rate) most commonly means VT is present but it could also mean junctional tachycardia, especially if the QRS is narrow.

Types of PSVT reviewed in the following text are: AV nodal reentry tachycardia (AVNRT), AV reentrant tachycardia (AVRT), Wolff-Parkinson-White (WPW) syndrome, AT, atrial fibrillation, and atrial flutter.

AV Nodal Reentrant Tachycardia

AVNRT is the most common reentrant SVT. It is usually seen in young adults without structural heart disease, and more than 60% of cases are observed in women.[48] The ventricular rate is usually 160 beats/min to 200 beats/min but can range from 110 beats/min to more than 250 beats/min (in rare cases, the rate can be <100 beats/min).[49] Symptoms caused by AVNRT include palpitations, lightheadedness, and near-syncope; rarely patients may be asymptomatic. True syncope is unusual. Atrial contraction on a closed AV valve may produce neck pounding.[50]

The anatomic substrate of AVNRT is dual AV nodal physiology. In 76% to 90% of cases, antegrade conduction proceeds along the posterior (slow) AV nodal pathway and retrograde conduction along the anterior (fast) AV nodal pathway[51,52]; this is typical slow-fast AVNRT. Because retrograde conduction is so rapid, atrial and ventricular activation are virtually simultaneous. P waves are usually not visible on the surface ECG or may appear in the terminal portion of the QRS complex (pseudo R′ in lead V1 or pseudo-S waves in the inferior leads) (see Fig. 31.12). Less common (so-called atypical) variants (fast-slow, slow-slow, and slow–sort of slow) of AV nodal reentry also exist, and all are easily amenable to catheter ablation.[52] In the less common types, the inverted retrograde P waves may be seen on the 12-lead ECG anywhere in the ST segment. Medical treatment of AVNRT is discussed later, and if medications fail, this arrhythmia is easily amenable to catheter ablation.

AV Reentrant Tachycardia and Wolff-Parkinson-White Syndrome

APs directly connect the atrium and ventricle, bypassing the normal conduction through the AV node and the His-Purkinje system. APs have conduction properties similar to those of myocardium and are therefore capable of very rapid conduction. The pathways are considered "manifest" if they conduct in the anterograde direction, demonstrating preexcitation with a delta wave on the ECG. The ECG pattern of preexcitation is a short PR interval with a slurred, wide upstroke (delta wave) of the QRS complex. Manifest pathways occur in 0.1% to 0.3% of the population, are more common in men than women, and can conduct in both the anterograde and retrograde directions or, less commonly, only in the anterograde direction.[53] Anterograde pathways that are capable of conducting very rapidly place patients at risk of SCD when AF occurs leading to very rapid sequential activation of the ventricles, causing the ventricles to fibrillate. "Concealed" pathways conduct only in the retrograde direction and therefore do not cause preexcitation on the 12-lead ECG and do not place patients at risk of SCD.

AVRT is a reentrant arrhythmia that uses the AP as one limb of the tachycardia circuit and the AV node as the other limb. Orthodromic AVRT uses the AV node as the antegrade limb and the AP as the retrograde limb; usually a narrow QRS is seen on the surface ECG with a retrograde P wave seen in the ST segment (Fig. 31.13).

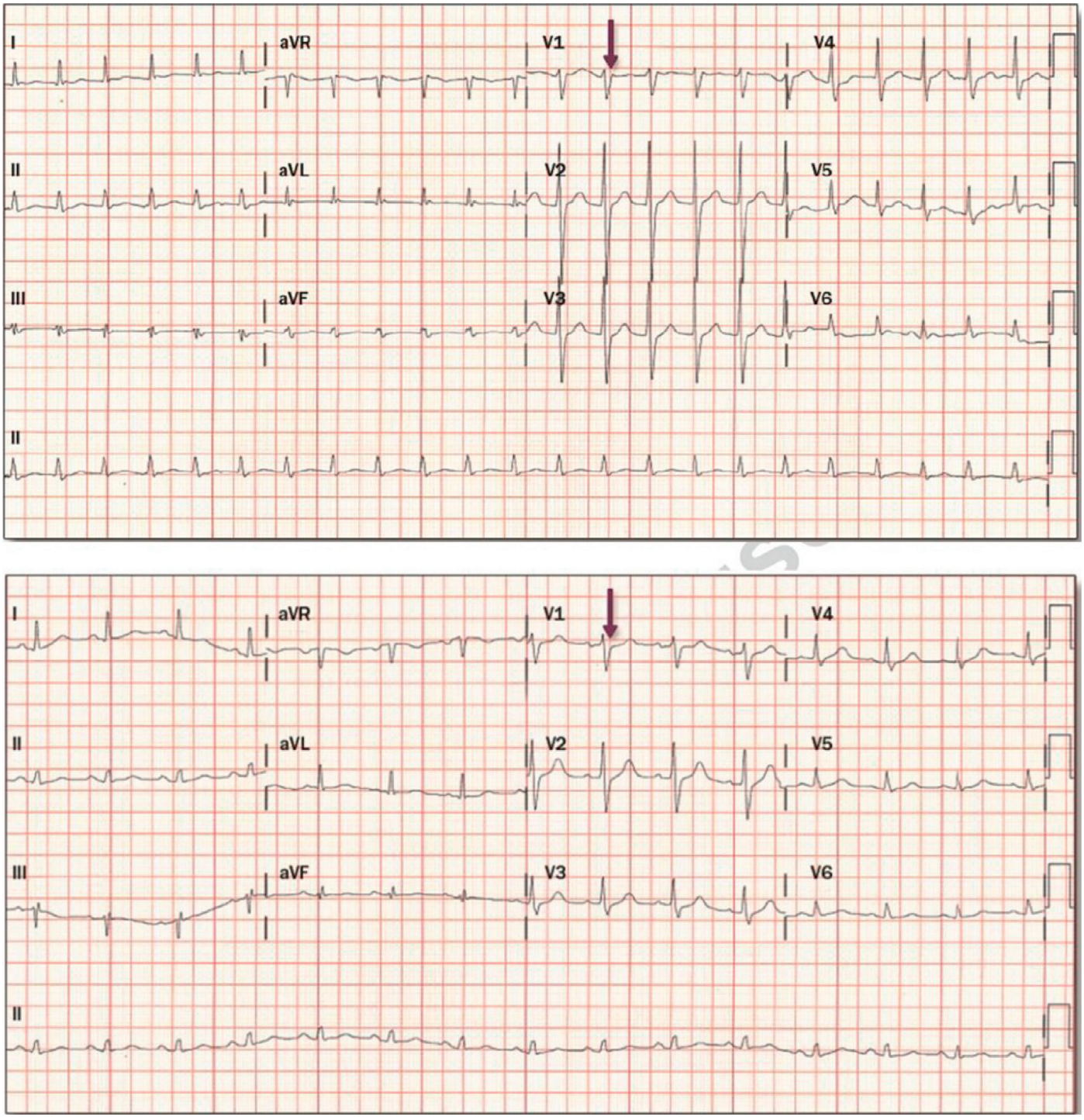
Antidromic AVRT uses the AP as the antegrade limb and the AV node as the retrograde limb; this tachycardia almost always has a wide QRS morphology. The resulting maximally preexcited wide QRS rhythm of antidromic AVRT may be difficult to distinguish from VT on an ECG (Fig. 31.14).

AVRT has a longer RP interval during tachycardia compared with that seen in AVNRT. In both AVNRT and AVRT P waves (if visible on surface ECG) will be negative in the inferior leads because the atria are activated in the retrograde direction. AV block is unusual during AVNRT and *excludes* the diagnosis of AVRT (which requires both atrial and ventricular participation).

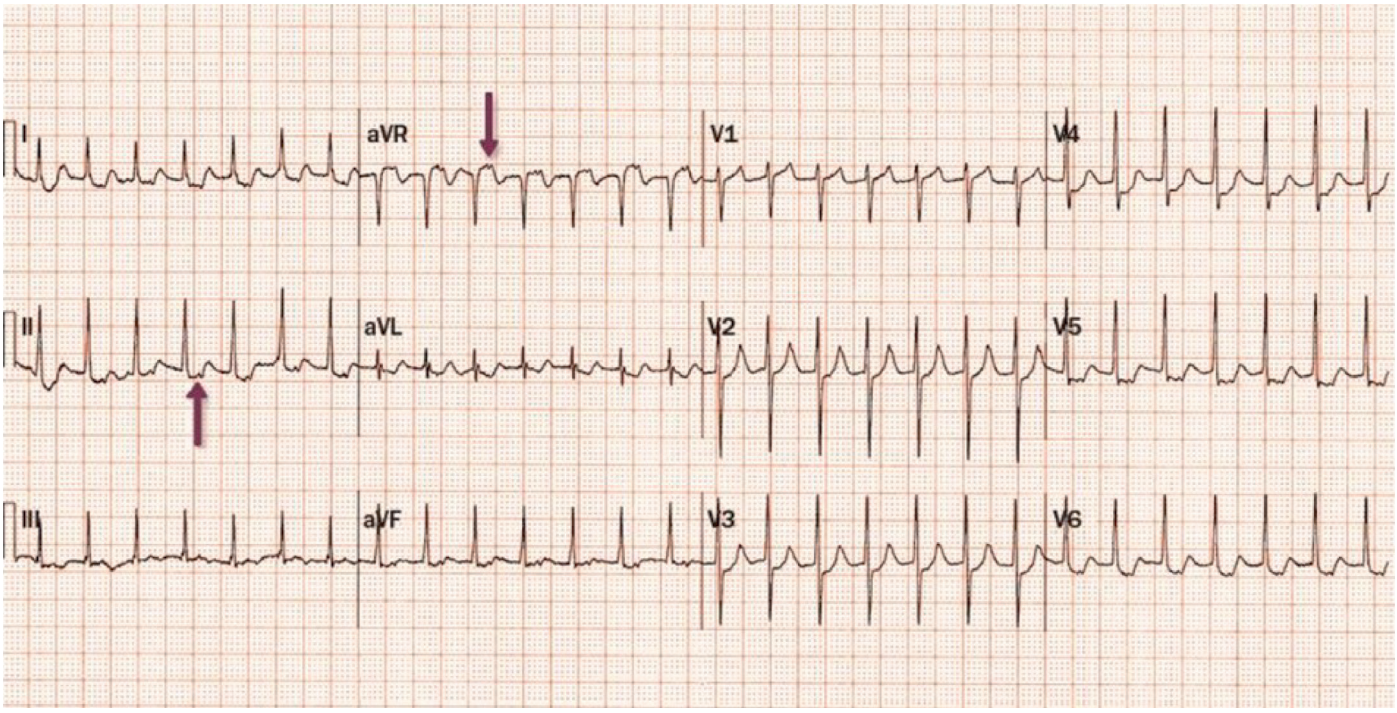
WPW is a congenital condition involving strands of abnormal conductive cardiac tissue between the atria and ventricles that cause a preexcitation pattern on an ECG and provide an AP as one limb of a reentrant tachycardia circuit or SVT. Symptomatic presentation usually occurs during the teenage years or early adulthood. Pregnancy may exacerbate symptoms. Approximately 25% of patients with a Wolff-Parkinson-White ECG pattern are incapable of retrograde conduction via the AP and therefore cannot have orthodromic AVRT, but they can have antidromic AVRT or preexcited AF with rapid rates as described earlier (Fig. 31.15).

Asymptomatic patients generally have a benign prognosis; however, the initial presentation may be ventricular fibrillation (VF).[56] The risk of SCD associated with WPW is highest in the first two decades of life.[55–57]

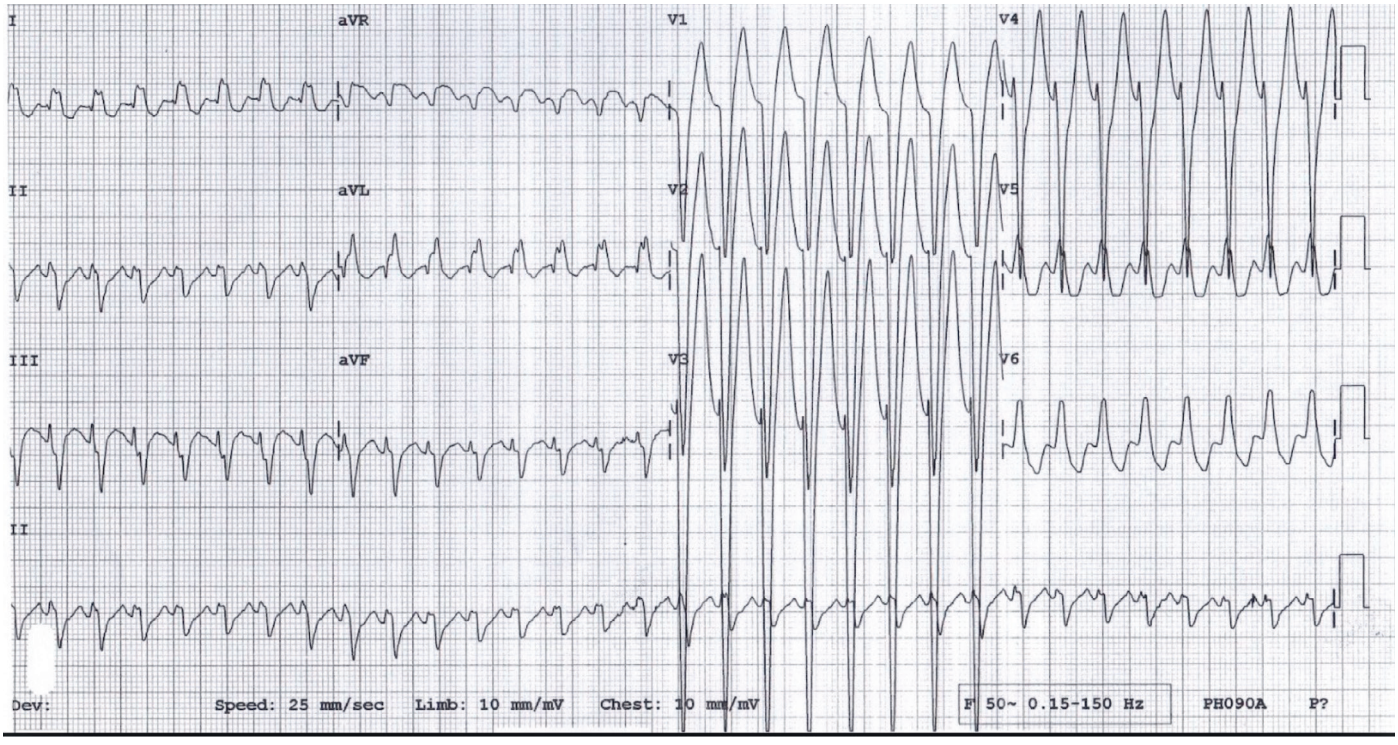
In recent years, the use of ECGs for screening before sports participation or before medical and surgical procedures has identified increasing numbers of asymptomatic individuals with a WPW ECG pattern. The optimal management of these patients is not definitively known. In its simplest form, risk stratification uses



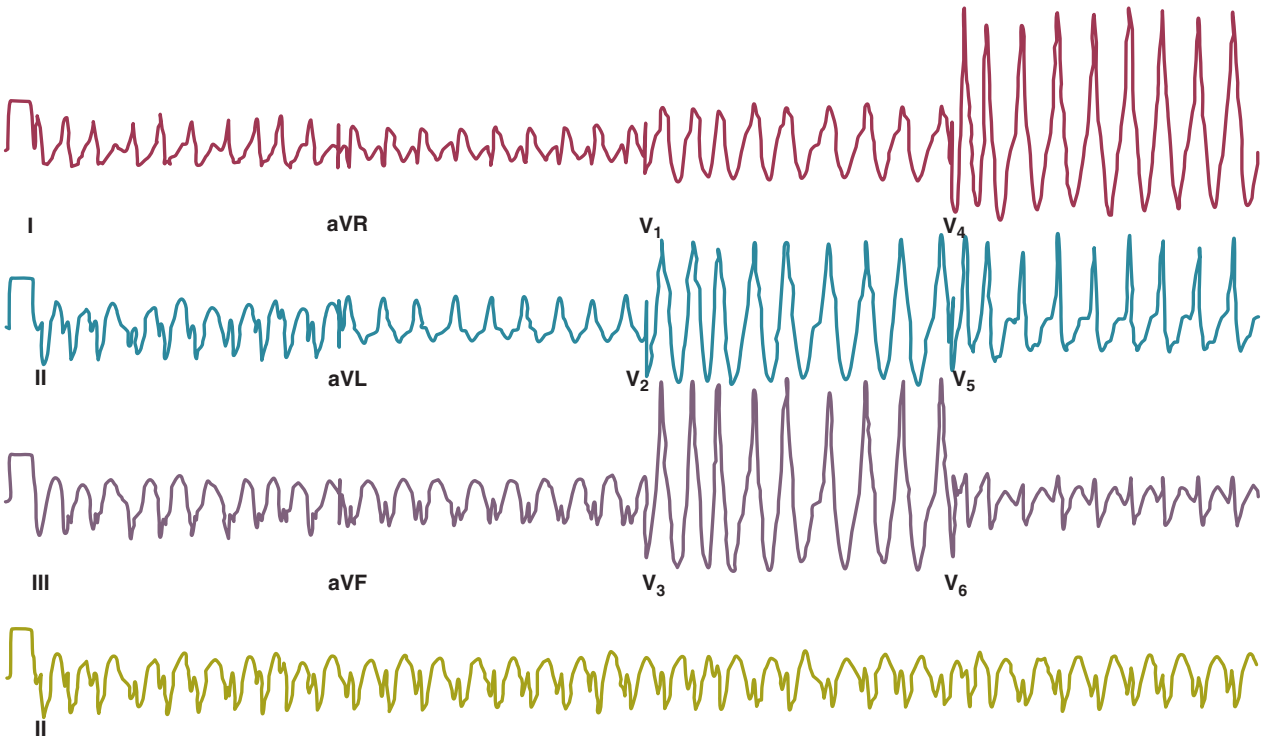
• **Fig. 31.12** Typical atrioventricular nodal reentry tachycardia (AVNRT) and normal sinus rhythm after conversion. *Upper panel,* the arrow points to the P waves, which are inscribed at the end of the QRS complex, seen best in the inferior leads and as a slightly positive R′ (pseudo-R′) in lead V1. The reentrant circuit involves anterograde conduction over a slow atrioventricular node pathway, followed by retrograde conduction in a fast atrioventricular node pathway. Typical AVNRT is a type of short RP tachycardia. *Lower panel,* when the patient is in sinus rhythm, the *arrow* indicates where the R′ is absent in V1.



• **Fig. 31.13** Orthodromic atrioventricular reentrant tachycardia. The *arrows* point to the P waves, which are inscribed in the ST segment after the QRS complex. The reentrant circuit involves anterograde conduction over the atrioventricular node, followed by retrograde conduction over an accessory pathway; this results in a retrograde P wave with short RP interval.



• **Fig. 31.14** Antidromic atrioventricular reentrant tachycardia using an R-sided accessory pathway as the antegrade limb of the reentrant circuit, and the atrioventricular node as the retrograde limb.



• **Fig. 31.15** Twelve-lead electrocardiogram (ECG) tracing from a patient with atrial fibrillation and Wolff-Parkinson-White syndrome. A 12-lead electrocardiogram (ECG) tracing from a patient with Wolff-Parkinson-White syndrome shows preexcited atrial fibrillation with rapid ventricular response. A rapid, "irregularly irregular" wide QRS tachycardia is present. Preexcited atrial fibrillation, as seen here, may degenerate to ventricular fibrillation.

noninvasive testing (e.g., Holter or exercise stress test) to ascertain the true loss of preexcitation at physiologic heart rates, which suggests a benign pathway that would not be able to conduct rapidly to the ventricles[58,59] (Fig. 31.16). Inability to clearly demonstrate loss of manifest preexcitation during stress testing warrants consideration for more invasive EP testing depending on the patient's preference and occupation.

Treatment of Preexcited AF

If the patient is hemodynamically stable, IV ibutilide or IV procainamide can be used to slow conduction over the AP with the additional benefit of possibly terminating AF.[60,61] β-Blockers, calcium blockers, digoxin, or any drug that slows conduction over the AV node is absolutely contraindicated because they will slow AV node conduction and cause more conduction over the rapidly conducting AP and put the patient at risk for VF. If the patient is hemodynamically unstable, direct current cardioversion should be performed.

Preexcitation Variants

Although APs may be located anywhere along the right or left AV grooves, two variants with characteristic locations deserve mention. *Paroxysmal junctional reciprocating tachycardia* is a form of AV reentry that can be incessant. The antegrade limb of the circuit is the normal AV conduction system. The retrograde limb is a concealed, decrementally conducting AP usually located in the posterior septum.

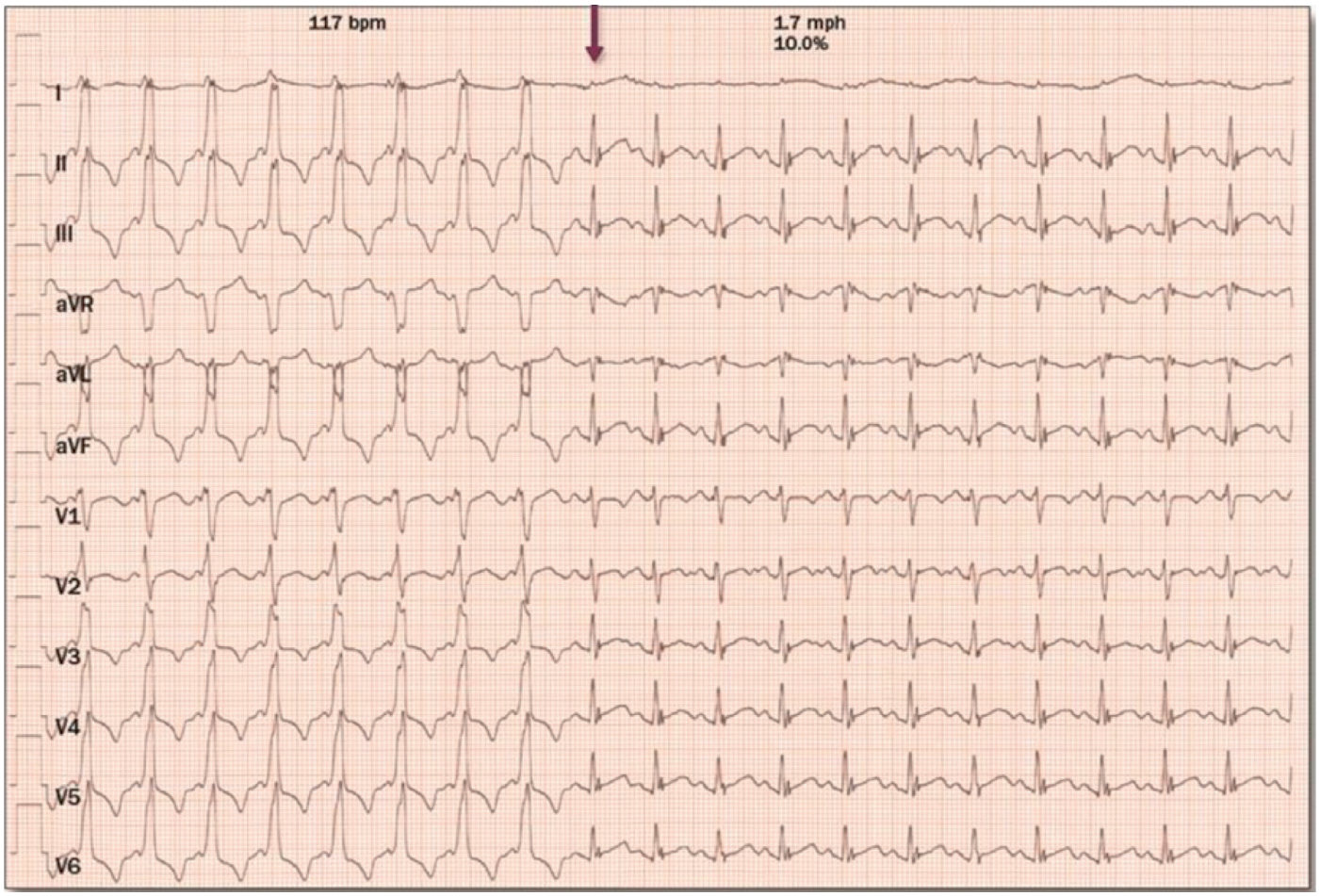
Atriofascicular pathways (Mahaim fibers) connect the right atrium to various locations along the right bundle branch and conduct only in the antegrade direction with decremental properties similar to the AV node. During sinus rhythm, preexcitation is minimal or absent. During SVT, a regular wide QRS typical left bundle branch block (LBBB) pattern tachycardia with 1:1 retrograde P waves is seen because the tachycardia uses the Mahaim pathway in the antegrade limb and the AV node in the retrograde limb.[62]

There are rare tachycardias that use two APs for the SVT circuit, one in the antegrade direction and one in the retrograde direction bypassing the AV node entirely. These usually have a wide complex on the ECG with 1:1 retrograde P waves and do not respond to any treatments directed at the AV node.

Atrial Tachycardia

Focal AT is a fast rhythm from a discrete atrial origin, discharging at a rate that is generally regular between 100 and 250 beats/min.[63] A long RP interval is typical of AT because the rhythm is driven by the atrium and conducts normally to the ventricles; the ECG typically shows a P wave with a morphology that differs from sinus and is seen near the end of or shortly after the T wave (Fig. 31.17).

Automatic ATs can occur along the crista terminalis, near the ostium of the coronary sinus, along the tricuspid and mitral annulus, in either atrial appendage, or within or in close proximity to the pulmonary veins. Automatic ATs are very sensitive to catecholamines.[64] Although they may manifest in the absence of structural heart disease or obvious precipitants, they also are commonly associated with chronic lung disease, pneumonia, myocardial (atrial) infarction, and acute alcoholic binges. Amphetamine or cocaine abuse also may precipitate automatic ATs. Nonsustained focal AT



• **Fig. 31.16** Abrupt loss of preexcitation during exercise testing. During exercise treadmill testing, this patient abruptly lost preexcitation at a heart rate of 117 beats/min. Beginning abruptly with the beat under the *arrow,* the PR interval normalizes and the QRS changes from preexcited to narrow. *bpm,* Beats/min; *mph,* miles/hr.

is common, especially in the ICU setting, and often does not require treatment. However, sustained ATs with rapid ventricular rates can lead to hemodynamic instability and, if left untreated, tachycardia-mediated cardiomyopathy.

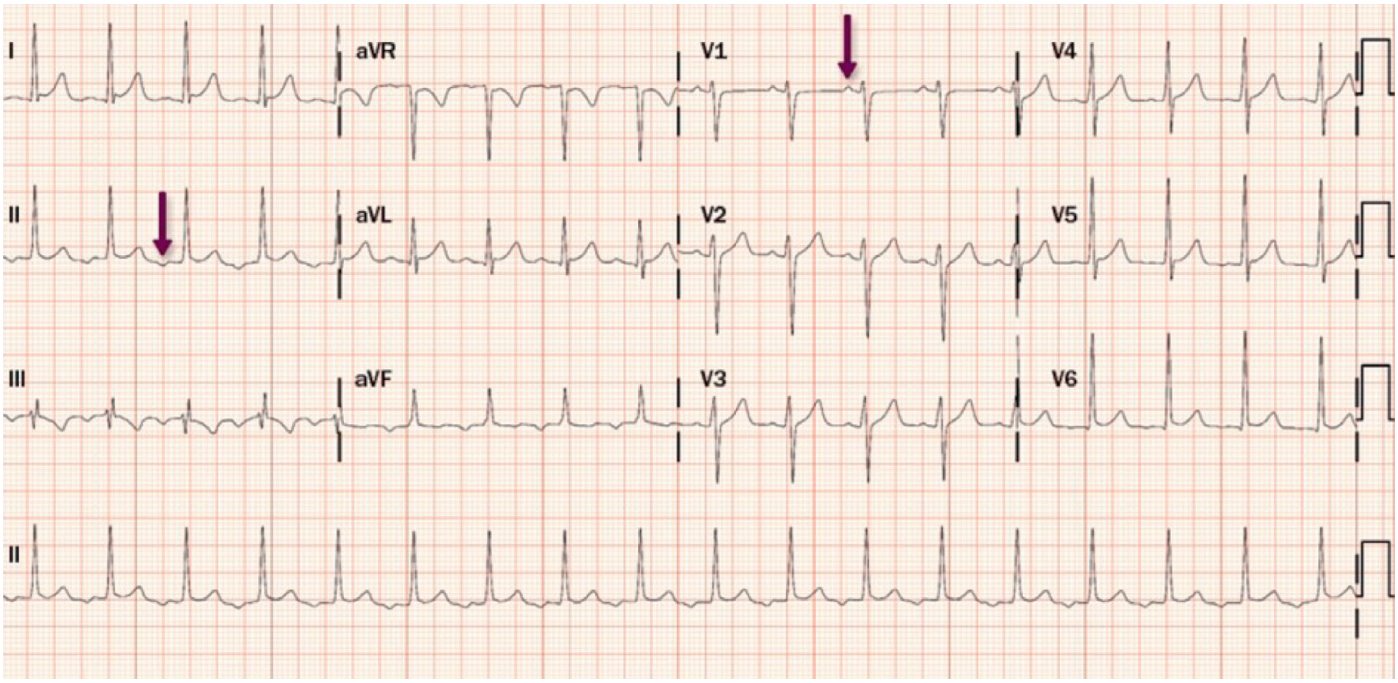
Intraatrial reentry is another form of AT usually associated with structural heart disease[65]; approximately 50% of patients with intraatrial reentry have evidence of structural heart disease. In patients without obvious structural disease, subtle changes such as scarring and fibrosis as the result of hypertension, diabetes, or other systemic diseases provide the substrate for reentry. Microreentrant or macroreentrant ATs from the left atrium after AF ablation occur in approximately 50% of patients.[65,66] A variety of reentry circuits have been described after AF ablation, including a path around the mitral annulus (perimitral flutter), reentry involving the left atrial roof, and reentry around regions of scarring in the right or left atria.

The ECG of intraatrial reentry shows flutter waves of variable morphologies depending on the origin of the flutter and variable AV block. Persistent elevation of the ventricular rate may result in a tachycardia-mediated cardiomyopathy, which can be reversed when the ventricular rate is controlled. Intraatrial reentry tachycardia is prone to develop after cardiac surgery for congenital anomalies; reentry occurs around structural barriers such as suture lines.

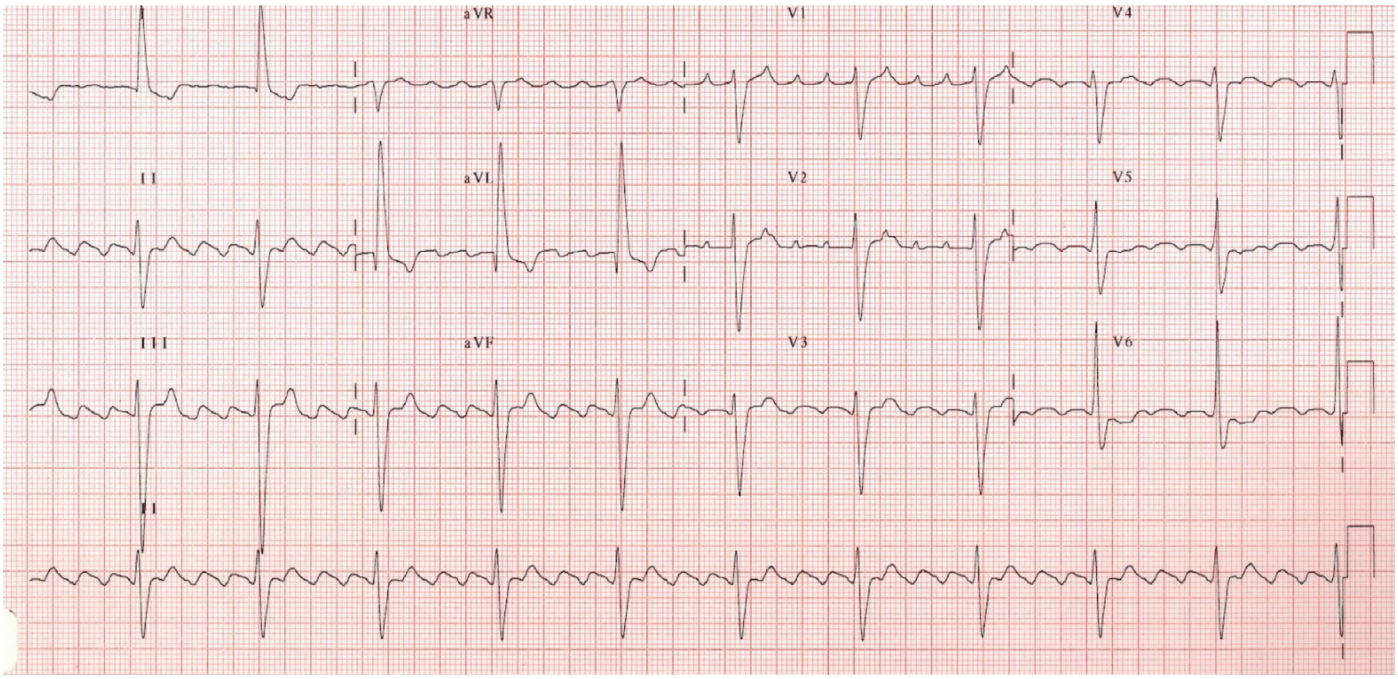
Atrial Flutter

Atrial flutter is the most common type of intraatrial reentry. The reentrant circuit of typical atrial flutter traverses (with either counterclockwise or clockwise rotation) through an isthmus formed by the inferior vena cava, tricuspid valve, eustachian ridge, and coronary sinus ostium. Counterclockwise rotation is most common and results in negative "flutter" waves in ECG leads II, III, aVF, and V6. Atrial activity in lead V1 is positively directed if there is no underlying structural heart disease (Fig. 31.18). Clockwise atrial flutter produces oppositely directed flutter waves in these leads.

Atrial rates generally range between 250 and 350 beats/min; however, slower rates may be seen in the presence of pharmacotherapy, marked right atrial enlargement, or a large amount of atrial tissue scarring.[67] Ventricular rates in atrial flutter are variable but can be rapid at 150 beats/min when there is 2:1 atrial conduction to the ventricles. When a patient with SVT presents with a heart rate of 150 beats/min, atrial flutter with 2:1 AV conduction should be high in the differential diagnosis.



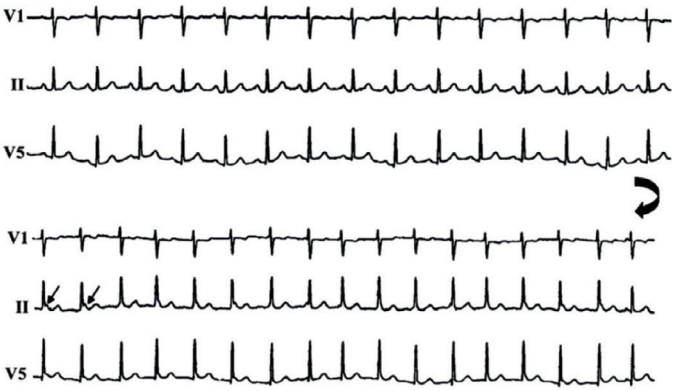
• **Fig. 31.17** Atrial tachycardia. The *arrows* point to the P wave, which are inscribed before the QRS complex. The focus of this atrial tachycardia was mapped during electrophysiologic study to an area near the left inferior pulmonary vein.



• **Fig. 31.18** Typical counterclockwise right atrial flutter.

Treatment for (typical and atypical) intraatrial reentry is similar to that outlined for AF (see following text). Patients with atrial flutter are thought to have the same risk of thromboembolism as patients with AF; therefore recommendations for anticoagulation should mirror those for patients with AF. The next step in the decision tree for intraatrial reentry is rate control versus rhythm control, discussed in detail later. Special care must be taken to avoid inadvertent slowing of the intraatrial reentry with antiarrhythmic medications (typically class IC agents such as propafenone) enough to precipitate 1:1 AV conduction and subsequent hemodynamic deterioration. Radiofrequency ablation is first-line curative therapy for typical atrial flutter if medications fail. Most other types of intraatrial reentry can also be mapped and cured with radiofrequency ablation.

• **Fig. 31.19** Multifocal atrial tachycardia is characterized by three or more morphologically distinct (nonsinus) P waves, atrial rates of 100 to 130 beats/min, and variable atrioventricular block. Note the irregularity of the rhythm as well as the different P-wave morphologic appearances *(arrows)* with different PR intervals.



• **Fig. 31.20** Surface electrocardiographic recording from leads V1, II, and V5 in a patient with junctional tachycardia. The *upper panel* shows sinus rhythm. The *lower panel* shows tachycardia onset with the characteristic finding of dissociation of the QRS and P waves (*narrow arrows* on P waves). The *large arrow* signifies continuous recording.

Sinus node reentry is a particular type of intraatrial reentry that occurs within the sinus node, the perinodal atrial tissue, or both. Although the mechanism may be difficult to prove clinically, most investigators agree that the P wave may be *nearly* identical to sinus rhythm, suggesting that the reentry exit point may differ slightly from sinus pacemaker beats. Average rates generally are 130 to 140 beats/min (range 80–200 beats/min). This arrhythmia can be treated medically or with catheter ablation.

Multifocal Atrial Tachycardia

Multifocal atrial tachycardia (MAT) is defined as a rapid, irregular rhythm with at least three distinct P-wave morphologies (nonsinus), atrial rates of 100 to 130 beats/min, and variable AV block (Fig. 31.19). It may be difficult to distinguish MAT from AF on physical examination or even on a single ECG tracing, so a 12-lead ECG is indicated to confirm the diagnosis.[68] On the ECG of MAT, unlike AF, there is a distinct isoelectric period between P waves.

MAT is commonly associated with pulmonary disease and sometimes occurs in the setting of CHF; therefore it is frequently seen in the ICU setting. It has been reported in patients with cancer, lactic acidosis, pulmonary emboli, renal disease, and infection. Hypoxemia frequently is present. MAT may be exacerbated by digitalis or theophylline toxicity, hypokalemia, hypomagnesemia, and hyponatremia.

Treatment of Multifocal Atrial Tachycardia

Treatment is usually is directed at elimination of the underlying precipitants and slowing conduction at the AV nodal level to control the heart rate. Metoprolol (used cautiously when bronchospasm is present) or verapamil may provide atrial and ventricular rate control and occasionally restore sinus rhythm.[69,70] Potassium and magnesium supplements may help suppress MAT. Amiodarone has also been useful in restoring sinus rhythm.[71] Digoxin toxic MAT is managed by withholding digoxin and/or administering potassium, lidocaine, phenytoin, and/or digoxin-specific antigen-binding fragments. MAT does not respond to direct current cardioversion[72] and is not amenable to catheter ablation because of the multiple origins of atrial beats. *Digoxin will not slow the rate of MAT.*

Nonparoxysmal AV Junctional Tachycardia, and Junctional Ectopic Tachycardia

Nonparoxysmal AV junctional tachycardia is an automatic tachycardia originating in the AV node caused by enhanced (abnormal) automaticity from an ectopic focus in the AV junction (including the His bundle) (Fig. 31.20). It occurs at a rate of 70 to 130 beats/min; AV dissociation (often isorhythmic) may be seen, and when present, excludes the diagnosis of AVRT and makes AVNRT highly unlikely.

When it is irregular, junctional tachycardia may be misdiagnosed as AF or MAT. Nonparoxysmal AV junctional tachycardia is associated with injury to the myocardium such as cardiac surgery, MI, or rheumatic fever and can occur in the setting of digitalis toxicity.[73] Hypokalemia may cause or exacerbate this arrhythmia. Sympathetic stimulation increases the tachycardia rate.

Junctional ectopic tachycardia, a specific type of junctional tachycardia, is also an automatic tachycardia originating in the AV node. It primarily affects children and infants and can be incessant, causing tachycardia-mediated cardiomyopathy. Infants and children with acquired or congenital junctional ectopic tachycardia have a high rate of death owing to SCD, heart failure, or uncontrollable, incessant tachyarrhythmias.[74] Amiodarone, which may suppress the tachycardia or control its rate, should be administered when heart rates less than 150 beats/min cannot be achieved by other means.[75]

Treatment of Junctional Tachycardia

β-Blockers and calcium channel blockers are first-line therapy for junctional tachycardia, simultaneous with treatment of the underlying cause. Catheter ablation can eliminate tachycardia while preserving AV conduction if the arrhythmia cannot be controlled by medications.[76–78]

Sinus Tachycardia

In normal individuals, the sinus rate at rest is between 60 and 100 beats/min. Sinus tachycardia is usually a normal reflex response to changes in physiologic, pharmacologic, or pathophysiologic stimuli, such as exercise, emotional upset, fever, infection, hemodynamic or respiratory compromise, thyrotoxicosis, poor physical conditioning, sympathomimetic or vagolytic agents, or anemia. The resulting increase in cardiac output usually is beneficial and appropriate for the underlying condition. The sinus heart rate generally does not exceed 180 beats/min, except in young patients, who may achieve rates higher than 200 beats/min during vigorous exercise.[79] Sinus tachycardia usually resolves when conditions return to baseline.

TABLE 31.1 Differential Diagnosis of Sinus Tachycardia

Etiologic Category	Specific Disorders
Hemodynamic	Heart failure—systolic and diastolic heart failure caused by ischemic, valvular, or nonischemic myopathy Loss of circulating blood volume—gastrointestinal bleeding, anemia, shifts of intravascular fluid owing to changes in colloidal osmotic pressure or inflammation Septic shock—dehydration Vascular shunts—intracardiac as well as aortovenous malformations, fistulas Pulmonary embolism
Metabolic and neurohumoral	Sepsis—infections and inflammatory conditions Hyperthyroidism Paget disease of the bone Pheochromocytoma Carcinoid syndrome Beriberi heart disease Carcinoma Hyperpyrexia Acidosis Exercise
Pharmacologic	Sympathomimetic agents—isoproterenol, epinephrine, or dopamine Vagolytic agents, atropine, acopolamine Vasodilators—nitrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hydrazine, as well as centrally acting vasodilators Thyroid preparations, caffeine, and nicotine Bronchodilators, including theophylline and terbutaline Anesthetic agents, including spinal anesthetics, causing peripheral vasodilation Drugs of abuse—amphetamines, cocaine, "ecstasy," cannabis
Neurologic/psychological	Pain Fear, anxiety, and hysteria Hyper–β-adrenergic phase of neurocardiogenic syncope Autonomic dysfunction such as with diabetes

The differential diagnosis for sinus tachycardia is presented in Table 31.1.

Sinus tachycardia is often present in ICU patients and sometimes is difficult to distinguish from other SVTs. When observed over time, sinus tachycardia has a variable rate that gradually accelerates and gradually decelerates without abrupt changes. The P-wave morphology of sinus tachycardia is upright in leads I, II, aVF, and V4 to V6. Sinus tachycardia should slow transiently with vagal maneuvers or IV adenosine. If adenosine administration produces AV block, the P-wave morphology can be clearly seen if a 12-lead ECG is run in rhythm strip mode. A negative P wave in any of leads I, II, aVF, and V4 to V6 excludes a sinus mechanism. P waves that are negative in lead I suggest a left atrial origin. Differentiation of "high" right AT P waves from sinus tachycardia can be difficult. Comparison of the 12-lead P-wave morphology to that of an older 12-lead ECG tracing (if obtainable) when the patient was clearly in normal sinus rhythm may help to distinguish normal sinus rhythm from AT.

Inappropriate sinus tachycardia (IST) is defined as sinus tachycardia that is unexplained by physiologic demands at rest, with minimal exertion, or during recovery from exercise. Crucial to this definition is the presence of associated symptoms that include weakness, fatigue, lightheadedness, and uncomfortable sensations, such as heart racing. Patients with IST commonly show resting heart rates above 100 beats/min and average rates that are above 90 beats/min in a 24-hour period.[80] The cause of IST is unclear, and mechanisms related to dysautonomia, neurohormonal dysregulation, and intrinsic sinus node hyperactivity have been proposed.

Management of SVT

Management of Regular Narrow Complex Supraventricular Tachycardia

Acute tachycardia treatment begins with careful assessment of the 12-lead ECG, to make an estimated diagnosis of the tachycardia mechanism (Box 31.2). The first step in treatment of narrow complex PSVT is vagal maneuvers: Valsalva and carotid sinus massage (after auscultation of the carotids to exclude bruits). These maneuvers should be performed with the patient in the supine position, and if executed properly, will often terminate the SVT or unveil a primary atrial mechanism (AT, AF, or atrial flutter). If the arrhythmia does not have an atrial mechanism, medical interventions should then be designed to interrupt AV nodal conduction.

Adenosine is the initial drug of choice for acute management of PSVT. An initial intravenous dose of 6 mg may be followed (2 minutes) by 12 mg if 6 mg is unsuccessful. Adenosine should terminate more than 90% of AVNRT and AVRT. This agent is also effective for terminating sinus node reentry and automatic ATs, particularly those originating near the crista terminalis where vagal innervation is rich. Termination may be transient because of adenosine's short half-life (10 seconds) but at least the tachycardia

• BOX 31.2 Differential Diagnosis of Narrow and Wide QRS Tachycardias

Narrow QRS (≤120 msec) Tachycardias

Regular
- Physiologic sinus tachycardia
- Inappropriate sinus tachycardia
- Sinus nodal reentrant tachycardia
- Focal atrial tachycardia
- Atrial flutter
- Atrial fibrillation with very fast ventricular response
- Atrioventricular nodal reentrant tachycardia
- Nonparoxysmal or focal junctional tachycardia
- Orthodromic atrioventricular reentrant tachycardia
- Idiopathic ventricular tachycardia (especially high septal ventricular tachycardia)

Irregular
- Atrial fibrillation
- Atrial focal tachycardia or atrial flutter with varying atrioventricular block
- Multifocal atrial tachycardia

Wide QRS (>120 msec) Tachycardias

Regular
- Antidromic atrioventricular reentrant tachycardia
- Any regular atrial or junctional reentrant tachycardias with:
  - Aberration/bundle branch block
  - Preexcitation/bystander accessory pathway
- Ventricular tachycardia/flutter

Irregular
- Atrial fibrillation or atrial tachycardia with varying block conducted with aberration
- Antidromic atrioventricular reentrant tachycardia with a variable ventriculoatrial conduction
- Preexcited atrial fibrillation
- Polymorphic ventricular tachycardia
- Torsades de pointes
- Ventricular fibrillation

mechanism will be elucidated. Tachycardia termination suggests a supraventricular mechanism that includes the AV node as a requisite part of the circuit. Transient AV block unveiling rapid P waves suggests AT. No response to adenosine suggests a possible ventricular origin.[81,82]

IV verapamil, IV diltiazem, or IV β-blockers are next in line to interrupt AV nodal conduction; they are usually effective for PSVT termination when adenosine fails. AV block without arrhythmia termination again suggests the diagnosis of AT. Because of their longer half-lives these agents may be effective for treatment of tachycardia recurrences after initial success with adenosine. Sinus node reentry may respond to any of the therapies described earlier.

Emergent or urgent direct current cardioversion is indicated when PSVT results in angina pectoris, CHF, or hypotension. Techniques for, and limitations of, direct current cardioversion are discussed later in the chapter. Automatic tachycardias (including MAT), as discussed earlier, usually do not respond to direct current cardioversion.

Management of Irregular Narrow Complex Supraventricular Tachycardia

Acute tachycardia treatment begins with careful assessment of the 12-lead ECG to make an estimated diagnosis of the tachycardia mechanism (see Box 31.2). Irregular narrow complex SVTs are most commonly AF (discussed later) or AT. Automatic AT can be difficult to manage with pharmacotherapy. Vagal maneuvers may produce AV block but may not terminate ATs. Precipitants, such as hypoxia, lactic acidosis, pulmonary emboli, renal disease, and infection, should be treated or eliminated whenever possible. β-Blockers may slow the atrial rate but rarely restore sinus rhythm. Adenosine may produce sinus rhythm; however, tachycardia may resume as soon as the drug is metabolized.[83] IV amiodarone is first-line therapy if it is important to eliminate the tachycardia because of rapid ventricular rates; it usually does not exacerbate heart failure or cause proarrhythmia in the setting of preexisting LV dysfunction.

Management of Regular and Irregular Wide Complex Supraventricular Tachycardia

Again, acute tachycardia treatment begins with careful assessment of the 12-lead ECG to make an estimated diagnosis of the tachycardia mechanism (see Box 31.2). When SVT is wide complex, it is very important to examine a 12-lead ECG when the patient is in normal rhythm (if one is available) to determine if the wide complex simply represents a preexisting bundle branch block. If there is evidence of AV dissociation, the wide complex tachycardia is almost certainly VT and should be treated as such. If 1:1 conduction is seen, the mechanism is likely SVT. Vagal maneuvers—Valsalva and carotid sinus massage (after auscultation of the carotids to exclude bruits)—should again be performed as first-line treatment.

Treatment of regular wide QRS tachycardia with 1:1 AV association should be directed at blocking conduction via the AP. Adenosine can be used as first-line therapy; because of its short half-life adenosine poses little risk, unless it precipitates AF. Adenosine may terminate antidromic tachycardia (at the AV node in the retrograde direction), but it will not affect ATs conducting rapidly across an AP, and may actually cause that conduction to be transiently faster. Intravenous ibutilide (1 mg infused over 10 minutes; a second 1-mg dose may be given by infusion after a 10-minute wait, if necessary) or IV procainamide will block antegrade AP conduction and may terminate acute episodes of AF or flutter with conduction over an AP.[60]

IV verapamil and IV diltiazem are contraindicated in the presence of wide QRS tachycardia (especially irregular wide QRS tachycardia) because they will block AV nodal conduction and allow preferential, more rapid conduction to occur over an AP. Their hypotensive effects may make patients hemodynamically unstable and contribute to the onset of VF. IV digoxin is contraindicated for the same reasons.

Direct current cardioversion should be available whenever treatment of a wide QRS tachycardia is undertaken. If, at baseline, the patient exhibits signs of hemodynamic compromise (angina, heart failure, or hypotension), drug therapy should be eschewed and direct current cardioversion used to promptly restore sinus rhythm. If hemodynamic instability develops during drug therapy, direct current cardioversion should be performed immediately. Direct current cardioversion also should be the next elective therapy when pharmacotherapy is unsuccessful.

Chronic Treatment of Supraventricular Tachycardia

First-line chronic therapy for most reentrant SVTs is catheter ablation after medical therapy fails.

TABLE 31.2 Definition of Atrial Fibrillation: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 days of onset • Episodes may recur with variable frequency
Persistent AF	• Continuous AF that is sustained >7 days
Long-standing persistent AF	• Continuous AF >12 months in duration
Permanent AF	• The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiologic attribute of AF • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

AF, Arial fibrillation.

Atrial Fibrillation

AF is the most common sustained supraventricular arrhythmia and places patients with concomitant risk factors at increased risk of stroke. More than 2 million people in the United States have AF and this number is expected to rise as the population ages. In the United States, the percentage of Medicare fee-of-service beneficiaries with AF in 2010 was reported as 2% for those younger than 65 years of age and 9% for those older than 65 years of age.[84] The prevalence of AF increases with increasing age.

AF is an SVT with uncoordinated atrial activation and consequently ineffective atrial contraction. Symptoms of AF range from nonexistent (asymptomatic) to severe; the most common symptom is fatigue. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality. AF is associated with a fivefold increased risk of stroke,[85] and stroke risk increases with increasing age.[86] A pathognomonic ECG has (1) irregular R-R intervals (when AV conduction is present), (2) absence of distinct P waves, and (3) irregular atrial activity. Table 31.2 outlines the types of AF.

Any disturbance of atrial architecture potentially increases susceptibility to AF. Such changes (e.g., inflammation, fibrosis, and hypertrophy) occur most commonly in the setting of underlying heart disease as the result of hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, and heart failure, which tend to increase left atrial pressure, cause atrial dilation, and alter wall stress.[87] Similarly, atrial ischemia from CAD and infiltrative diseases such as amyloidosis, hemochromatosis, and sarcoidosis can also promote AF. Extracardiac factors that promote AF include hypertension, sleep apnea, obesity, use of alcohol/drugs, and hyperthyroidism, all of which have pathophysiologic effects on atrial cellular structure and/or function.

In the critically ill, AF may be a sign of disease severity rather than an arrhythmic disease entity. Critically ill patients are often in a hyperadrenergic state, which may increase ectopic triggers and shorten atrial refractoriness when fibrosis has already created a suitable reentrant substrate.[88]

Management of AF

The mechanisms of AF are shown in Fig. 31.21.[89]

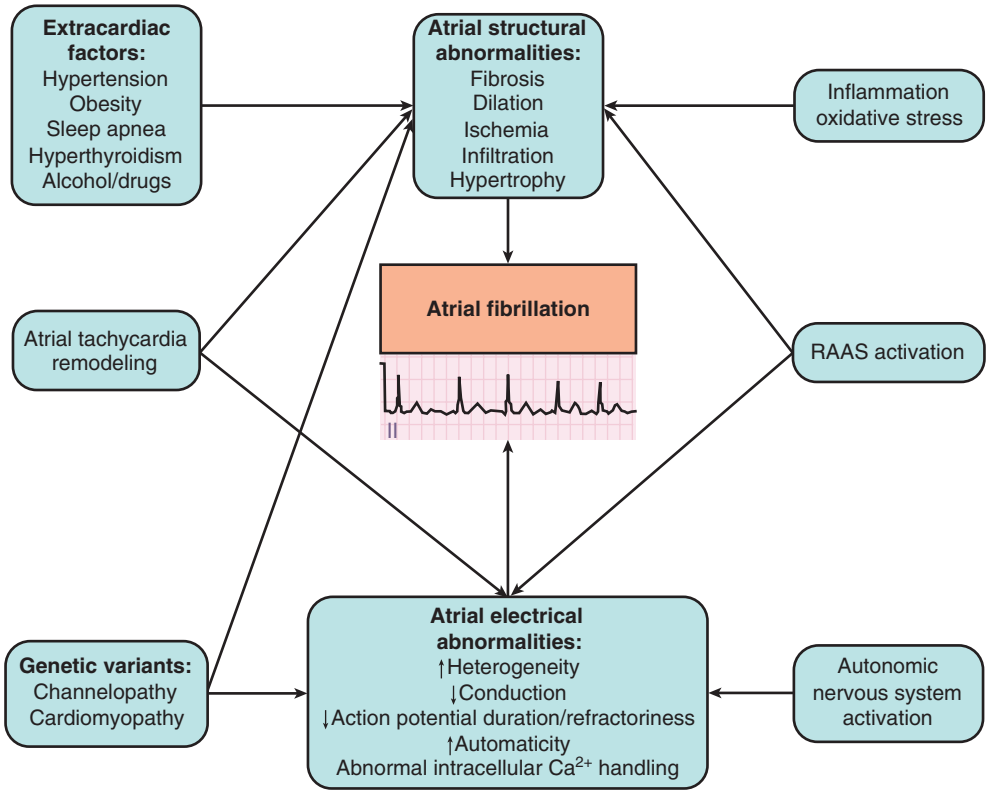
Rate Control

Control of the ventricular rate is the first line of therapy for AF. Rate control is most frequently achieved using digoxin, β-blockers, calcium channel blockers (verapamil or diltiazem), or combinations of these agents. IV diltiazem has the combination of efficacy, ease of parenteral delivery, and tolerance that makes this agent an attractive option in the critical care setting. Verapamil should be administered cautiously to patients with significant LV dysfunction. Although digoxin is effective in controlling rates at rest, exercise rate control is not often achieved. Digoxin has traditionally been used for rate control in patients with concomitant LV dysfunction and CHF, but some recent studies have shown an increased mortality, so it should be used with caution and careful monitoring.[90] IV amiodarone may result in less hypotension than diltiazem when used for rate control in the ICU,[91,92] and it has the advantage of being 100% bioavailable (critically ill patients may not absorb oral drugs). The target heart rate for an effective rate control target was liberalized in the 2010 guidelines to a resting heart rate less than 100 beats/min.[93] Approaches to selecting drugs for rate control for AF are shown in Fig. 31.22.

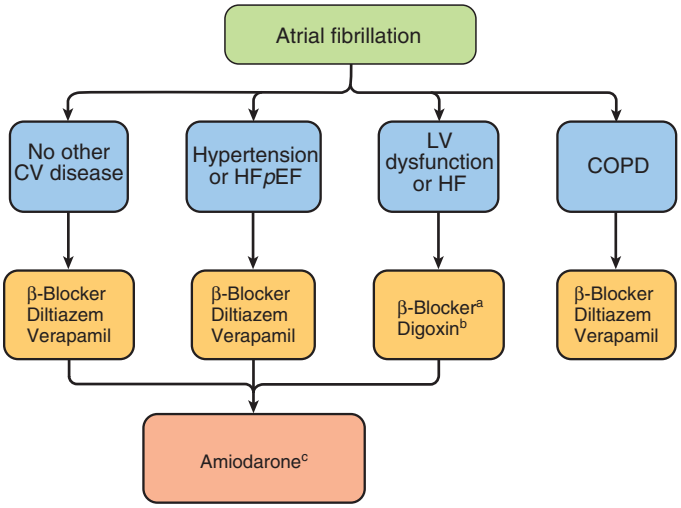
Rhythm Control

To achieve rhythm control for AF a combination of approaches, including cardioversion, antiarrhythmic drugs, and radiofrequency catheter ablation, can be used in the setting of appropriate anticoagulation and rate control. Randomized clinical trials comparing outcomes of a rhythm control strategy using antiarrhythmic drugs with a rate control strategy in patients with AF failed to show a superiority of rhythm control on mortality for either strategy.[94,95]

Strategies for rhythm control based on type of heart disease are outlined in Fig. 31.23. In the ICU setting, rate control should always be the first line of therapy unless a patient is hemodynamically unstable and effective rate control cannot be achieved because of the risk of hypotension from the medications. In that setting, urgent cardioversion is recommended. If the patient is hemodynamically stable, decisions to restore normal sinus rhythm, and by what method, can be made electively once the rate is controlled and the patient is stabilized. If rhythm control is favored in the ICU setting, IV amiodarone would be the first drug of choice. Once the patient's condition has stabilized, transition to a less toxic oral



• **Fig. 31.21** Mechanisms of atrial fibrillation. *Ca^{2+},* ionized calcium; *RAAS,* renin-angiotensin-aldosterone system.



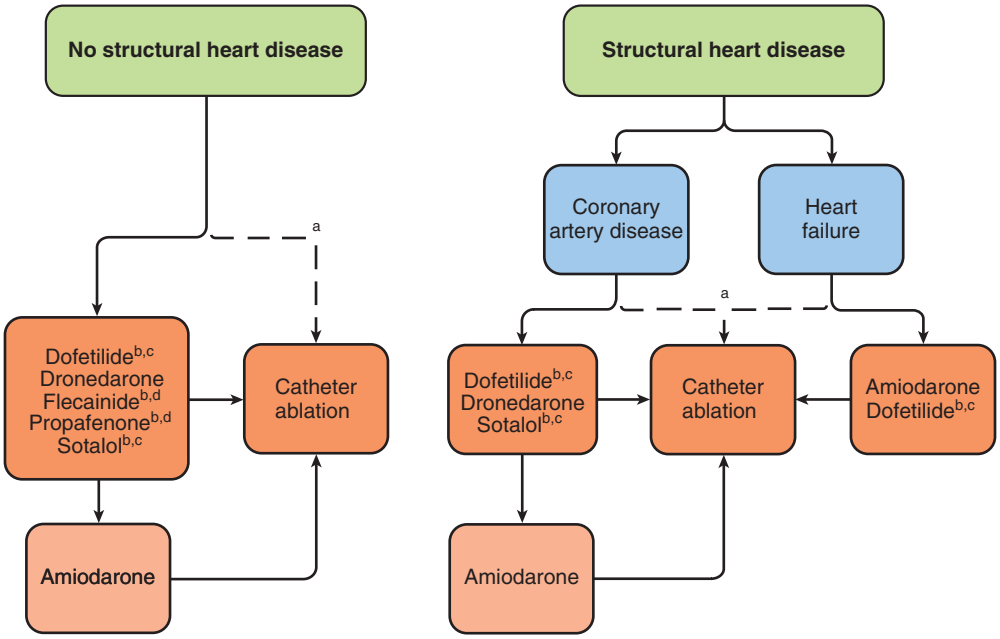
• **Fig. 31.22** Approach to selecting drug therapy for ventricular rate control. Drugs are listed alphabetically. [a]β-Blockers should be instituted after stabilization of patients with decompensated heart failure *(HF)*. The choice of β-blocker (e.g., cardioselective) depends on the patient's clinical condition. [b]Digoxin is not usually first-line therapy. It may be combined with a β-blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with heart failure. [c]In part because of concern over its side effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of β-blockers or nondihydropyridine calcium antagonists. *COPD,* Chronic obstructive pulmonary disease; *CV,* cardiovascular; *HF,* heart failure; *HFpEF,* heart failure with preserved ejection fraction; *LV,* left ventricular.

medication can be made, and often there is no ongoing requirement for antiarrhythmic therapy at all once the critical illness has passed.

Stroke Prevention

Prevention of embolic strokes is the most important goal of therapy for AF. Ischemic stroke risk among patients with nonvalvular AF is stratified using the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism [doubled]) and CHA_2DS_2-VASc (CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Prior Stroke or TIA or thromboembolism [doubled], Vascular disease, Age 65 to 74 years, Sex category) risk scoring systems outlined in Table 31.3.[96–97,98] Antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and relative risks of stroke and bleeding, and the patient's values and preferences (see Table 31.3). Bleeding risk can be assessed using the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio, Elderly [≥65 years], Drugs/alcohol concomitantly).[99]

Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent. For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF. For patients with nonvalvular AF (see Table 31.2 for definitions) and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy. For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant may be considered. For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 2 or higher,



• **Fig. 31.23** Strategies for rhythm control in patients with paroxysmal and persistent atrial fibrillation (AF). Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (class IIa recommendation). Drugs are listed alphabetically. [a]Depending on patient preference when performed in experienced centers. [b]Not recommended with severe LVH (wall thickness >1.5 cm). [c]Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia. [d]Should be combined with atrioventricular nodal blocking agents. *AF,* Atrial fibrillation; *LVH,* left ventricular hypertrophy.

treatment with anticoagulation is indicated.[89] With the advent and proven safety profile of the novel oral anticoagulants (NOACs), there are currently several choices for oral anticoagulation in AF. Efficacy and safely of NOACs are shown in Table 31.4.[100] All NOACs have been extensively studied and show improved rates of stroke prevention and lower bleeding risks than warfarin.

No studies, with the exception of the SPAF (Stroke Prevention in Atrial Fibrillation)-1 trial, show benefit for aspirin alone in preventing stroke in patients with AF.[101,102] The usefulness of ASA in stroke prevention for AF has recently been questioned and currently may not have any role at all.[103]

Valvular AF is defined (see Table 31.2) as that occurring in a patient with rheumatic mitral stenosis, mitral valve repair, and mechanical or bioprosthetic heart valve. All other types of AF are nonvalvular. For patients with AF who have mechanical heart valves, warfarin is the only choice for anticoagulation, and the target international normalized ratio (INR) intensity (2.0–3.0 or 2.5–3.5) should be based on the type and location of the prosthesis.

Management of AF in the ICU

Appropriate management of AF in the ICU should include treatment (or elimination) of potential precipitants and β-blockade (given the hyperadrenergic state of many ICU patients) as the initial pharmacotherapy of choice. Hemodynamic impairment owing to AF should be treated with urgent or emergent direct current cardioversion.[88] Restoration of sinus rhythm may be very difficult and impractical when a severe metabolic derangement or multisystem organ failure is present.[104] Patients with adrenergically mediated AF should be managed with β-blockers or calcium blockers if blood pressure permits. Amiodarone is another option for both rate control and ultimate restoration of normal sinus rhythm in patients with AF refractory to β-blockade alone.

IV ibutilide is a class III agent that prolongs action potential by blocking the rapid component of the delayed rectifier current and can be used for AF termination.[105,106] Patients receiving IV ibutilide should be carefully monitored (on telemetry for 4 to 8 hours) for QT prolongation and possible development of torsades de pointes (TdP).[105] If AF recurrence needs to be prevented and sinus rhythm maintained, institution of antiarrhythmic therapy with IV amiodarone is recommended in the ICU setting.

Anticoagulation in the ICU

The intensivist rarely sees ideal candidates for classic anticoagulation because many patients have recent or active bleeding (gastrointestinal, intracerebral), and a variety of coagulopathies that make anticoagulation absolutely or relatively contraindicated. The intensivist must carefully weigh the risks and benefits of anticoagulation for each individual patient. Difficult decisions about the safety of both short-term and long-term anticoagulation may be compounded by concomitant disease processes. At times, transesophageal echocardiography TEE may be the only possible (partial) insurance against emboli.

Direct Current Cardioversion

Direct current cardioversion should be performed with the patient under deep sedation. The preferred drug for deep sedation before cardioversion is propofol.[107] Dosing must be individualized based on body weight, level of illness, and other intercurrent medical conditions. A bolus of 2 mg/kg usually is effective for elective cardioversion but may be excessive in a critically ill patient.[108] Propofol's adverse effects include apnea, bradycardia, hypotension, nausea, and pain and burning at the IV injection site, which can be minimized by giving local lidocaine. Propofol overdose is treated with ventilation and oxygen, elevation of the legs, increasing flow

TABLE 31.3 Comparison of the $CHADS_2$ and CHA_2DS_2-Vasc Risk Stratification Scores for Subjects With Nonvalvular Atrial Fibrillation

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (%/year)
$CHADS_2$		**$CHADS_2$**[a]	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 years	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		**CHA_2DS_2-VASc**	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 years	1	6	9.8
Sex category (i.e., female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

[a]These adjusted stroke rates are based on data for hospitalized patients with AF and were published in 2001. Because stroke rates are decreasing, actual stroke rates in contemporary nonhospitalized cohorts might vary from these estimates.

$CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); *CHA_2DS_2-VASc,* Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; *HF,* heart failure; *MI,* myocardial infarction; *PAD,* peripheral artery disease; *TE,* thromboembolism; *TIA,* transient ischemic attack.[96,97]

rates of IV fluids, and if needed, administration of pressor agents and anticholinergic agents. Regardless of who administers sedation, expert ability to manage the patient's airway must be immediately available when propofol is used.

Transthoracic impedance influences current flow and procedural outcome of cardioversion. Impedance is influenced by a variety of factors, including placement of the defibrillation pads, the phase of ventilation (impedance is lower with expiration than with inspiration), distance between electrodes, pressure on electrodes (air does not conduct well), size of electrodes, time between discharges (waiting as long as 3 minutes may provide continued decreases in impedance), and patient body habitus (heavier weight or increased body mass index decreases success).[109,110] Optimal paddle size ranges from 8 to 12 cm. Anteroposterior position of the patches are the best vectors for energy delivery to the atria[109] (Fig. 31.24).

A conductive gel or paste must be used between the metal electrodes and the chest skin to lower impedance and prevent skin burns.[109] Modern defibrillators have biphasic waveforms that are more effective per joule output than monophasic waveform defibrillators. When initial attempt at cardioversion is not successful, switching from self-adhesive pads to handheld paddles applied with manual pressure can increase current delivery and promote procedural success.

R-wave synchronization should be ensured during cardioversion of any arrhythmias with well-defined QRS complexes. Failure to do so could lead to shock delivery within the "vulnerable period" of the T wave and induction of VF. Electrical cardioversion is contraindicated in the presence of digitalis toxicity; VF may ensue.

Poor success of cardioversion for AF can be related to arrhythmia duration (>1 year), larger left atrial diameters (>5 cm), untreated hyperthyroidism, mitral stenosis, electrolyte disturbances, CHF, or improper performance of the cardioversion procedure itself. Use of concomitant antiarrhythmic drugs (especially amiodarone) may help maintain sinus rhythm when early recurrence is suspected.

Anticoagulation for Cardioversion

Anticoagulation plays a pivotal role in minimizing the risk of emboli (and strokes) during elective cardioversion of AF.[111] Classic recommendations for management of AF of more than 48 hours duration include 3 weeks of therapeutic warfarin (to achieve a prothrombin time [PT]/INR of 2.0–3.0) before direct current shock administration and (at least) 4 more weeks of warfarin after the procedure. The same efficacy is currently being demonstrated with all of the NOACs in randomized clinical trials.[112–114] Although emboli may be less frequent with atrial flutter,[109] it is clear that they occur[115] and the recommendations are the same as for AF.

Short-term therapeutic anticoagulation with heparin before cardioversion (followed by oral anticoagulants in the usual manner) combined with TEE is also an acceptable way to proceed if cardioversion is to be done immediately.[116] TEE is useful for detecting left atrial thrombi because it provides an excellent, minimally invasive view of the left atrial appendage. Embolic rates (0.5% vs. 0.8%) are similar between conventional and TEE-guided approaches.[117] Patients with thrombi seen on TEE should receive anticoagulation for 4 to 6 weeks and have demonstrable resolution of clot by repeat TEE before cardioversion is attempted again.[114]

Perioperative AF

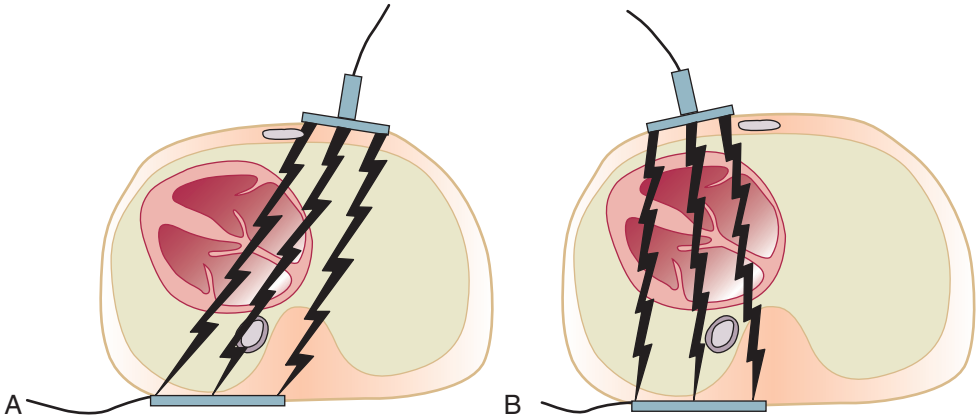
Postoperative AF occurs in 25% to 50% of patients after open heart surgery. Increased age is the most consistent risk factor.[118] With the projected increase in the number of elderly patients undergoing cardiac operations, the incidence of postoperative AF is likely to increase. Postoperative AF is associated with stroke,[119] increased cost,[120] and mortality.[121] β-Blockers, nondihydropyridine calcium channel blockers, and amiodarone are useful as treatments in patients with postoperative AF and may be initiated preoperatively in some patients.[120]

In a meta-analysis of patients undergoing coronary revascularization, those who received preoperative statin therapy had less AF

TABLE 31.4 Efficacy and Safety of Novel Nonvitamin K Antagonists Versus Warfarin in Patients With and Without Significant Valvular Heart Disease

Drug/Dosage	VHD	No VHD	Interaction *P*
Stroke or Systemic Embolism			
Dabigatran 150 mg vs. warfarin	HR, 0.59 95% CI, 0.37–0.93	HR, 0.67 95% CI, 0.52–0.86	0.63
Dabigatran 110 mg vs. warfarin	HR, 0.97 95% CI, 0.65–1.45	HR, 0.88 95% CI, 0.70–1.10	0.65
Apixaban vs. warfarin	HR, 0.70 95% CI, 0.51–0.97	HR, 0.84 95% CI, 0.67–1.04	0.38
Rivaroxaban vs. warfarin	HR, 0.83 95% CI, 0.55–1.27	HR, 0.89 95% CI, 0.75–1.07	0.76
Major Bleeding			
Dabigatran 150 mg vs. warfarin	HR, 0.89 95% CI, 0.68–1.16	HR, 0.99 95% CI, 0.83–1.17	0.24
Dabigatran 110 mg vs. warfarin	HR, 0.72 95% CI, 0.54–0.96	HR, 0.85 95% CI, 0.71–1.02	0.38
Apixaban vs. warfarin	HR, 0.79 95% CI, 0.61–1.04	HR, 0.65 95% CI, 0.55–0.77	0.23
Rivaroxaban vs. warfarin	HR, 1.25 95% CI, 1.05–1.49	HR, 1.01 95% CI, 0.94–1.10	0.034

CI, Confidence interval; *HR,* hazard ratio; *NOAC,* novel nonvitamin K antagonist; *VHD,* valvular heart disease.



• **Fig. 31.24** Anteroposterior electrode placement for cardioversion of atrial fibrillation and flutter. Anteroposterior electrode placement for cardioversion of atrial fibrillation and flutter. A, Right parasternal anteroposterior electrode placement. B, Left parasternal anteroposterior electrode placement. In each instance, the current vector transverses a critical mass of atrial myocardium. The right parasternal position has more of the right atrium between the electrodes and may be advantageous in patients with biatrial disease. The left parasternal position has a smaller interelectrode distance and less lung between electrodes. (Adapted from Ewy GA. The optimal technique for electrical cardioversion of atrial fibrillation. *Clin Cardiol.* 1994;17:79–84.)

than those not treated with statins.[123] No published data exist for patients undergoing valvular or other heart surgery. The COPPS (Colchicine for the Prevention of the Postpericardiotomy Syndrome) substudy examined the efficacy and safety of colchicine for AF prevention.[122] Patients receiving colchicine had a reduced incidence of AF (12% vs. 22% at 30 days postoperatively). The colchicine group also had a shorter length of hospital stay. This has yet to become the standard of care because further study is still required.

The Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early after Revascularization, Valve Replacement, or Repair (PAPABEAR), a large randomized controlled trial, compared perioperative amiodarone with placebo and showed significant reduction in postoperative atrial tachyarrhythmias in the Amiodarone treated group.[124] Toxicity risks were reduced because amiodarone was used only for a short duration. The study did not demonstrate any reduction in mortality rates. The data for

perioperative amiodarone use for cardiac surgery are intriguing; however, incremental benefit beyond β-blockade alone has not yet been shown. Currently amiodarone should be reserved for postoperative AF in patients for whom β-blockers alone have failed, and use of amiodarone should be limited to 6 to 12 weeks postoperatively to prevent long term-side effects.

Antithrombotic medication should be administered to patients in whom postoperative AF develops, as is recommended for nonsurgical patients, taking into account bleeding risks associated with the recent surgery.[125]

Special Considerations for the Intensivist Treating AF

Patients in an intensive care setting frequently have the substrate for reinitiation of atrial or ventricular arrhythmias even after they are apparently controlled. Such factors include hypoxemia, excess circulating (endogenous and exogenous) catecholamines, CHF, fever (sepsis), and pulmonary emboli, Many of these conditions have overlapping features. Prophylaxis against arrhythmia recurrence shares many of the limitations of acute antiarrhythmic therapy. Drugs administered orally may not be well absorbed and IV agents (amiodarone) may be most useful. Digoxin, dofetilide, and sotalol are renally excreted and must be carefully managed (or avoided) to prevent complications in patients with renal failure or insufficiency. Amiodarone is hepatically excreted and has the benefit of safety in patients with renal insufficiency or renal failure on dialysis.

Most digitalis toxicity–related supraventricular arrhythmias result in relatively slow heart rates and are reasonably well tolerated hemodynamically. Accelerated junctional rhythm and paroxysmal AT with block tend to terminate spontaneously after digoxin is stopped.

Antiarrhythmic Drugs for Maintenance of Sinus Rhythm

AF is associated with an increased incidence of death and embolic events.[126,127] However, large randomized studies comparing rate control (allowing the patient to remain in AF with a controlled rate) versus rhythm control with antiarrhythmic drugs (AADs) have not shown a reduction in mortality or thromboembolic events.[128–131] In fact, the rhythm control strategy was associated with higher rates of adverse events: drug side effects, hospitalizations, and stroke. The failure to show a benefit of the rhythm control strategy may have been secondary discontinuation of anticoagulation in the rhythm control arm that resulted in an increase incidence of strokes from episodes of subclinical/asymptomatic AF. A higher percentage of the rate control group remained on anticoagulation during follow-up. Because of these data, the American College of Cardiology, American Heart Association, European Society of Cardiology, and the Heart Rhythm Society have published guidelines recommending the rhythm control strategy with AADs only as a means to reduce symptoms attributable to AF, and not as a way to reduce mortality or thromboembolic risk.[132] However, many physicians still consider a rhythm control strategy in patients younger than 60 years because that group was not well represented in the randomized studies. In addition, chronic AF renders future attempts at rate control more difficult, and the long-term consequences of AF are still unclear.[133]

AADs are classified by the Vaughn-Williams classifications into four groups. Class I drugs affect sodium channels. Class II drugs act on β-receptors. Class III drugs affect potassium channels. Class IV drugs act on calcium channels. Class I drugs are further divided into class IA, IB, and IC based on their relative affinity for sodium channels.

Class 1A drugs such as quinidine, procainamide, and disopyramide are rarely used because of their risk of QT prolongation and resultant TdP, low efficacy rates, and increased risk of noncardiac side effects.[134,135]

Flecainide, a class 1C drug, was developed in the 1970s. Its primary electrophysiologic effect is block of the rapid sodium current responsible for phase 0 of the cardiac action potential. It is administered twice daily at a dose of 50 to 200 mg.[136] The Cardiac Arrhythmia Suppression Trial (CAST) demonstrated an increased mortality associated with flecainide use in patients with a prior MI when it was used to suppress premature ventricular beats.[137] Therefore flecainide is not recommended in patients with coronary disease, prior MI, or decreased LV function.[138] One adverse effect is QRS widening on the ECG; when this is seen at normal heart rates, the drug should be discontinued. Flecainide has negative inotropic effects related both to its sodium channel blocking properties and to the reduced drug clearance in patients with heart failure. Flecainide can also convert AF to atrial flutter with a slowing of the atrial cycle length, which can result in 1:1 conduction through the AV node and resultant rapid ventricular rate. Therefore flecainide should always be used concomitantly with another drug that slows AV nodal conduction such as a β-blocker or calcium blocker. Uncommon noncardiac side effects include dizziness, visual disturbances, nausea, and neurologic symptoms.

Propafenone, a class 1C drug, was approved in the United States in 1989. It has sodium channel blocking properties similar to flecainide. However, unlike flecainide it also can block potassium channels, calcium channels, and β-adrenergic receptors.[139] Like flecainide, propafenone should not be used in patients with structural heart disease, CAD, or prior MI. Also like flecainide, it can convert AF to atrial flutter, resulting in atrial cycle length slowing with potentially rapid 1:1 AV conduction, and should be given concomitantly with a β-blocker or calcium blocker.

Sotalol, a class III drug, was developed in the 1960s. It is a nonselective β-blocker that exerts it antiarrhythmic effects through inhibition of the delayed rectifier potassium current, which causes a dose-dependent prolongation of the action potential duration, atrial and atrioventricular nodal refractory periods, and the QT interval.[140] Despite its β-blocking properties, it is not a negative inotrope because of a concomitant increase in contractility caused by action potential duration prolongation.[141] However, the β-blocking properties can still exacerbate reactive airway disease. Even though sotalol prolongs the QT interval, when it is used properly, the risk of TdP is less than 1%.[142] TdP attributed to sotalol is usually the result of drug interactions when it is used concomitantly with other drugs that prolong the QT interval.

Sotalol is administered twice daily at a starting dose of 80 mg and has a half-life of approximately 8 hours. In patients with a creatinine clearance of 40 to 60 mL/min, the dose should be reduced to once daily. If the creatinine clearance is less than 40 mL/min, sotalol use is not recommended. Per U.S. Food and Drug Administration guidelines, sotalol must be initiated in the hospital with telemetry monitoring. The ECG should be checked daily to evaluate the QT interval. If the QT interval is less than 500 msec and the patient is not bradycardic, the dose can be increased in 40-mg increments to a maximum dose of 240 mg twice daily.

Dofetilide, a class III drug, was approved in the United States in 2000. Dofetelide blocks the rapid component of the delayed rectifier potassium current, and unlike most other antiarrhythmic drugs it has minimal effects on other ion channels. It prolongs the QT interval; thus its main adverse effect is TdP. Initiation of dofetelide requires a 3-day hospitalization for telemetry monitoring

to observe the QT interval and adjust dosing. The starting dose of dofetelide is 125 to 500 μg twice daily based on creatinine clearance. An ECG to access the QT interval must be taken 2 hours after each dose and the dose should be adjusted as needed.

Dofetilide has demonstrated efficacy and safety when used in patients with reduced LV systolic function and/or CAD.[143,144] In the Symptomatic Atrial Fibrillation Investigative Research on Dofetelide (SAFIRE-D) study, 40% to 60% of patients receiving dofetilide remained in sinus rhythm at 1 year compared with only 25% given placebo ($P = 0.001$).[145] In the Danish Investigations of Arrhythmias and Mortality On Dofetilide (DIAMOND) study, 1518 patients with LV dysfunction and symptomatic heart failure were randomly assigned to receive placebo or dofetilide; there was no difference in mortality between the 2 groups at 18 months.[146]

Amiodarone, a class III drug, is the most commonly used AAD for maintenance of normal sinus rhythm in AF. It was first developed in the 1960s for the treatment of angina, and subsequently in the 1970s, its antiarrhythmic properties were recognized. Amiodarone blocks multiple ion channels and therefore has a wide range of electrophysiologic effects on cardiac tissue.[147] Amiodarone is highly lipophilic with a very large volume of distribution and an extremely long and variable elimination half-life on the order of weeks to months.[148] The loading dose of amiodarone is 800 mg daily divided into 2 to 3 doses per day for 7 to 10 days. The dose is then reduced to 400 mg daily for several weeks and ultimately the maintenance dose is 200 mg daily. [148]

Amiodarone is consistently the most effective AAD for AF suppression in all studies of comparative drug efficacy. Unfortunately, amiodarone has multiple short-term and long-term side effects that limit its use. Amiodarone contains a significant amount of iodine, and is structurally similar to thyroid hormone triiodothyronine (T_3), and thyroxine (T_4). Therefore it inhibits both peripheral conversion of T_4 to T_3 and entry of T_3 and T_4 into cells, resulting in both hypothyroidism and hyperthyroidism.[149] Up to one-quarter of patients may develop clinically relevant thyroid dysfunction while using the drug.[149] Nonspecific gastroenterologic symptoms, such as nausea, are common and may resolve with dose reduction.[148] Severe hepatotoxicity is rare (<3%) but minor abnormalities in transaminases are common.[148] Pulmonary toxicity occurs in approximately 2% of patients; patient age and duration of therapy are significant risk factors.[150] Pulmonary toxicity may present at any time during amiodarone treatment and usually presents as cough with subsequent development of dyspnea and fever.[151] Chest radiography reveals diffuse infiltrates, consolidation, and pleural thickening. Pulmonary function tests show evidence of restrictive physiology and impaired diffusion capacity. Computed tomography scanning of the chest shows evidence of fibrosis and ground-glass opacities.[151,152] Electrophysiologic side effects include bradycardia and QT prolongation, which occur in almost all patients, but the incidence of TdP is rare (<0.5%). Cutaneous side effects include photosensitivity, and rarely a blue discoloration of the skin. Neurologic side effects include tremor, neuropathy, and cognitive impairment, which is rare.[153]

In the Canadian Trial of Atrial Fibrillation (CTAF), amiodarone was superior to both sotalol and propafenone for maintaining normal sinus rhythm. Sixty-five percent of patients using amiodarone versus 37% of patients using sotalol or propafenone were free of AF recurrence.[154] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), sotalol was superior to placebo but inferior to amiodarone for maintaining sinus rhythm in patients with persistent AF ($P < 0.001$). In the subset of patients with ischemic heart disease, amiodarone and sotalol were equally efficacious.[155]

Dronedarone, a class III drug, is a noniodinated benzofuran derivative with a structure similar to amiodarone. Dronedarone has the addition of a methy-sulfonyl group instead of the toxic iodine moieties, which reduces its interaction with thyroid physiology, decreases its lipophilicity, and shortens its plasma half-life.[156,157] Similar to amiodarone, dronedarone blocks a wide array of cardiac ion channels.[157] Dronaderone is administered at a dose of 400 mg twice a day, and pharmacokinetics are not significantly influenced by age, gender, weight, or renal function. Serum creatinine can rise with dronedarone because of inhibition of creatinine secretion but this does not reflect renal impairment.[156] In the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in patients with Atrial Fibrillation/Atrial Flutter) trial, dronedarone was associated with a reduction in the composite endpoint of hospitalization owing to cardiovascular events or death when compared with placebo.[159] However, in another study (ANDROMEDA [Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease], dronedarone was associated with an increase in mortality when compared with placebo.[158] Based on this study, dronedarone should be avoided in patients with CHF and should not be used as a rate control agent in patients with long-standing persistent or permanent AF.

Ranolazine is currently approved as an antianginal medication, but because of its ability to block sodium, potassium, and calcium currents, it is being evaluated for the treatment of both atrial and ventricular arrhythmias.[161] Ranolazine is administered twice daily and has a half-life of 7 hours. It is predominately metabolized in the liver, and the manufacturer does not recommend dose adjustment for renal and hepatic failure.[162] There have been several studies that have shown ranolazine is effective for AF suppression,[163,164] but current guidelines do not recommend it as a primary rhythm control agent. One recent study [165] showed that the combination of ranolazine and dronedarone was superior to placebo for suppression of AF; therefore ranolazine may have a role as a second AAD in select patients. The most common side effects include headache, dizziness, nausea, and constipation. Ranolzine prolongs the QT interval, but its inhibition of the late sodium current is protective against TdP.[166]

Ibutelide, a class III drug, is an IV-only potassium channel blocker that activates late inward sodium current. It has a structure similar to sotalol and is used for acute termination of AF and atrial flutter.[167] It has minimal hemodynamic effects and can be used safely in patients with structural heart disease and prior MI. Ibutelide prolongs the QT interval and has been associated with an increased risk of TdP (~0.4%).[168] It is administered as a 1-mg infusion over 10 minutes, with a repeat 1-mg infusion 10 minutes later if the first dose is not effective. Patients must be monitored closely for at least 4 hours after the infusion is complete to ensure that the QT interval returns to baseline.

Ventricular Arrhythmias

The intensivist must be prepared to recognize and manage ventricular arrhythmias. Cardiologists and electrophysiologists are often available to help management and prescribe long-term treatments. Therefore this section focuses on pathophysiology, ECG patterns, and intensive care treatment of ventricular arrhythmias. We briefly address chronic therapy.

The emergency treatment of cardiac arrest, implantable defibrillators, and pacemakers is covered in Chapters 1 and 5.

Mechanisms of Ventricular Arrhythmias

Reentry is the most common mechanism for sustained ventricular arrhythmias. Three conditions are required for reentry. The first is the presence of two contiguous pathways separated by a central region of inexcitable tissue. Second is unidirectional block in one of the pathways. Third is a zone of slow conduction in one of the pathways to allow recovery and excitation of the region of block, which allows the circuit to perpetuate. Reentry conditions can occur in the border zone of a healed MI scar or from functional disturbances in conduction and refractoriness as can happen during ischemia, CHF, or electrolyte disturbances.

The second mechanism of sustained VT is *enhanced automaticity* caused by impulse formation in cells that otherwise do not activate spontaneously. Diseased cardiac tissue is particularly susceptible to development of enhanced automaticity. Automatic cells (in the AV node, the His-Purkinje system, or the ventricles) may usurp the sinus node by means of enhanced automaticity in the setting of increased sympathetic activity, metabolic disturbances, or drug toxicity.

The third mechanism of VT is *triggered activity*, which can be caused by either early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). Both types of afterdepolarizations occur when oscillations in membrane potential reach the threshold for action potential formation, resulting in abnormal impulse formation. EADs are caused by delayed inactivation of inward ion currents during the plateau phase of the action potential. EADs are thought to be important in the genesis of TdP. DADs result from increased intracellular calcium, which can be caused by drug toxicity, metabolic disturbances, and ischemia. Digitalis toxicity is the classic example of DAD-induced triggered activity. Digitalis inhibits the sodium ion–potassium ion (Na^+-K^+) pump, thereby increasing intracellular Na^+, which in turn increases intracellular calcium ion (Ca^{2+}) via the Na^+-Ca^{2+} exchange current.[169] Idiopathic outflow tract VT may also result from DADs (cyclic adenosine monophosphate–mediated triggered activity).[170]

Approach to Ventricular Arrhythmias in the Critically Ill

New ventricular arrhythmias warrant an assessment of electrolytes, oxygenation, and acid-base status. An ECG should be obtained to distinguish monomorphic from polymorphic ventricular tachycardia (PMVT), to elucidate the morphology of ventricular premature contractions (PVCs) and non-sustained ventricular tachycardia (NSVT), and to examine the QT interval. Routine measurement of cardiac enzymes is not mandatory with the onset of each arrhythmia unless ischemia is suspected clinically, or there are ECG changes of ischemia. Movement of intracardiac catheters can result in mechanically induced arrhythmias. If arrhythmias are thought to be due to catheters, catheter position may be confirmed by radiography.

A comprehensive discussion of ACLS is beyond the scope of this chapter. Current recommendations for the management of adult cardiac arrest are discussed in Chapter 1 of this book and are summarized in recently published ACLS guidelines.[171]

Premature Ventricular Contractions

PVCs are common in patients with and without structural heart disease. Patients can be asymptomatic even when the PVCs are frequent or symptomatic with relatively few PVCs.[172] The vast majority of patients with PVCs without structural heart disease have a benign prognosis.[173] In the presence of CHF and LV dysfunction, PVC frequency does not predict SCD,[174] but several studies have demonstrated an association between frequent PVCs and a potentially reversible cardiomyopathy, which can resolve after catheter ablation.[175–180] It is currently believed that a PVC burden greater than 24% can be responsible for a cardiomyopathy.[181]

Diagnostic evaluation of PVCs should include a 12-lead ECG to determine the possible presence of underlying structural or electrical heart disease, such as myocardial scar (Q waves or fractionated QRS complex), prolonged or shortened QT interval, or presence of ventricular hypertrophy. The ECG is also important to determine the morphology of the PVCs, which can help determine their origin. In any patient with frequent or symptomatic PVCs, an echocardiogram should be obtained to exclude underlying structural heart disease. In selected cases a magnetic resonance imaging scan can be useful to determine pathologic etiologies of PVCs, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, sarcoidosis, amyloidosis, and arrhythmogenic right ventricular (RV) cardiomyopathy.

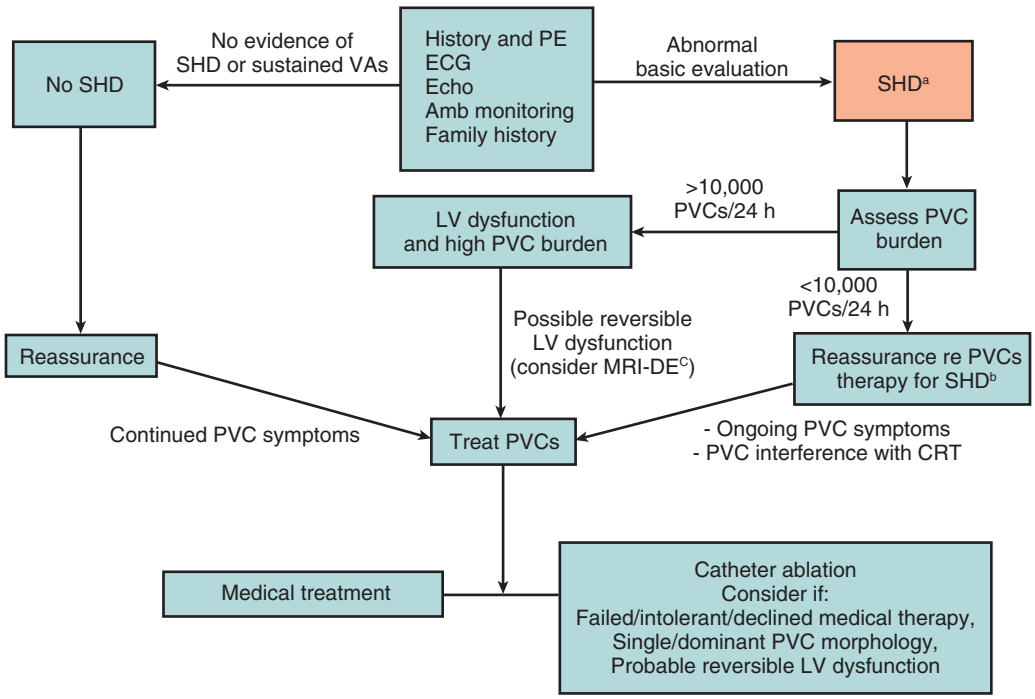
Treatment of PVCs

In patients without structural heart disease and mild symptoms, the first step in treatment is to reassure and educate patients that they are not at risk for any serious adverse events. For patients with moderate or severe symptoms and structurally normal hearts, medication with β-blockers or nondihydropyridine calcium antagonists is first-line therapy, although their effectiveness in suppressing the PVCs may be limited.[182] When β-blockers and calcium blockers fail, antiarrhythmic drugs can be used, but the risk-benefit ratio in patients without structural heart disease is unknown and proarrhythmia is a concern. Catheter ablation of PVCs is recommended for highly selective patients who remain very symptomatic despite conservative treatment, or for patients with a very high PVC burden associated with a decline in LV function (Fig. 31.25).

Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia (NSVT) is defined as consecutive ventricular beats lasting between 3 complexes and 30 seconds' duration with a cycle length exceeding 100 beats/min.[183] It is a common finding both in patients with structurally normal or abnormal hearts.[184,185] NSVT is common in patients with ischemic heart disease and dilated cardiomyopathies.[183] Although NSVT in a structurally normal heart is generally benign, there are certain things to consider. Polymorphic NSVT requires a careful assessment for coronary ischemia. Athletes have an increased incidence of NSVT[186,187] and when seen, an evaluation for the presence of a hypertrophic cardiomyopathy is warranted. Catecholaminergic polymorphic ventricular tachycardia (CPVT) can present as exercise-induced NSVT (see later). NSVT in a structurally normal heart can also represent idiopathic VT, an inherited arrhythmia syndrome, such as long QT, short QT, or Brugada syndrome (see later). The finding of NSVT warrants further evaluation (Box 31.3 and Table 31.5).

Diagnostic evaluation of NSVT should begin with a 12-lead ECG to determine the possible presence of underlying structural or electrical heart disease such as myocardial scar (Q waves or fractionated QRS complex), prolonged or shortened QT interval, or presence of ventricular hypertrophy. ECG is also helpful for



• **Fig. 31.25** Management of premature ventricular complexes *(PVCs)*. *CRT,* Cardiac resynchronization therapy; *ECG,* electrocardiogram; *LV,* left ventricular; *MRI-DE,* magnetic resonance imaging with delayed enhancement; *PE,* physical examination; *PVC,* premature ventricular contraction; *SHD*, structural heart disease; *VAs,* ventricular arrhythmias.

• BOX 31.3 Evaluation of Patients With Nonsustained Ventricular Tachycardia

Standard Evaluation

History
- Prior cardiovascular disease?
- Hypertension, known cardiac disease?
- Syncope or near-syncope?
- Sustained palpitations?
- Relation of symptoms to exercise?

Family history
- SCD, inherited arrhythmia syndromes, coronary artery disease, cardiomyopathy?

Medications
- QT-prolonging drugs, sodium channel blockers, drug interactions?

Physical examination
- Evidence of cardiac disease

Twelve-lead ECG
- Q-waves, ischemic changes, prolonged or fractionated QRS, QT prolongation or shortening, ST elevation V1-V3, early repolarization, epsilon waves, or anterior T-wave inversion

Echocardiography
- Ventricular chamber dimensions and thickness, wall motion, systolic and diastolic function, valvular function, congenital anomalies, pulmonary arterial systolic pressure

Laboratory
- Serum electrolytes, renal function

Further Evaluation

Exercise testing
- Suspicion of coronary artery disease, exercise-related symptoms, borderline QT interval

Coronary arteriography
- Suspicion of coronary artery disease or coronary artery anomaly

Cardiac MRI
- Suspicion of ARVC, HCM, cardiac sarcoidosis, congenital anomalies

Genetic testing
- Suspicion of inherited arrhythmia syndrome, family history of inherited arrhythmia syndrome

Electrophysiologic testing
- Sustained palpitations without diagnosis, suspicion of AV block, coronary artery disease with NSVT, and moderate LV dysfunction

ARVC, *Arrhythmogenic right ventricular cardiomyopathy;* AV, *atrioventricular;* ECG, *electrocardiogram;* HCM, *hypertrophic cardiomyopathy;* LV, *left ventricular;* MRI, *magnetic resonance imaging;* NSVT, *nonsustained ventricular tachycardia;* SCD, *sudden cardiac death.*

TABLE 31.5 Nonsustained Ventricular Tachycardia With Apparently Normal Heart

NSVT Clinical Presentation	ECG	Risk of Sudden Cardiac Death	Diagnostic Evaluation	Alternative Diagnostic Considerations	Treatment	Treatment to Be Considered	Key References
Typical RVOT	LBBB, inferior axis, axis transition V3-V4	Very rare	Standard	Differentiate from ARVC	β-Blocker, verapamil, IC drugs with symptoms	Catheter ablation	Latif et al.[187a]
Typical LVOT	Inferior axis, transition, V3	Very rare	Standard	RVOT VT	β-Blocker, verapamil, class IC drugs with symptoms	Catheter ablation	Latif et al.[187a]
Idiopathic reentrant LV tachycardia	RBBB, LS axis	Very rare	Standard EP testing	Ischemic heart disease, CM	Verapamil if symptomatic	Catheter ablation	Latif et al.[187a]
Other focal VT	Multiple morphologies, monomorphic	Uncommon	Exercise testing or catecholamine stimulation	Ischemic heart disease, CM	β-Blocker for the arrhythmia	Catheter ablation	Latif et al.[187a]
Exercise	Multiple	Increased risk when NSVT in recovery	Ischemic heart disease, cardiomyopathy	CPVT	Underlying disease	β-Blockers, flecainide	Jouven et al.[187b], Frolkis et al.[187c]
Athlete	Multiple	If it disappears with increased exercise, low risk	Evaluate for latent HCM or ischemic heart disease	HCM	No treatment, training can continue	None	Biffi et al.[187d,187e]
Hypertension valvular disease	Multiple morphology	As without arrhythmia	Consider ischemic heart disease	Ischemic heart disease, CM	Treat HTN	β-Blocker	Zipes et al.[187f]
Polymorphic VT	Polymorphic	High	Evaluated for CAD, CPVT, inherited arrhythmia syndromes	Purkinje fiber–triggering focus	Underlying disease	Revascularization, ICD, β-blocker, catheter ablation	Sauer and Newton-Cheh[187g]
TdP VT	Long QT, TdP	High	Medications, congenital LQTS	Medications, K^+, Mg^{2+}, Ca^{2+}	Stop medications, correct electrolytes	ICD, β-blocker	

ARVC, Arrhythmogenic right ventricular cardiomyopathy; *Ca^{2+},* calcium ion; *CAD,* coronary artery disease; *CM,* cardiomyopathy; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *ECG,* electrocardiogram; *EP,* electrophysiology; *HCM,* hypertrophic cardiomyopathy; *HTN,* hypertension; *ICD,* implantable cardioverter-defibrillator; *K^+,* potassium ion; *LBBB,* left bundle branch block; *LQTS,* long QT syndrome; *LS,* left-superior; *LV,* left ventricular; *LVOT,* left ventricular outflow tract; *Mg^{2+},* magnesium ion; *NSVT,* non-sustained ventricular tachycardia; *RBBB,* right bundle branch block; *RVOT,* right ventricular outflow tract; *TdP,* torsades de pointes; *VT,* ventricular tachycardia.

From Pedersen CT, Kay GN, Kalman J, Borggrefe, M, et al. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Heart Rhythm.* 2014;11:166–196.

determining the morphology of the NSVT, which can help determine its origin. An echocardiogram should be obtained to exclude underlying heart disease. In selected cases, an MRI can be useful to determine pathologic etiologies of NSVT such as dilated cardiomyopathy, hypertrophic cardiomyopathy, sarcoidosis, amyloidosis, or arrhythmogenic RV cardiomyopathy.

Treatment of Nonsustained Ventricular Tachycardia

Treatment of NSVT originating from the RV or LV outflow tract is required only if the arrhythmia is symptomatic, incessant, or produces LV dysfunction. The treatment of LV or RV outflow tract NSVT is either medical with a β-blocker, a nonhydropyridine calcium blocker, a class IC antiarrhythmic medication, or with catheter ablation. NSVT owing to a focal mechanism can also occur from a LV papillary muscle and can be treated medically with β-blockers, nonhydropyridine calcium blockers, or with catheter ablation.

Treatment of NSVT and suspected ischemic heart disease warrants an evaluation for coronary ischemia and should be focused on improving coronary perfusion. A patient with a LV ejection fraction less than 35% and NSVT should be considered for an ICD.[188–190] In patients with less severe LV dysfunction (ejection fraction 35%–50%) and a history of a prior MI, syncope, or symptomatic NSVT, an electrophysiologic study may be indicated. If the electrophysiologic study demonstrates inducible sustained VT, an ICD should be implanted.[191] NSVT is one of several risk factors for SCD in hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy should have their risk scores calculated to determine if implantation of an ICD is warranted.[192] If the nonsustained VT is determined to be CPVT, the risk of SCD is high and β-blocker therapy and possible placement of an implantable cardioverter-defibrillator (ICD) are recommended[193] (see later text).

If the NSVT is TdP, electrolyte abnormalities that can prolong repolarization need to be corrected and medications that can prolong the QT interval eliminated.

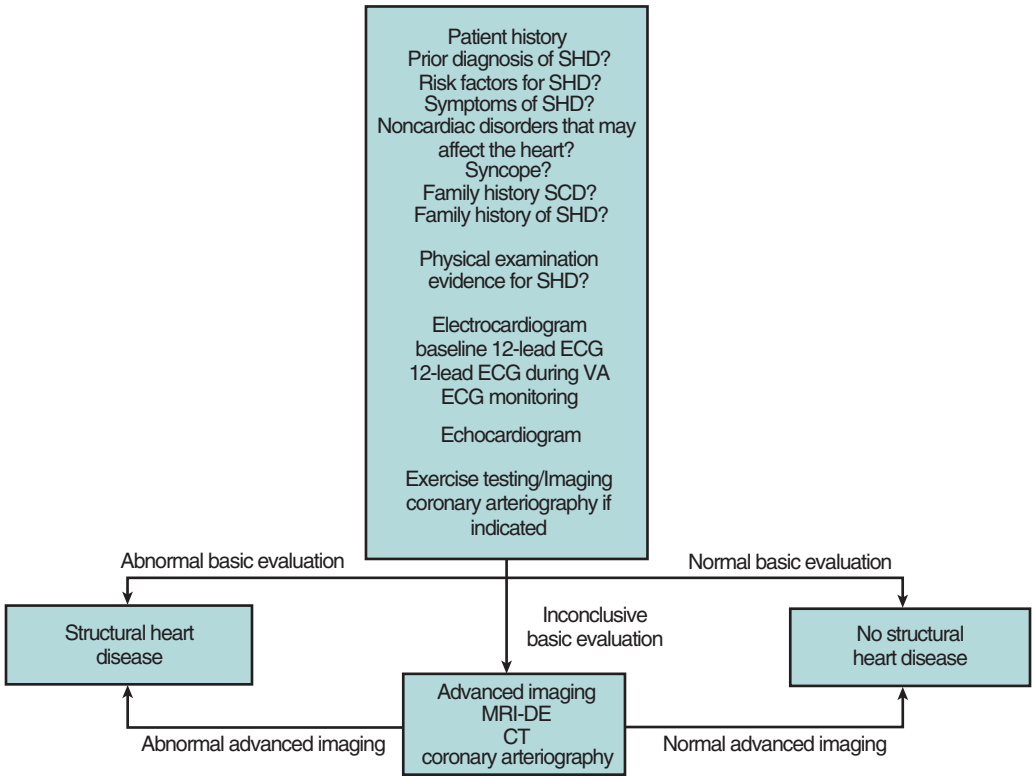
Antiarrhythmic drug therapy can be considered for patients with symptomatic recurrent NSVT that is not alleviated by revascularization, optimization of medical therapy, or treatment of reversible causes, but no study has demonstrated a mortality benefit of suppression of NSVT either with antiarrhythmic medication or catheter ablation. Patients with defibrillators (ICDs) and NSVT have an increased frequency of shocks and all-cause mortality. These patients should have their ICDs programmed with long VT detection times and high VF detection rates to avoid unnecessary shocks and to potentially improve prognosis.[194,195]

Sustained Ventricular Tachycardia

Monomorphic ventricular tachycardia is defined as sustained when it lasts longer than 30 seconds. In evaluating a patient with sustained ventricular tachycardia it is important to determine if the patient has any structural heart disease (Fig. 31.26). A 12-lead ECG, an echocardiogram, and often a cardiac catheterization are essential to make this determination. If the echocardiogram is normal, a cardiac magnetic resonance imaging scan is sometimes indicated to look for myocardial scar not seen on the echocardiogram, arrhythmogenic RV cardiomyopathy, nonischemic cardiomyopathy, hypertrophic cardiomyopathy, cardiac sarcoidosis, or amyloidosis.

Ischemic Sustained Ventricular Tachycardia

The vast majority of patients with sustained monomorphic VT (SMVT) have structural heart disease with most—54% to 59%—having ischemic heart disease. Most patients with SMVT and



• **Fig. 31.26** Evaluation for the presence or absence of structural heart disease. *CT,* Computed tomography; *ECG,* electrocardiogram; *MRI-DE,* magnetic resonance imaging with delayed enhancement; *SHD,* structural heart disease; *VA,* ventricular arrhythmia.

ischemic heart disease have a myocardial scar that is a sequel of a prior MI, which is the substrate for the VT. Transient myocardial ischemia is an uncommon cause of SMVT. Therefore while most patients will be referred for a coronary angiogram, it is unlikely that treatment of the ischemia alone will prevent recurrence of the monomorphic ventricular tachycardia.[196,197]

Treatment of SMVT

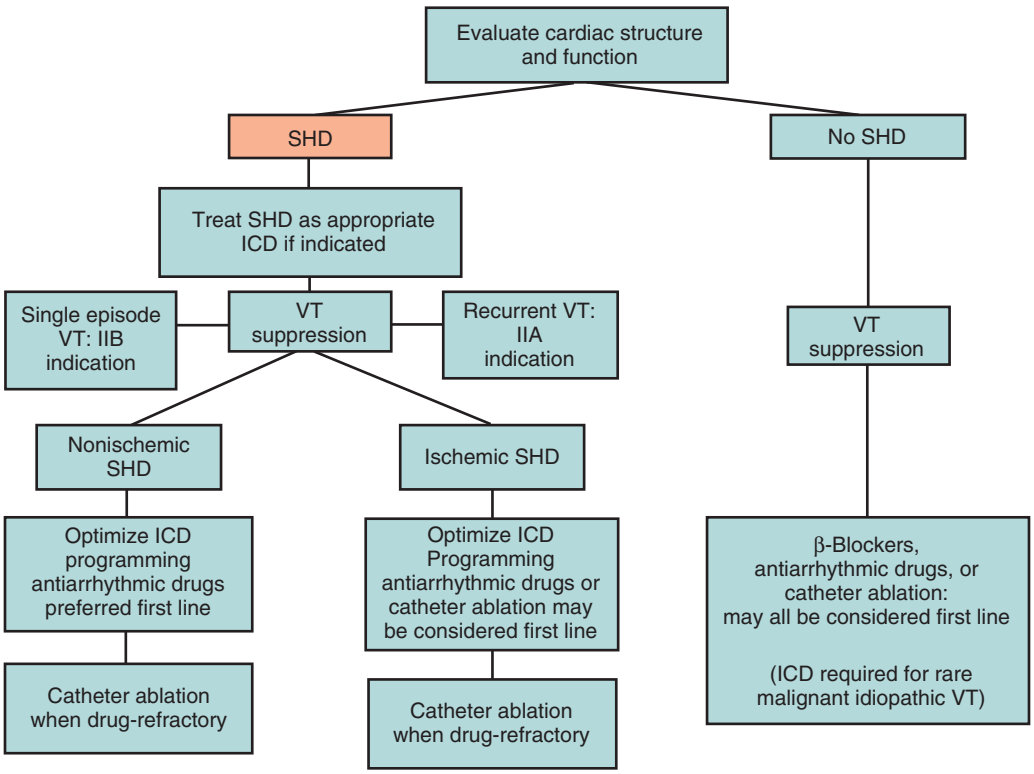
The treatment of SMVT is dependent on the patient's symptoms, hemodynamic status, and underlying heart disease. When it occurs in patients without structural heart disease it generally has an excellent prognosis.[191,199] Rarely idiopathic VT can be life-threatening when the arrhythmia has a short coupling interval or rapid rate.[200] In patients without structural heart disease and an ECG showing a QRS morphology consistent with an outflow tract tachycardia an IV β-blocker may be effective in terminating the VT (see later text) (Fig. 31.27).

The single most effective agent for terminating VT in the presence of structural heart disease is amiodarone.[191] Sustained VT in the setting of reduced ventricular systolic function is associated with an increased mortality.[196,197,201,204] Implantation of an ICD is indicated for patients with structural heart disease and sustained VT[205] because it has been demonstrated to improve survival.[196,197,208] There is no evidence that antiarrhythmic therapy alone improves survival. Further, AADs have a significant risk of proarrhythmia and thus they should be used only when an ICD is implanted. Sotalol and amiodarone have been shown to decrease number of appropriate ICD therapies, but they should not be used without an ICD in place.[209] For patients with ischemic myocardial scar and near-normal systolic function, ICD implantation is also recommended because it can simplify management and follow-up of these patients. However, there is no study that has shown a mortality benefit of this strategy. Both appropriate and inappropriate ICD shocks are associated with an increased mortality and reduced quality of life. The increase in mortality is usually attributed to worsening cardiac disease and not a specific consequence of the shocks.[210–212]

Catheter ablation is becoming an important alternative to the use of antiarrhythmic medication for the treatment of SMVT. In patients with a prior MI, reduced ejection fraction, and sustained VT, catheter ablation has been shown to significantly reduce recurrence of VT.[213] Consensus statement and guidelines recommend catheter ablation for VT only when antiarrhythmic drugs are not effective. More recent studies, however, have shown that catheter ablation is preferred over escalation of antiarrhythmic drug therapy.[214]

Sustained Polymorphic VT/VF

PMVT is defined as a ventricular arrhythmia where the morphology of the QRS complexes changes with each beat, at a rate of more than 100 beats/min. This differs from VF, which is a chaotic tachycardia without identifiable QRS complexes. TdP is a PMVT, which occurs in the setting of a prolonged QT interval where the QRS complexes twist around an isoelectric baseline[215] (Fig. 31.28). TdP is strongly associated with electrolyte abnormalities or drugs that delay repolarization. When this arrhythmia is suspected, a search for underlying factors that can be corrected should be undertaken. PMVT or VF in the absence of ischemia, electrolyte abnormalities, or drugs that prolong the QT interval suggests the presence of an inherited arrhythmia syndrome such as long QT, short QT, Brugada, or CPVT (Table 31.6) (see later text). To make

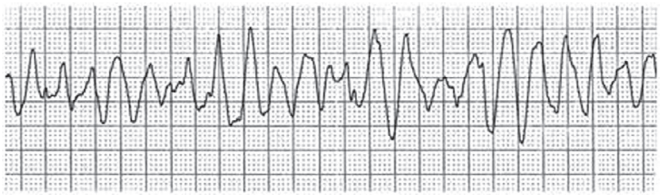


• **Fig. 31.27** Evaluation and management of sustained monomorphic ventricular tachycardia. *ICD,* Implantable cardioverter-defibrillator; *SHD,* structural heart disease; *VT,* ventricular tachycardia.

these rarer diagnoses, it is important to obtain a 12-lead ECG as close as possible to the arrhythmic event where the pathognomonic abnormalities will be seen on the ECG (Fig. 31.29).

Treatment of Polymorphic VT or VF

A detailed discussion of the management of cardiac arrest is provided in Chapter 1. The treatment of VF is immediate defibrillation.



• **Fig. 31.28** Torsades de pointes. The ventricular tachycardia on the electrocardiogram appears to rotate around a horizontal axis—hence, the name torsades de pointes, from the French "twisting of the points." (Adapted from Gupta A, Lawrence AT, Krishnan K, et al. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsades de pointes. *Am Heart J.* 2007;153:891–899.)

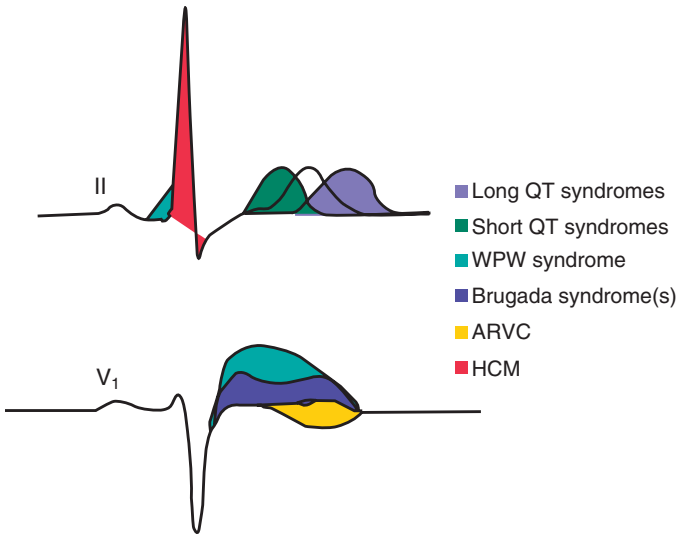
The rhythm in patients with TdP should be cardioverted if the arrhythmia is sustained; if it recurs, atrial pacing at rates of at least 90 beats/min can be effective. During cardiac arrest, patients treated with IV amiodarone have a higher probability of survival than those treated with IV lidocaine. Once patients are resuscitated from VF or PMVT, the initial diagnostic step is to exclude an acute coronary syndrome or MI.[217–218] Emergency coronary angiography and revascularization may significantly improve prognosis.[216,219,220] Once ischemia is treated or ruled out, an echocardiogram is recommended to assess structure and function of the ventricles. When there is no reversible cause of PMVT or VF, ICD implantation is the next step.[221,222] Catheter ablation may be considered for patients with recurrent PMVT or VF when a consistent PVC morphology triggers the arrhythmia.[223,224,226] These VPCs are repetitive, usually narrow, and originate from the Purkinje network where they can be targeted for catheter ablation. Even if catheter ablation is effective in these patients, an ICD is usually still indicated.[225]

Post-MI patients with a LV ejection fraction of less than 35% are at high risk for SCD in the first 3 months while the ventricle is healing. They may benefit from a wearable defibrillator during this healing phase. The LV function should be reassessed 40 days

TABLE 31.6 Conditions That Can Cause Polymorphic VT/VF in the Absence of Structural Heart Disease and Potential Therapies

Clues	Test to Consider	Diagnoses	Therapies
Long QT/T-wave alternans	ECG/monitor	Congenital LQTS	β-Blockers/stellatectomy
TdP pattern	Epinephrine challenge		Avoid QT-prolonging drugs
History of seizures	Genetic testing		Mexilitine/flecainide (LTQ3)
Specific trigger (loud noise)			Pacemaker/ICD
Long QT/T-wave alternans	ECG/Monitor	Acquired LQTS	Mg^{2+}/K^{+}
TdP pattern			Stop offending drug
Renal failure			Temporary pacing
New medication or drug abuse			
AV block	ECG/monitor	Bradycardia	Pacemaker
Incomplete RBBB with STE in leads V1 and V2	ECG	Brugada syndrome	Isoproterenol/quinidine
Fever	Drug challenge Genetic testing		Antipyretic Ablation ICD
Monomorphic PVC trigger	ECG/Monitor	Focal PVC origin	Ablation/ICD
J-point elevation	ECG	Early repolarization	ICD
Ventricular preexcitation	ECG	WPW	Ablation
Short QT interval	ECG	Short QTS	ICD
Bidirectional VT pattern exercise-induced	Digoxin level Exercise test Genetic testing	CPVT Andersen-Tawil syndrome Digoxin toxicity	Stop digoxin β-Blockers/CCBs/flecainide ICD
STE and chest pain	Proactive testing	Coronary spasm	Vasodilators/coronary stent ICD
Short-coupled PVC trigger	ECG/Monitor	Idiopathic	ICD

CCBs, Calcium channel blockers; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *ECG,* electrocardiogram; *ICD,* implantable cardioverter-defibrillator; *K^{+},* potassium ion; *LQTS,* long QT syndrome; *Mg^{2+},* magnesium ion; *PVC,* premature ventricular complex; *RBBB,* right bundle branch block; *short QTS,* short QT syndrome; *STE,* ST elevation; *TdP,* torsade de pointes; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White (syndrome).

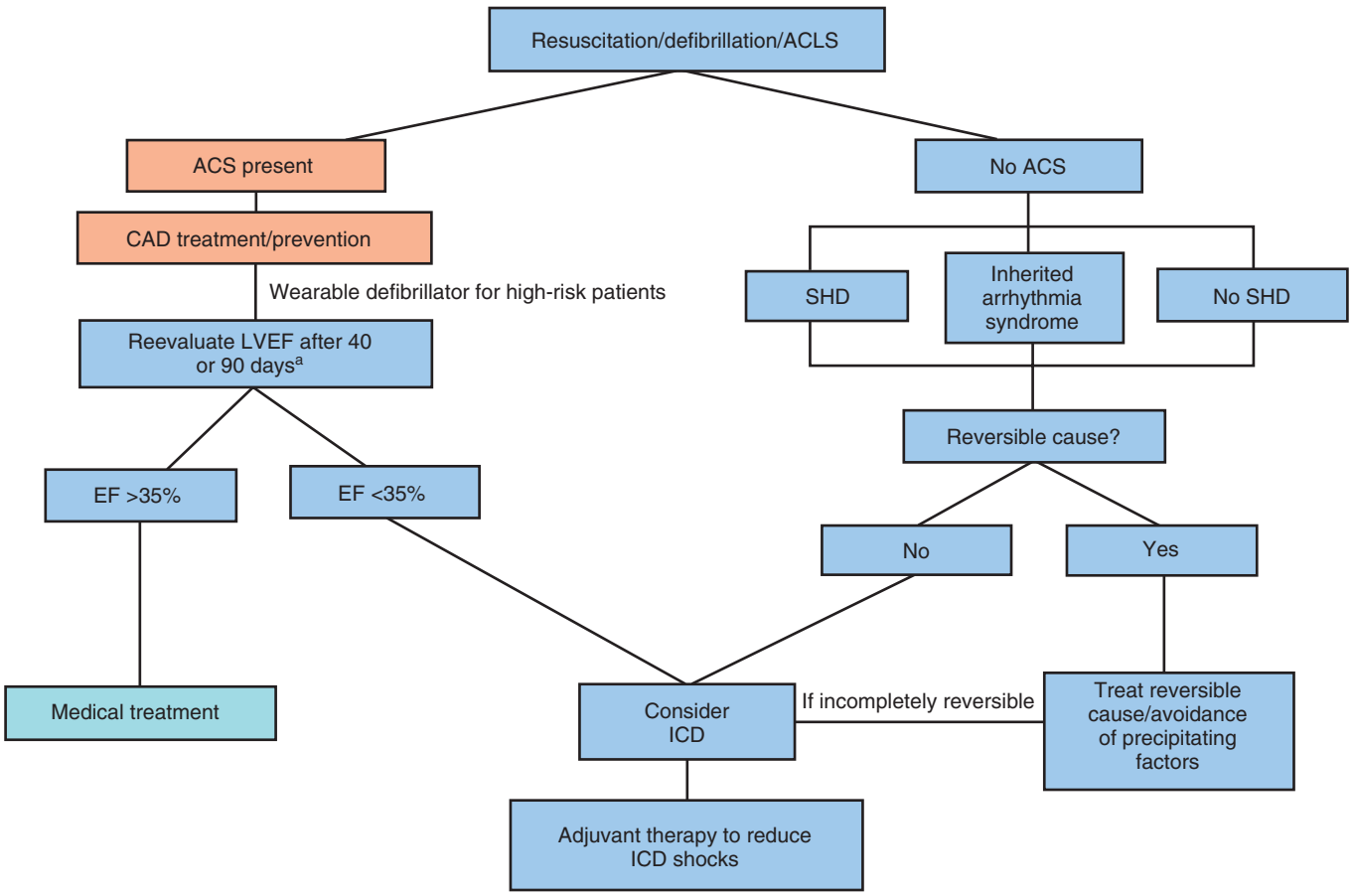


• **Fig. 31.29** Electrocardiograms of long QT syndrome, short QT syndrome, Wolff-Parkinson-White syndrome *(WPW)* syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy *(ARVC),* and hypertrophic cardiomyopathy *(HCM).*

after infarction, and if still less than 35%, implantation of an ICD is recommended. Patients who are treated with coronary revascularization after an MI are also at risk if the LV ejection fraction is less than 35% and may also benefit from a wearable defibrillator. LV function should be reassessed at 90 days after revascularization in that group to determine if they are candidates for ICD implant (Fig. 31.30).

VT/VF Storm

VT/VF storm is defined as three or more episodes of VT or VF within 24 hours requiring either cardioversion/defibrillation or antitachycardia pacing therapy from an ICD.[227,232] These patients should be evaluated for reversible causes such as electrolyte disturbances, proarrhythmia from a medication, acute ischemia, or valvular disease. Patients with VT/VF storm should be evaluated for treatment with sedation, intubation, or mechanical hemodynamic support, which by themselves can reduce arrhythmia burden. β-Blockers have been shown to improve short-term outcomes and can be used with amiodarone to improve outcomes.[233] Lidocaine is rarely effective in this setting.[234] Implantable defibrillator detection criteria and therapies should be reprogrammed to prevent shocks from potentially self-terminating episodes of VT and favor antitachycardia pacing therapy. Catheter ablation should be considered



• **Fig. 31.30** Algorithm for treatment of sustained polymorphic ventricular tachycardia/ventricular fibrillation. Left ventricular function should be reassessed at 40 days after myocardial infarction or 90 days after revascularization. *ACS,* Acute coronary syndrome; *ACLS,* Advance Cardiovascular Life Support; *CAD,* coronary artery disease; *EF,* ejection fraction; *ICD,* implantable cardioverter-defibrillator; *LVEF,* left ventricular ejection fraction; *SHD,* structural heart disease.

early after hospitalization for patients with continued arrhythmias; studies have shown a beneficial effect on both VT recurrence and long-term survival.[235,236] As a last resort, neuroaxial modulation with left cardiac sympathetic denervation and spinal cord stimulation can be used for patients who cannot be stabilized by other means to reduce arrhythmia burden.[227,229,237]

Ventricular Arrhythmias in Patients With LV Assist Devices

Left ventricular assist devices (LVADs) are used both as a bridge to transplantation and as permanent destination therapy. However, their use does not eliminate ventricular arrhythmias, which still occur in 25% to 49% of patients after LVAD implantation.[216,234,238–248] LVADs provide hemodynamic support during episodes of ventricular arrhythmias, but patients may still experience palpitations, dyspnea, and right heart failure. Antiarrhythmic drugs are rarely effective in patients with LVADs; thus catheter ablation often is required.[241,246,249,250] Ventricular arrhythmias in patients with LVADs are associated with an increased risk of overall mortality.

Ventricular Arrhythmias Associated With an Acute Myocardial Infarction

The incidence of VT and VF during acute ST-elevation MIs from the Gusto-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial was 10.2%, 3.5% VT, 4.1% VF, and 2.7% both VT and VF.[251] Of these arrhythmias, 80% to 85% occurred in the first 48 hours. In patients with acute non–ST-elevation MIs or unstable angina, the overall incidence of VT or VF was only 2.1%.[252] VT occurred in 0.8%, VF in 1%, and VT and VF in 0.3%. The median time to arrhythmia was 78 hours.

Classification of ventricular arrhythmias during AMI is based on the time of arrhythmia onset. VT or VF occurring in the first 48 hours is considered an epiphenomenon and does not require long-term treatment. VT or VF occurring after the first 48 hours reflects the development of an arrhythmic substrate and may require permanent solutions because of the increased risk of SCD in these patients.

Phase 1a ventricular arrhythmias occur in the first 2 to 10 minutes and it is postulated that reentry is the dominant mechanism.[253–256] Phase 1b arrhythmias occur after approximately 10 to 60 minutes of coronary occlusion. Although the exact mechanism of phase 1b arrhythmias is unknown, it has been postulated that they may reflect abnormal automaticity induced by LV wall stress[257] or may be due to increased catecholamine release.[160,258,259] Delayed phase arrhythmias occurring 6 to 48 hours after MI are VPCs, nonsustained VT, and accelerated idioventricular rhythm, which can occur in up to 50% of patients.[260,261] It is believed that delayed arrhythmias arise from abnormal automaticity in surviving Purkinje cells located in the subendocardium.[262,263] Chronic phase arrhythmias occur after 48 hours of an AMI. Patients in whom sustained monomorphic VT develops after 48 hours usually have sustained large infarcts with resultant severe LV dysfunction. The VT is usually reentrant around the area of scar and can be quite rapid with heart rates greater than 180 beats/min.[264–266]

The autonomic nervous system contributes to the development of ventricular arrhythmias associated with an MI; excess sympathetic tone may be responsible.[267,268] Autonomic imbalance can increase sodium-potassium adenosine triphosphate (Na-K-ATPase) activity and enhance potassium conductance, which lead to hyperpolarization of the myocardial cell membrane.[269] Sympathetic activity will also increase the influx of calcium, which can enhance both automaticity and triggered activity. The evidence that sympathetic activity is important in the genesis of arrhythmias associated with AMIs comes from a study of 49 patients with VT storm.[270] Compared with patients receiving antiarrhythmic therapy, those treated with a β-blocker or stellate ganglionic blockade had a lower 1-week (22% vs. 82%) and overall mortality (33% vs. 95%) at 1 year. It was once thought that serious ventricular arrhythmias could occur within a period of minutes after reperfusion in patients with an AMI. However, it has been shown that serious ventricular arrhythmias rarely occur, although the incidence of accelerated idioventricular rhythm may be increased.[271,272]

Less Common Substrates

Idiopathic VT

Idiopathic VTs originate from a "line of fire"—areas in the RV outflow tract (90%), LV outflow tract, aortic cusps, or mitral annulus—that have a higher potential to become electrically active than the rest of the ventricle.[273] The most common form (RV outflow tract tachycardia) has a typical ECG pattern of left bundle branch block with an inferior frontal lead axis (tall R waves in leads II, III, and aVF). When the precordial transition occurs in lead V3 and the ratio of the R and S waves in lead V2 during VT divided by this ratio during sinus rhythm exceeds 0.6, a LV outflow tract origin is suspected (Fig. 31.31). Outflow tract tachycardias are adenosine-sensitive and are thought to be the result of cyclic adenosine monophosphate–mediated DADs.[170] They can be facilitated by catecholamine infusion.

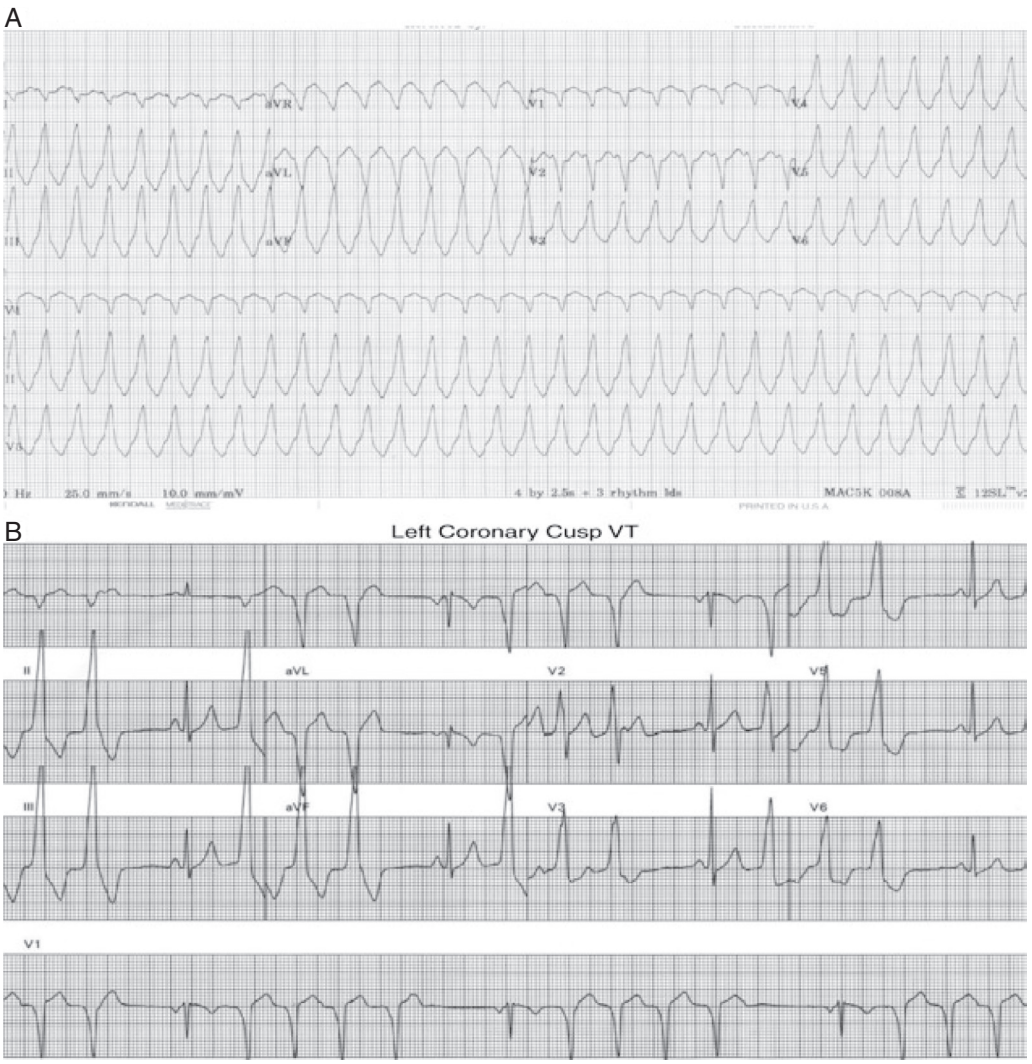
Another idiopathic LV tachycardia manifests as a relatively narrow right bundle branch block (RBBB), left-axis deviation tachycardia. This reentrant tachycardia is referred to by several different names, including fascicular VT, verapamil-sensitive VT, and Belhassen VT. The arrhythmia is due to macroentry in the terminal Purkinje fibers in the left distal third of the apical septum (Fig. 31.32). To ablate it, the lower third of the septum is mapped to look for the sharpest, earliest Purkinje potential during the tachycardia.[274,275]

Treatment of Idiopathic VT

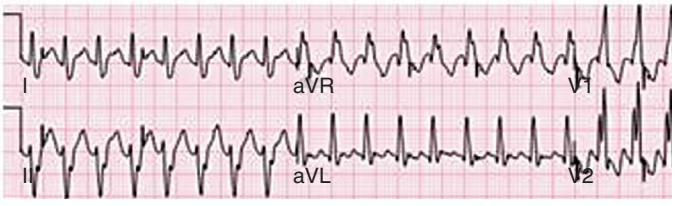
Treatment depends on patients' symptoms and the effect on overall LV function. Treatment is required only if the arrhythmia is symptomatic, incessant, or produces LV dysfunction. β-Blockers and nonhydropyridine calcium channel blockade are low-risk therapies to be used as first-line therapy but they have modest effectiveness.[276,277] Treatment with antiarrhythmic medication such as sotalol, flecainide, mexiletine, or amiodarone is more effective but has the inherent risks of side effects and proarrhythmia. Catheter ablation for RV outflow tract tachycardia is very successful with a low risk of complications. Catheter ablation for LV outflow tract tachycardia, fascicular VT, and focal VT from sites such as the papillary muscles are more procedurally complex and success rates are lower, but ablation therapy can still be curative.[278–280]

Arrhythmogenic RV Dysplasia

The ECG of patients with arrhythmogenic right ventricular dysplasia may have inverted T waves in the right precordial leads (V1, V2, and V3). In addition, an upward deflection, called an epsilon wave, may be seen just after the QRS complex and is due to late RV activation (Fig. 31.33).[281] The QRS duration may be prolonged, often with a complete or incomplete RBBB pattern. Ventricular arrhythmias in ARVD have a left bundle branch block



• **Fig. 31.31** A, Right ventricular outflow tract ventricular tachycardia *(VT).* B, Left coronary cusp VT.



• **Fig. 31.32** Verapamil-sensitive ventricular tachycardia in a 12-year-old.

configuration, as they originate from the right ventricle, and may be catecholamine-sensitive and exacerbated during exercise. VT caused by ARVD may be confused with right ventricular outflow tract VT because they have similar ECG appearances and similar clinical characteristics.

Presentation is most common between the ages of 10 and 50 years, with a mean age at diagnosis of approximately 30 years.[282] The male gender has been reported to have a more malignant course. The majority of patients who are diagnosed with ARVC are symptomatic at presentation; the most common symptoms are palpitations, syncope, atypical chest pain dyspnea, and RV failure.[283] The first manifestation of the disease can be SCD. In northern Italy it has been reported that ARVC accounts for 22% of sudden deaths in patients younger than 35 years, but in the United States ARVC appears to be a less common cause of sudden death, accounting for only 4% of deaths in young athletes.[284]

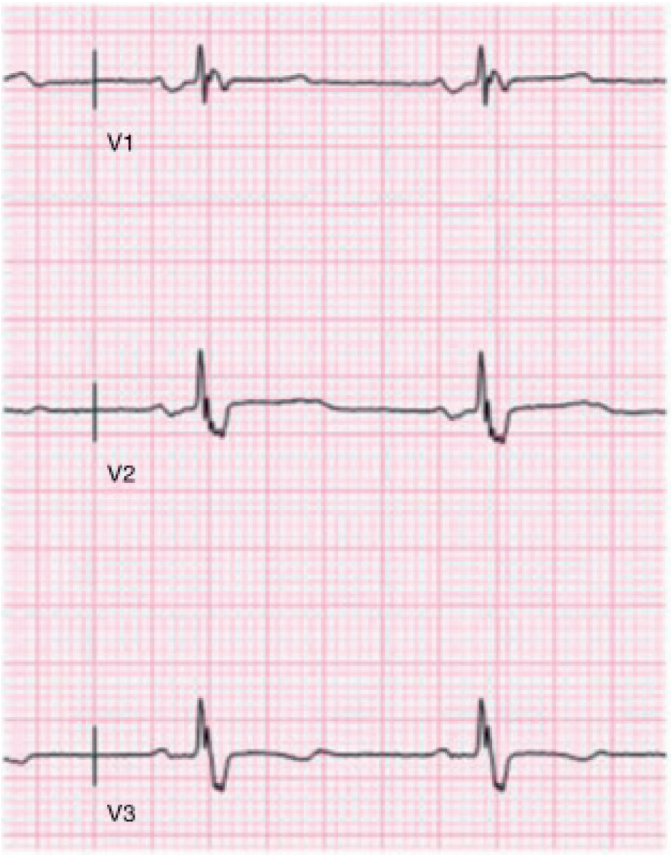
ARVD is caused by mutations in a variety of genes, most of which encode desmosomal proteins; more than 30% of cases are familial. There are two patterns of inheritance: the more common autosomal dominate form, and an autosomal recessive form associated with a cardiocutaneous syndrome including hyperkeratosis of the palms and soles and wooly hair (Naxos disease).[285] ARVD occurs in patients with significant RV disease; hallmark findings are RV dilatation, RV dysfunction, and regional RV wall motion abnormalities. LV involvement is also common in patient with ARVD and increases with age and duration of ARVD.[286] These findings are best seen on magnetic resonance imaging.

Treatment of Arrhythmogenic RV Dysplasia

Electrophysiologic studies are not predictive in defining a high-risk group for SCD. Sotalol and amiodarone seem to be effective to treat arrhythmias in ARVD. Patients diagnosed with ARVD who have had syncope episodes have NSVT, or moderate ventricular dysfunction (either RV or LV), and should have implantation of a prophylactic ICD.[287,288]

Long QT Syndrome

Long QT syndrome (LQTS) is a potentially life-threatening condition characterized by delayed myocardial repolarization that produces a long corrected QT interval.[289] The incidence is estimated to be 1 in 2000. Patients with LQTS are at risk for TdP-mediated syncope, seizures, and SCD (Fig. 31.34). There is a 13% incidence of cardiac arrest or SCD in untreated patients.[290] Although there are now 13 mutations that can cause LQTS, mutations in three major LQTS genes (*KCNQ1, KCNH2,* and *SCN51*) account for more than 75% of cases and are characterized, respectively, as LQT1, LQT2, and LQT3. LQT1 is associated with events during exertion, LQT2 is associated with events occurring after hearing a sudden loud noise, and LQT3 is associated with events at rest or sleep. There are characteristic ECG patterns for each of the three variants, although the clinical scenario often correlates to the specific gene mutation better than the ECG pattern. LQT1 has a broad T wave, LQT2 has a bifid T wave, and LQT3 has a long isoelectric segment and a narrow T wave (Fig. 31.35). The LQT3 pattern appears similar to the ECG seen in hypocalcemia.[291,292]



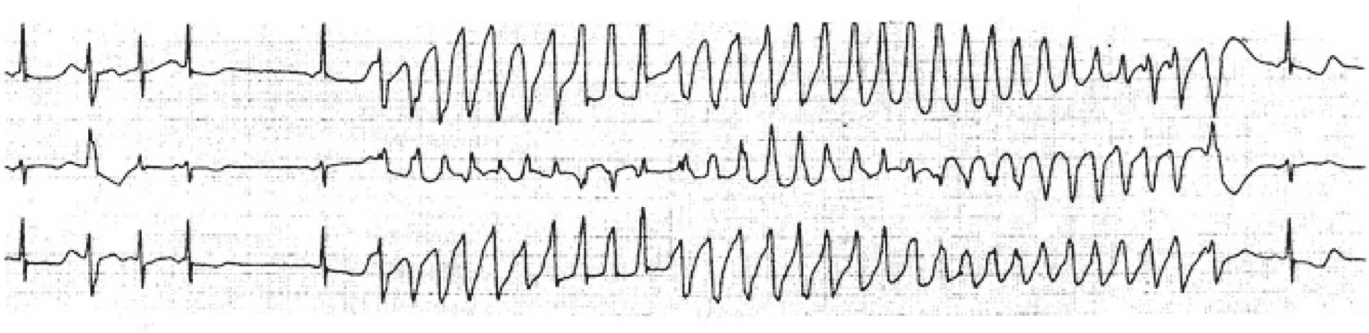
• **Fig. 31.33** The electrocardiogram shows arrhythmogenic right ventricular dysplasia (ARVD) with epsilon wave. Note the T-wave inversion in V3 and the incomplete right bundle branch block pattern. The upward deflection after the QRS in V1 is termed an epsilon wave and is classic for ARVD.

Treatment of Long QT Syndrome

Risk stratification of patients is made based on symptoms, genotype, sex, and corrected QT interval as shown in Fig. 31.36.[290] The mainstay of treatment is β-blockers, which are very effective in LQT1 and moderately effective for LQT2 and LQT3.[293] Cardiac pacing may be used in patients with LQTS who remain symptomatic despite β-blockers, particularly those in whom bradycardia facilitates TdP or bradycardia limits β-blocker administration. Patients with LQT3 may derive particular benefit from pacing because bradycardia is common in these patients.[294] ICDs are used in patients with continued symptoms despite β-blockers. It has now become accepted practice to place ICDs in patients who have recurrent TdP despite conventional therapy, aborted cardiac arrest, or other high-risk features.[295] Left cardiac sympathetic denervation (left stellate cardiac ganglionectomy) is another rarely used method to reduce cardiac events in patients with LQTS, which can be effective for patients who have multiple ICD shocks despite medial therapy.[296]

Brugada Syndrome

The Brugada syndrome (first described in 1992) is characterized by an ECG showing RBBB (complete or incomplete) with ST-segment elevation in leads V1 to V3 and ventricular arrhythmias: PMVT or VF.[297] Three distinct ECG patterns have been identified. Type 1 features a "coved"-type ST segment (>2 mm) elevation and a negative T wave in leads V1 and V2. Type 2 features a "saddleback" ST-T configuration in those leads caused by two notches in the T wave. Type 3 patterns can have a coved or



• **Fig. 31.34** Arrhythmia onset in long QT syndrome. Three simultaneous (and distinct) electrocardiogram channel recordings in a patient with QT prolongation and runs of continuously varying polymorphic ventricular tachycardia (torsades de pointes [TdP]). TdP may resolve spontaneously or progress to ventricular fibrillation and cardiac arrest. (From Chiang C, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol.* 2000;36:1–12.)

• **Fig. 31.35** Long QT *(LQT)* patterns. (From Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med.* 2008;358:169–176.)

saddleback morphology in leads V1 and V2 (Fig. 31.37). Moving the right precordial leads up to the second or third intercostal space or using bipolar chest leads may increase the sensitivity of detecting these abnormalities and should be performed when there is doubt about the diagnosis.[298,299] The cellular mechanism responsible for the ST-segment elevation is early repolarization of the ventricular epicardium as a result of rebalancing of currents at the end of phase I of the action potential. The transient outward potassium current overwhelms inward currents. The ECG abnormalities may be unmasked by procainamide and flecainide.

Brugada syndrome is caused by a mutation in the sodium channel gene *SCN5A,* which decreases the sodium channel activity. The mutation has an autosomal dominant pattern with variable penetrance. Males are more likely to be affected and also have an increased risk of sudden death. Different mutations in *SCN5A* account for LQT3 and a recent report suggests a genetic (and perhaps clinical) link between the Brugada syndrome and LQT3. In Japan and Southeast Asia, the Brugada syndrome may account for 40% to 60% of cases of idiopathic VF. Febrile illnesses may trigger arrhythmic events in patients with Brugada syndrome.[300]

Treatment of Brugada Syndrome

Currently there is no effective drug therapy for this disease. A patient with any of the Brugada pattern ECGs coupled with a history of cardiac arrest, syncope, or VT should have an ICD implanted. Asymptomatic patients with the Brugada pattern on ECG should not receive a defibrillator; clinical monitoring is advised. During electrical storm caused by Brugada syndrome, isoproterenol infusion can be useful in lessening arrhythmia burden.[301]

Catecholaminergic Polymorphic VT

CPVT, also known as familial catecholaminergic polymorphic VT, occurs in the absence of structural heart disease or other syndromes.[302–311] It typically manifests in childhood as syncope or aborted cardiac arrest. The ECG is normal in sinus rhythm. Two types of PMVTs have been described. The first is typical PMVT with continuously varying QRS morphology. The second is a bidirectional tachycardia demonstrating alternans of the QRS complexes.[307,310] CPVT is caused by calcium overload, delayed afterdepolarizations, and triggered activity that causes VT or VF. Mutations in two genes have been identified to cause CPVT: the cardiac ryanodine receptor gene (autosomal dominant) and the calsequestrin 2 gene (autosomal recessive).[307–309]

Treatment of Catecholaminergic Polymorphic VT

β-Blockers are the cornerstone of therapy and dosing may be titrated according to exercise response.[312] In 40% of patients, arrhythmia control remains inadequate despite dose optimization during repeat exercise testing. ICDs are the therapeutic option of choice in these patients.[222,313,314]

Short QT Syndrome

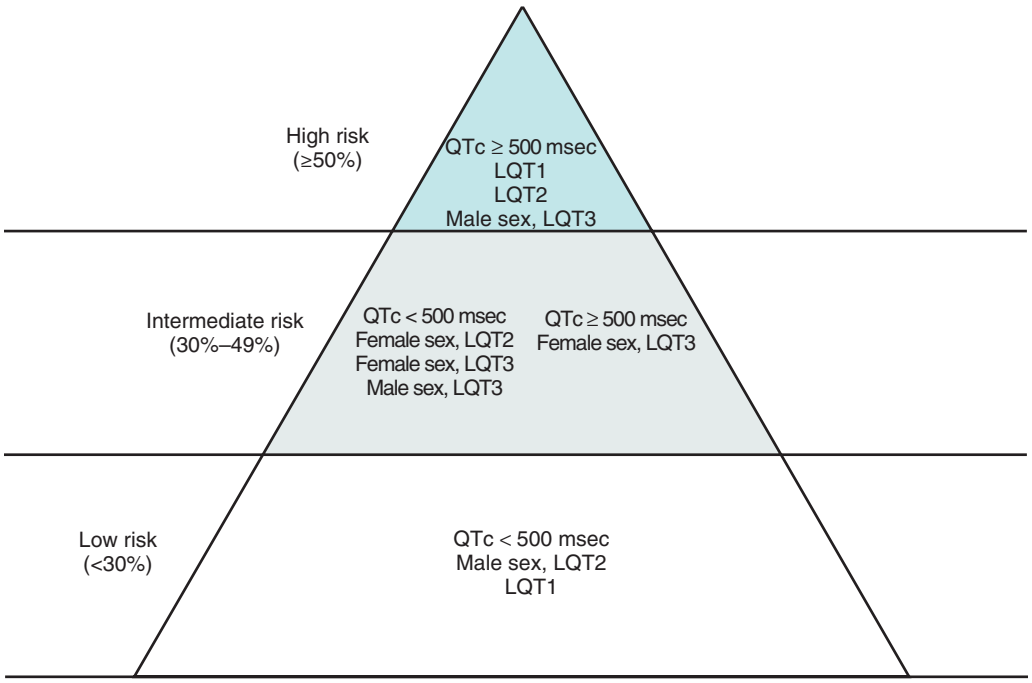
Short QT syndrome (SQTS) is a heritable primary electrical disease characterized by an abnormally short QT interval (<350 msec) and a propensity for AF, SCD, or both[315] (Fig. 31.38). Shortening of effective refractory periods combined with increased dispersion of repolarization is the likely substrate for reentry and life-threatening tachyarrhythmias. It is important to differentiate patients who have an isolated short QT interval and those who meet the criteria for SQTS.[316] As in LQTS, more than one relevant genetic mutation has been identified.

Treatment of Short QT Syndrome

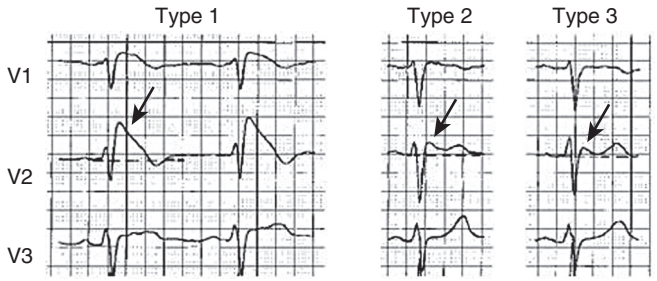
Patients with a short QT interval only (≥330 msec) and no clinical history, family history, or genotype criteria are classified as low risk and warrant no therapy. Patients with a markedly short QT (<330 msec) and no clinical history, family history, or genotype criteria are classified as intermediate probability for SQTS; referral to an electrophysiologist for additional evaluation is warranted. Patients with a QT interval less than 350 msec and a positive clinical history, positive family history, or positive genotype criteria are classified as high risk and treatment with an ICD is recommended (Table 31.7).[317,318] The relative value of diagnostic criteria points is summarized at the bottom of the table.

Short-Coupled Torsades de Pointes

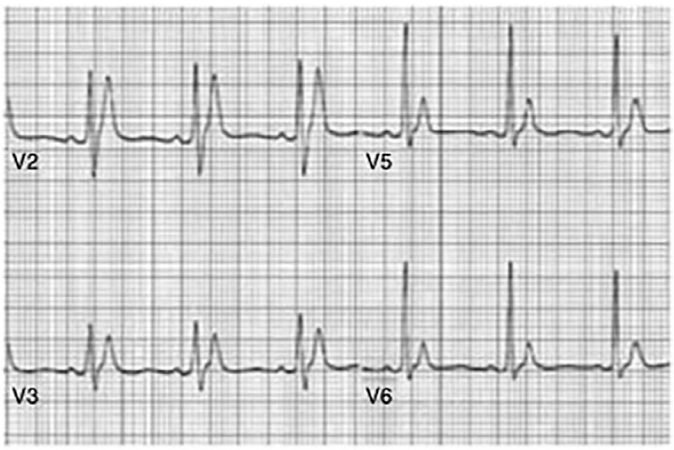
Short-coupled TdP (SC-TdP) occurs in patients with structurally normal hearts and unremarkable ECGs (normal QT intervals). In this syndrome, TdP is caused by short-coupled (<300 msec)



• **Fig. 31.36** Proposed scheme for risk stratification of patients with long QT *(LQT)* syndrome according to genotype and sex. *QTc,* Corrected QT interval. (From Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med.* 2003;348:1866–1874.)



• **Fig. 31.37** Brugada pattern electrocardiograms type 1, 2, and 3. (From Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation.* 2002;106: 2514–2519.)



• **Fig. 31.38** Electrocardiogram of congenital short QT syndrome. (From Short QT syndrome: diagnosis. Available at: http://www.shortqtsyndrome.org/dr_diagnosis.htm.)

ventricular premature beats. It is a rare, potentially fatal disorder whose pathophysiology is unknown. The prognosis is poor and effective pharmacologic therapy has not been identified. ICDs may be the best option. Short-coupled TdP shares features with idiopathic VT, and speculation is that it may respond to catheter ablation if a single PVC focus (usually from the Purkinje system) is the consistent trigger.[223,319]

Electrical Shocks

Patients who experience electrical shock (including lightning strikes) sustain a wide spectrum of injuries with unique pathophysiologic characteristics that require special management. Patients with serious electrical burns admitted to the ICU are trauma patients and should be treated accordingly. Initial prediction of outcome for patients who have experienced an electrical shock is difficult, because the full degree of injury often is not initially apparent. SCD resulting from VF is more common with low-voltage alternating current, whereas asystole is more frequent with electric shocks from direct current or high-voltage alternating current. Fatal arrhythmias are more likely to be caused by horizontal current flow (hand to hand); current passing in a vertical fashion (from head to foot) more commonly causes myocardial tissue damage. Lightning strike is unique because it causes cardiac and respiratory arrest, resulting in a 25% to 30% mortality rate.[320]

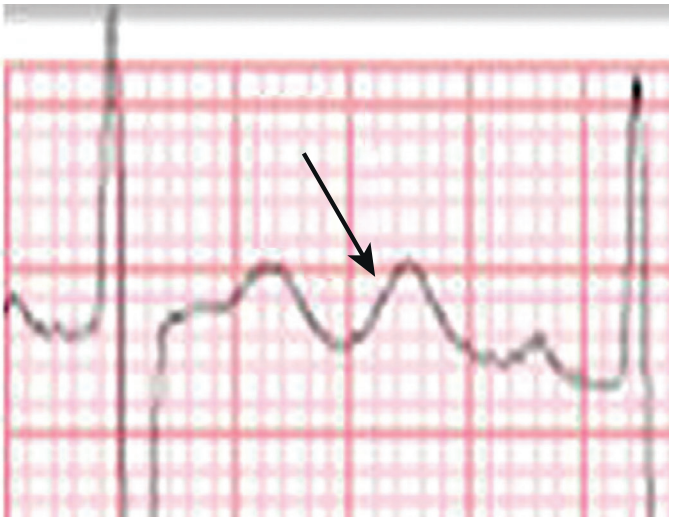
Aggressive and prolonged cardiopulmonary resuscitation (CPR) in patients who have experienced electrical shock is indicated for several reasons.[321] First, cardiac arrhythmias and prolonged respiratory arrest may be the only clinical problem, especially in patients struck by lightning. Second, patients who experience electrical

TABLE 31.7 Proposed Diagnostic Criteria for Short QT Syndrome

Criteria	Points
QTc (msec)	
<370	1
<350	2
<330	3
J-point–T peak interval <120 msec	1
Clinical History[a]	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family History[a]	
First- or second-degree relative with high probability of SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype[a]	
Genotype-positive	2
Mutation of undetermined significance in a culprit gene	1
Total	
High-probability SQTS	≥4
Intermediate-probability SQTS	3
Low-probability SQTS:	≤2

[a]A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.
QT, Bazett-corrected QT interval; *SQTS,* short QT syndrome; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
Modified from Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol.* 2011;57:802–812.

shock commonly are young and have few or no comorbid conditions. These young patients may survive prolonged CPR with no or minor sequelae. Keraunoparalysis, in which the extremities (usually the legs), become transiently cold, cyanotic, pulseless, and mottled, may masquerade as irreversible neurologic injury in patients who have been electrocuted. For practical purposes, guidelines for CPR as issued by the American Heart Association[171] still apply. The algorithm for asystole acknowledges that "atypical clinical features" need to be considered in deciding whether CPR should be continued after initial unsuccessful attempts. If more than one person has been electrocuted at a scene of injury, standard triage practices need to be modified, especially in those struck by lightning. Most patients who do not experience cardiac or respiratory arrest will survive.[322] Thus the usual triage principles should be reversed: First responders should focus initially on patients who appear clinically dead *before* patients who show signs of life are treated.



• **Fig. 31.39** Hypokalemia. Prominent U waves are seen *(arrow).*

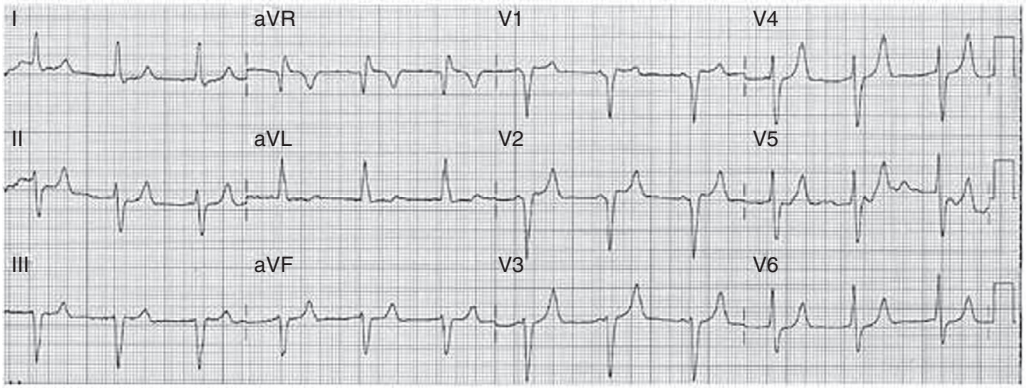
Electrolyte, Endocrine, and Metabolic Abnormalities

Electrolyte and metabolic abnormalities are common in the critically ill and may affect cardiac depolarization or repolarization. Patients may have synergistic or opposing effects of multiple abnormalities. Arrhythmias will develop when patients are exposed to factors resulting in enhanced automaticity, delayed conduction, or changes in refractoriness. The ECG may be the first clue that an electrolyte or metabolic abnormality is present.

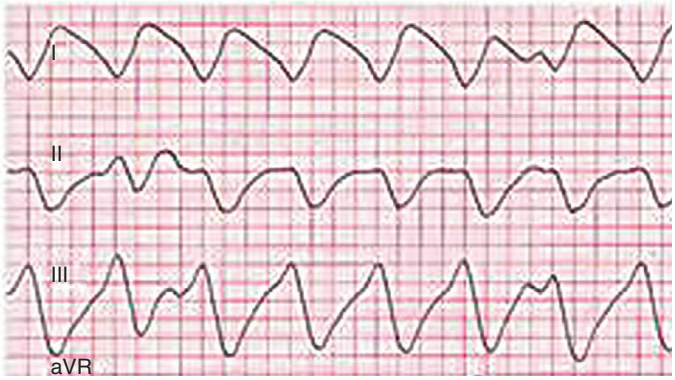
Hypokalemia delays repolarization and prolongs the action potential duration. Hypokalemia results in a characteristic U wave on the ECG (Fig. 31.39). As the hypokalemia becomes more severe, the U wave increases in amplitude, and T-wave amplitude decreases. Eventually the T wave and the U wave may fuse, giving the appearance of a single widened T wave. This creates a prolonged QT interval, which may result in TdP. Hypokalemia leads to EADs and triggered arrhythmias. The risk of hypokalemia-induced arrhythmia is increased in patients receiving digitalis and during myocardial ischemia.[323]

Hypomagnesemia and hypokalemia often coexist. Both contribute to QT prolongation, which can lead to TdP. Repletion of magnesium ion (Mg^{2+}) is an important adjunct to the management of hypokalemia. *Hypermagnesemia* is uncommon and is usually associated with renal failure. It usually is not associated with arrhythmogenesis.

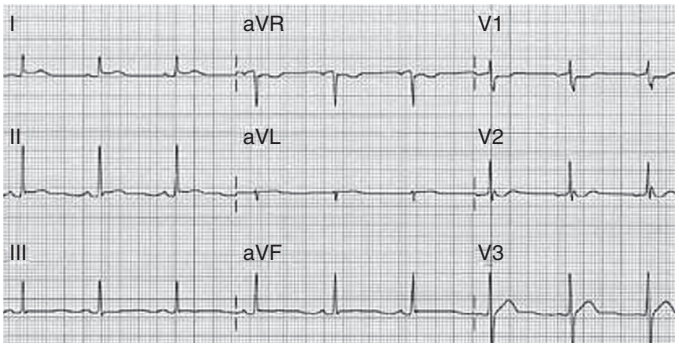
Hyperkalemia suppresses automaticity and slows conduction. As the serum potassium increases, the ECG follows a characteristic stepwise pattern of derangement. The first sign of hyperkalemia on the ECG is peaked T waves, defined as T waves greater than 10 mm in the precordium and 6 mm in the limb leads.[324] In addition to being peaked, the T waves typically appear narrow. At a potassium level of greater than 6.0 mmol/L, T-wave peaking is pronounced, the P wave will begin to lose amplitude, and the QRS complex begins to widen. At potassium levels greater than 7 mmol/L, the P wave is no longer visible and QRS widening progresses. The ensuing ECG pattern is known as sinoventricular rhythm (Fig. 31.40).[325] Sine waves may become present as the widened QRS complex blends into the T wave (Fig. 31.41).[323] An abnormal ECG may be the initial sign of dangerous hyperkalemia. and therapy should begin immediately to eliminate the hyperkalemia



• **Fig. 31.40** Sinoventricular rhythm, In severe hyperkalemia, P waves are no longer visible. QRS widening also occurs. This rhythm is difficult to distinguish from an accelerated idioventricular rhythm. (From Baltazar RF. *Basic and Bedside Electrocardiography.* Philadelphia: Lippincott Williams & Wilkins; 2009.)



• **Fig. 31.41** Sine waves seen in severe hyperkalemia. (From *New England Journal of Medicine* Image Challenge. Available at: http://www.nejm.org/action/showImageChallenge?ci=05032012. Accessed June 13, 2012.)



• **Fig. 31.42** Hypercalcemia. A short QT segment is noted. This patient had a calcium level of 16 mg/dL. (From Baltazar RF. *Basic and Bedside Electrocardiography.* Philadelphia: Lippincott Williams & Wilkins; 2009.)

and stabilize the heart. Patients with renal insufficiency may be particularly susceptible to hyperkalemia.

Treatment of Hyperkalemia

The most rapid means of treating arrhythmic toxicity of hyperkalemia is IV administration of calcium. The effect of IV calcium administration begins in minutes but is relatively short-lived (30–60 minutes). As a result, calcium should not be administered as monotherapy for hyperkalemia but should be combined with other therapies that drive extracellular potassium into the cells. The ECG should be monitored to ensure that signs of hyperkalemia are reversing. Calcium can be given as either calcium gluconate or calcium chloride. The dose of calcium gluconate usually administered is 1000 mg (10 mL of a 10% solution) infused over 5 to 10 minutes. The usual dose of calcium chloride is 500 to 1000 mg (5–10 mL of a 10% solution) infused over 5 to 10 minutes. Continuous cardiac monitoring is essential. The dose of either can be repeated after 6 hours if the ECG changers persist or recur.

Regular insulin (10 units) is another therapy for treatment of hyperkalemia. Insulin will redistribute K^+ from the extracellular to the intracellular space, but it will not lower total body potassium stores. Insulin administration should be followed by 50 mL of 50% glucose to ensure that the patient does not subsequently become hypoglycemic. After acute treatment of hyperkalemia has been accomplished by moving the potassium from the extracellular space to the intracellular space, treatment must focus on removal of potassium from the body. The most common method is administration of the cation-exchange resin sodium polystyrene sulfonate (Kayexalate). The usual dose is 15 g given 3 to 4 times daily. If medical therapies do not achieve sufficient reduction of potassium levels, hemodialysis can be performed to reduce total body potassium levels. When treating hyperkalemia by any means, care must be taken to avoid precipitous reduction, especially in patients taking digitalis glycosides.[171]

The principal electrocardiographic feature of *hypercalcemia* is a shortening of the QT interval (Fig. 31.42).[325] This finding is not associated with arrhythmias but needs to be differentiated from SQTS. The principal finding in *hypocalcemia* is prolongation of the QT interval. Unlike in hypokalemia, the T wave is normal in size. QT interval prolongation results from lengthening of the ST segment, not a broadening of the T wave (Fig. 31.43). In severe hypocalcemia, both PR and QRS intervals are prolonged.[325] Second-degree or third-degree AV block has also been reported. J waves have occasionally been reported owing to hypocalcemia.[323]

Acquired QT Prolongation

The most common causes of acquired QT prolongation are drugs or toxic substances, electrolyte abnormalities, hypothermia, and central nervous system injury. Drug-induced QT prolongation

• **Fig. 31.43** Hypocalcemia. A prolonged QT interval is the principal finding in hypocalcemia. The serum calcium level is 7.2 mg/dL. (From Baltazar RF. *Basic and Bedside Electrocardiography.* Philadelphia: Lippincott Williams & Wilkins; 2009.)

usually is the result of delayed rectifier potassium current (I_{Kr}) blockade.[106] Pharmacologic causes of QT prolongation are listed in Box 31.4. Drug-induced TdP is managed initially with IV magnesium sulfate. Isoproterenol and temporary pacing can be used to increase ventricular rates, shorten QT intervals, and help prevent recurrent arrhythmias until the effects of the offending agent diminish.

Metabolic Derangements

In addition to electrolyte abnormalities, metabolic derangements can cause arrhythmias and characteristic ECG changes. *Hypothermia*, both from accidental exposure as well as from therapeutic cooling after cardiac arrest, has classic findings on ECG (Fig. 31.44).[326] As the core body temperature drops below 32°C, conduction slows, resulting in sinus bradycardia, prolonged PR and QT intervals, as well as junctional rhythms.[327] The finding of an Osborn or J wave (an upward deflection at the terminal portion of the R wave, before the J point) is a hallmark of hypothermia. Although classically associated with hypothermia, the Osborn wave may also be a sign of other conditions such as sepsis and diabetic ketoacidosis (which can be hypothermic conditions), as well as normothermic conditions such as neurologic insult and hypercalcemia.[328] Hypothermia may also cause artifact or oscillations on the ECG tracing from shivering.

Hypothyroidism can cause slowing of conduction, resulting in sinus bradycardia, low voltage, prolonged PR and QT intervals, and intraventricular conduction delays. *Hyperthyroidism* may cause the opposite effect, resulting in sinus tachycardia, premature atrial complexes, and even may precipitate AF.

Conclusions

The intensivist must have a keen awareness of patterns, mechanisms, precipitants, and treatment of cardiac arrhythmias. The intensivist must remember that all antiarrhythmic therapies (pharmacologic and nonpharmacologic) have the potential for adverse effects. Reducing and eliminating arrhythmia precipitants may be safer and more effective than dramatic interventions. Antiarrhythmic drugs should be chosen carefully based on each patient's type of heart disease and the side effect profile of each drug, with telemetry monitoring always in place. Direct current cardioversion for both supraventricular and ventricular tachycardias should be used early whenever a patient is hemodynamically unstable. Anticoagulation for AF in the ICU can be challenging because of potential bleeding

• BOX 31.4 Drugs Reported to Cause Prolongation of QT Interval or Torsades De Pointes/Ventricular Tachycardia

Antiarrhythmic Medications

Class IA
Quinidine
Procainamide (metabolized to N-acetylprocainamide)
Disopyramide

Class III
Dofetilide
Ibutilide
Sotalol
Amiodarone

Class IV
Bepridil

Promotility Medications
Cisapride[a]

Antimicrobial Medications

Macrolides
Erythromycin
Clarithromycin

Fluoroquinolones
Sparfloxacin[a]

Antiprotozoals
Pentamidine

Antimalarials
Halofantrine
Chloroquine

Antipsychotic Medications

Phenothiazine Neuroleptics
Thioridazine
Chlorpromazine
Mesoridazine

Butyrophenone Neuroleptics
Droperidol
Haloperidol

Diphenylpiperidine Neuroleptics
Pimozide

Miscellaneous Agents
Arsenic trioxide
Methadone

Vitamins, Supplements, and Herbal Preparations
Cesium
Licorice
Zhigancao

[a]*Unavailable or severely limited availability in the United States.*
From Gupta A, Lawrence AT, Krishnan K, et al: Current concepts in the mechanisms and management of drug-induced QT prolongation and torsades de pointes. Am Heart J *2007;153:891–899.*

• **Fig. 31.44** Osborn waves in hypothermia. The patient's core body temperature was 27.1°C. The *triple arrows* show shivering artifact. The *single arrows* show Osborn waves (an upward deflection at the terminal portion of the R wave, before the J point). (From Sepehrdad R, Paulsen J Amsterdam EA. The ECG that came in from the cold. *Am J Med.* 2012;125:246–248.)

risks in the critically ill, but it must be addressed in all AF patients to reduce stroke risk. Acute treatment of AF should be rate control and anticoagulation; decisions about restoring normal sinus rhythm can be made electively (unless there is hemodynamic instability). Ablation therapy is effective for most SVTs, idiopathic VTs, and may be used as adjuvant therapy for patients with frequent appropriate ICD shocks. Ablation therapy is also successful for treatment of symptomatic AF, with the highest success in patients with paroxysmal AF. ICDs are the therapy of choice for primary prevention of SCD in patients with persistently (>3 months) decreased ejection fractions. ICDs are also indicated for secondary prevention of sustained VT or cardiac arrest or if no reversible, precipitating cause is identified. Consultation with a cardiac electrophysiologist should be an integral part of the critical care physician's routine.

Key Points

- Intensivists managing arrhythmias must have expertise in electrocardiography, pharmacokinetics, pharmacodynamics, and have bedside clinical acumen.
- Patients in an intensive care setting frequently have active arrhythmia precipitants: hypoxemia, excess circulating catecholamines, CHF, fever (sepsis), pulmonary emboli, and electrolyte and other metabolic disturbances. Treating these arrhythmia precipitants should be the first-line goal, because that alone may cure many arrhythmias.
- Intensivists may be the first to see a variety of clinical conditions that have distinct manifestations on the surface ECG. Recognition of these ECG patterns and their characteristic arrhythmias may be lifesaving in critically ill patients.
- Diagnosis and management of complex arrhythmias may be facilitated by consultation with a cardiac electrophysiologist.
- All antiarrhythmic therapies (pharmacologic and nonpharmacologic) have the potential for adverse effects and these effects must be understood before implementing each therapy.
- Antiarrhythmic drugs can slow the atrial rate in atrial flutter potentially allowing 1:1 AV conduction and very rapid ventricular rates. Antiarrhythmic drugs can slow the rate of VTs, resulting in potential failure of an ICD to sense a ventricular arrhythmia that is slower than the programmed rate cutoff. Antiarrhythmic drugs can raise pacing and defibrillation thresholds potentially necessitating device reprogramming.
- In patients with AF and preexcitation, AV nodal blocking agents must be avoided to prevent rapid conduction over the AP and dangerously rapid ventricular rates.
- Direct current cardioversion of any supraventricular or ventricular tachyarrhythmia should be performed urgently when there is concomitant angina pectoris, CHF, or hypotension.
- Anticoagulation for AF in the ICU can be challenging because of potential bleeding risks in the critically ill, but it must be addressed in all patients with AF to reduce stroke risk.
- Acute treatment of AF should be rate control and anticoagulation; decisions about restoring normal sinus rhythm can be made electively (unless there is hemodynamic instability).
- Stored electrogram data from permanent pacemakers and ICDs can be assessed to help the intensivist determine the recent history of arrhythmia type, frequency, rate, and duration.
- First-line elective therapy for most SVTs and some VTs in patients with structurally normal hearts is radiofrequency ablation.
- Ablation therapy using pulmonary vein isolation (plus or minus other ablation strategies) is successful for treatment of symptomatic AF, with the highest success in patients with paroxysmal AF and structurally normal hearts.
- Left ventricular dysfunction is the most important predictor of cardiac death in patients with ventricular arrhythmias. Long-term management of sustained ventricular arrhythmias in the setting of a decreased ejection fraction usually requires the implantation of an ICD.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. A patient under your care suddenly develops a paroxysmal supraventricular tachycardia. Which of the following is the drug of first choice to acutely increase atrioventricular (AV) nodal refractoriness?
a. Amiodarone
b. Adenosine
c. Diltiazem
d. Lidocaine
Answer: b. Adenosine is a naturally occurring substance and in 1990 was approved by the U.S. Food and Drug Administration as the treatment of choice for acute therapy of supraventricular tachycardia (SVT). Adenosine has negative chronotropic effects in the sinoatrial node, depresses conduction, and increases refractoriness in the AV node. Adenosine has a half-life of 10 seconds owing to rapid metabolism. Adenosine can cause flushing, dyspnea, chest pain, and nausea. These effects usually resolve within 30 to 60 seconds. Adenosine is a very effective drug for treatment of an acute SVT, with the ability to terminate the arrhythmia in more than 90% of cases. Adenosine is initially administered as a rapid bolus of 6 mg over 1 to 2 seconds. If the arrhythmia is not terminated within 3 minutes, a 12-mg bolus can be given in a similar fashion. Rarely a dose of 18 mg is used.

2. Which of the following is the most common cellular mechanism for the development of ventricular tachycardia in patients with ischemic heart disease?
a. Reentry
b. Early afterdepolarization
c. Delayed afterdepolarization
d. Enhanced automaticity
Answer: a. In the absence of structural heart disease, the primary mechanism for ventricular tachycardia is believed to be triggered activity or an automatic mechanism. In the presence of ischemic heart disease the predominate mechanism is reentry. After a myocardial infarction a scar is created with surviving islands of cardiac myocytes. This can result in slow and discontinuous conduction and/or block in conduction through the viable tissue. These changes create the ideal electrophysiologic and anatomic substrate for developing reentrant arrhythmias.

3. Which antiarrhythmic drug is not safe to use in a patient with a prior myocardial infarction?
a. Flecainide
b. Amiodarone
c. Dronedarone
d. Sotalol
Answer: a. Flecainide is a class IC antiarrhythmic drug and is recommended as a first-line agent for conversion and maintenance of sinus rhythm in patients with normal hearts and atrial fibrillation. It is not used in patients with a prior myocardial infarction or coronary artery disease based on the Cardiac Arrhythmia Suppression Trial published in 1989. This study was designed to investigate the efficacy of moricizine, flecainide, or encainide in patients after a myocardial infarction with reduced ejection fractions and frequent ventricular ectopic beats. Although flecainide was effective in suppressing ventricular ectopy, there was a threefold increase in arrhythmic deaths compared with placebo.

32

Hypertensive Crises

SERGIO L. ZANOTTI-CAVAZZONI

CHAPTER OUTLINE

Introduction and Terminology

Pathophysiology

Approach to Management
- Should the Blood Pressure Be Lowered Acutely?
- How Much Should the Blood Pressure Be Lowered?
- Which Medication Should Be Used to Lower the Blood Pressure?

Specific Clinical Considerations
- Hypertensive Encephalopathy
- Hypertensive Crisis in Cerebrovascular Accidents
- Acute Aortic Dissection
- Hypertensive Crises in Pregnancy
- Postoperative Hypertension
- Catecholamine-Associated Hypertensive Crisis

Conclusions

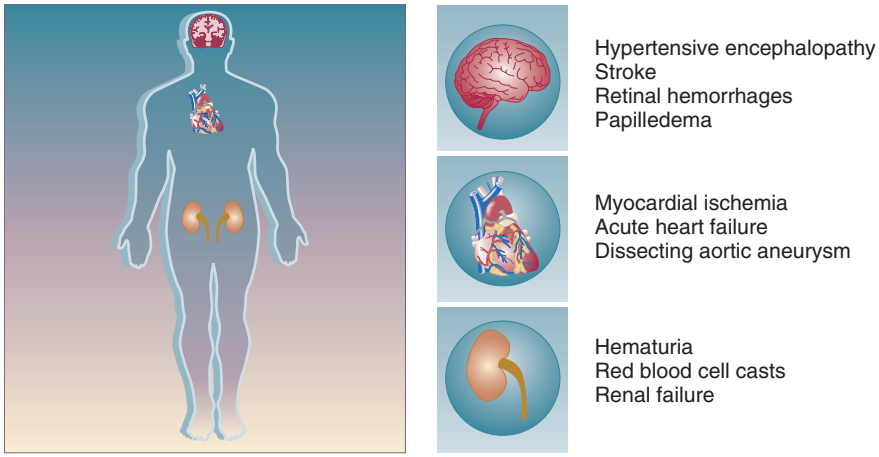
Introduction and Terminology

Hypertension is a common clinical disorder and one of the most common preventable contributors to disease and death. Estimates indicate that almost 30% of the U.S. adult population has elevated blood pressure.[1] Furthermore, one-third of these patients are unaware of their diagnosis, and of those who are diagnosed and treated, only 34% have adequate control of their blood pressure.[2] Severe elevations in blood pressure, hypertensive crises, occur in about 1% of patients with chronic hypertension.[1] Most patients with significantly elevated blood pressure (systolic pressure ≥180 mm Hg and/or diastolic pressure ≥120 mm Hg) do not have evidence of acute end-organ damage or symptoms. However, a small subset can experience significant acute end-organ damage and these patients require immediate treatment to prevent irreversible organ dysfunction.

The report of the Eighth Joint National Committee on Evidence-Based Guidelines for the Management of High Blood Pressure in Adults defines hypertension as a systolic pressure of 140 mm Hg or higher and/or a diastolic pressure of 90 mm Hg or higher.[3] The Eighth Joint National Committee on Evidence-Based Guidelines for the Management of High Blood Pressure in Adults also provides targets and guidelines for long-term treatment of patients with hypertension based on age and comorbid conditions such as diabetes mellitus and chronic renal disease. The terms *malignant hypertension* and *accelerated hypertension* are no longer used. Hypertensive crises are defined as severe elevations in blood pressure. Although some experts suggest reference blood pressure values (systolic pressure ≥180 mm Hg and/or diastolic pressure ≥120 mm Hg), it is preferable to evaluate acute elevations of blood pressure within the context of each individual patient and the effects of a given blood pressure on organ function in that patient. For example, an acute raise in diastolic blood pressure to a value of 100 mm Hg can cause significant damage in a previously normotensive individual, whereas a diastolic pressure of 130 mm Hg may be tolerated in a patient with a history of uncontrolled hypertension. As we will see, these patients will require different therapeutic approaches.

A *hypertensive emergency* is a severe elevation in blood pressure associated with the presence of acute end-organ damage. Hypertensive emergencies require immediate control of blood pressure, within 1 to 2 hours to prevent further organ damage. This usually requires the use of intravenous (IV) medications and invasive monitoring (arterial line) in a high-dependency unit such as the intensive care unit (ICU). The principal systems susceptible to acute end-organ damage from severe elevations in blood pressure include the central nervous, cardiovascular, and renal systems (Fig. 32.1). Several clinical situations are associated with hypertensive emergencies (Box 32.1). The absolute level of blood pressure and the time course of this elevation determine the development of a hypertensive emergency. However, acute end-organ damage can occur at different blood pressure values in different patients. Therefore it is more useful to define hypertensive emergencies with the presence of acute end-organ damage as opposed to specified numbers of systolic or diastolic blood pressure. True hypertensive emergencies are uncommon. Based on large claims databases it is estimated as one to two cases per million per year. Based on retrospective studies it is estimated that hypertensive emergencies constitute less than 1% of all visits to an adult emergency department for one year.[4] In addition to initiating immediate therapeutic interventions, patients with a hypertensive emergency may require further diagnostic evaluation to determine the cause of their elevated blood pressure. Depending on the population studied, 20% to 50% of patients presenting with a hypertensive emergency have a secondary cause of hypertension identified.[5]

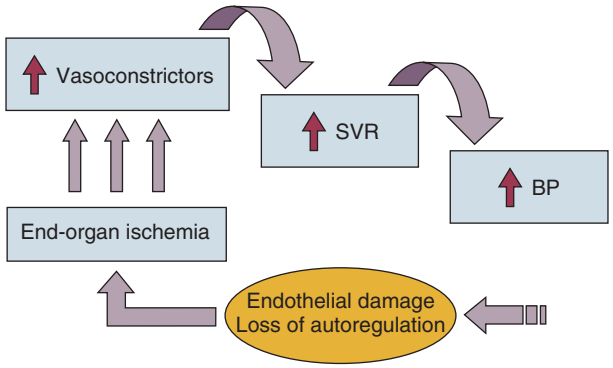
Severe elevations of blood pressure in the absence of acute-end organ damage do not constitute a hypertensive emergency and occur far more frequently. In these clinical situations blood pressure



• **Fig. 32.1** End-organ failure in hypertensive emergency.

• BOX 32.1 Hypertensive Emergencies

Hypertensive encephalopathy
Cerebrovascular accident
Acute aortic dissection
Acute left ventricular failure
Acute myocardial infarction
Acute renal failure
Preeclampsia/eclampsia
Catecholamine excess states
Postoperative hypertension



• **Fig. 32.2** Pathophysiology of hypertensive emergency. Increase in humoral vasoconstrictors leads to increased systemic vascular resistance *(SVR),* which raises blood pressure. As blood pressure *(BP)* increases, endothelial damage results in loss of autoregulation and organ ischemia. Organ ischemia increases release of vasoconstrictors, and a vicious circle is initiated.

can be lowered more gradually, over 24 to 48 hours. This usually can be accomplished with oral medications and does not require invasive hemodynamic monitoring in an ICU. These elevations of blood pressure can be associated with chronic stable organ dysfunction, such as stable angina, chronic renal insufficiency, or previous cerebrovascular accident, without evidence of acute end-organ damage.

Pathophysiology

The underlying pathophysiology of hypertensive crises is still not fully understood. The transition of mild hypertension or normotension to a hypertensive crisis is usually caused by an event that leads to an abrupt increase in blood pressure. Situations associated with this event may include cessation of hypertensive medications with potential rebound effects, consumption of illicit drugs, and severe pain, as well as several clinical syndromes. Blood pressure (BP) is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR): BP = CO × SVR. In most hypertensive crises, the initial rise in blood pressure is secondary to increased systemic vascular resistance. The rise in systemic vascular resistance is believed to be caused by humoral vasoconstrictors.[6] With the increase in blood pressure, mechanical stress on the arteriolar wall leads to endothelial damage and fibrinoid necrosis of the arterioles.[6,7] Vascular damage leads to loss of autoregulatory mechanisms, ischemia, and acute end-organ damage, which prompts further release of vasoconstrictors and initiates a vicious cycle (Fig. 32.2).[6,7]

Approach to Management

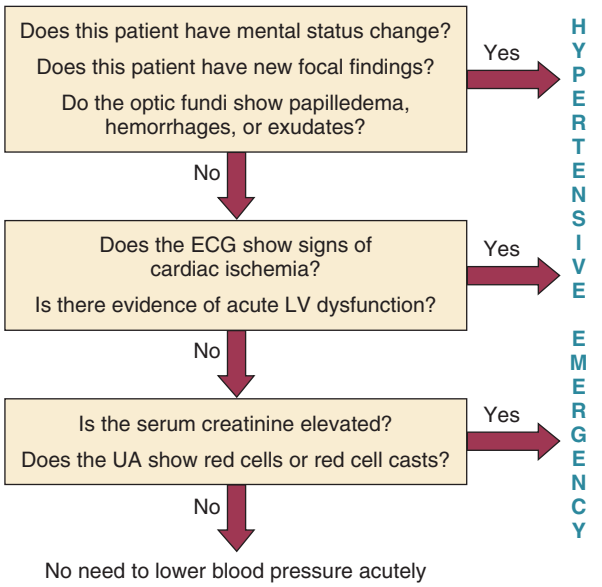
Despite the abundance of evidence providing guidance and support to the long-term benefits of treating chronic hypertension, there is a paucity of high-level evidence to guide clinicians in the treatment of hypertensive emergencies. However, a systematic approach with consideration of underlying pathophysiology can help the clinician to avoid common pitfalls in the clinical management of patients with hypertensive crises. The most common pitfall in treating patients with hypertensive crises involves treating numbers without evaluating individual patients for acute end-organ damage. This usually is associated with inappropriate use of IV drugs with the potential for precipitous and harmful drops in blood pressure. A methodical approach to patients with severe elevations in blood pressure can help establish safe and effective treatment. To that effect, the clinician should address three fundamental questions:

1. Should the blood pressure be lowered acutely?
2. How much should the blood pressure be lowered?
3. Which medication should be used to lower the blood pressure?

Should the Blood Pressure Be Lowered Acutely?

To answer this question, the clinician must determine if there is evidence of acute end-organ damage. In patients with hypertensive emergencies (the presence of acute end-organ damage), the blood pressure should be lowered acutely to a safe target to prevent further end-organ damage. An organized approach in the evaluation of the patient is necessary. A focused history should determine a previous diagnosis of hypertension, medication history, use of illicit drugs or over-the-counter agents with potential hypertensive effects, and the presence of symptoms consistent with neurologic, visual, cardiac, or renal dysfunction. Physical examination should confirm vital signs. It is important to measure blood pressure adequately and in both upper extremities. Pulses should also be checked in all extremities, as inequalities in blood pressure or pulses can exist with aortic dissection. In addition, a thorough neurologic and cardiopulmonary examination should evaluate possible signs of end-organ failure such as altered mentation, new focal neurologic deficits, or cardiogenic pulmonary edema. A funduscopic examination of the eyes should be done to look for signs of acute papillary edema or new retinal hemorrhages. A set of simple diagnostic tests can complete the evaluation for acute end-organ damage. An electrocardiogram (ECG) to rule out active ischemia and a chest x-ray to assess for pulmonary edema or signs of aortic pathology can help the clinician to evaluate the cardiopulmonary system. Abnormalities in blood urea nitrogen, creatinine, and the urinalysis (red blood cell casts) suggest renal involvement. Additional tests may be indicated based on the individual characteristics of each case. An algorithm to establish the presence of acute end-organ damage at the bedside when evaluating patients is presented in Fig. 32.3.

If there is evidence of acute end-organ damage based on the clinical evaluation, the patient's blood pressure should be lowered acutely. However, if after a careful systematic clinical evaluation, the examination and diagnostic tests do not show evidence of acute end-organ damage, the blood pressure does not require immediate reduction. It is important to emphasize that the presence or absence of acute end-organ damage and not the numerical value of the blood pressure should dictate the acuity with which blood pressure reduction should be achieved.

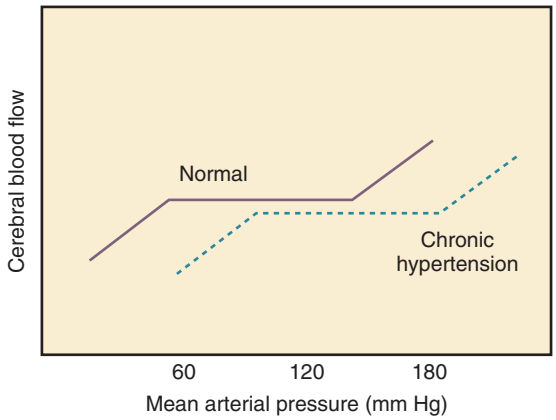


• **Fig. 32.3** Evaluation algorithm for hypertensive emergency. Systematic evaluation for possible acute end-organ damage can proceed according to this scheme. If the answer to any of the questions is "Yes," the patient has a hypertensive emergency and blood pressure should be lowered acutely. If the answer to all questions is "No," the patient does not have a hypertensive emergency and the blood pressure can be lowered gradually. *ECG,* Electrocardiogram; *LV,* left ventricular; *UA,* urinalysis.

How Much Should the Blood Pressure Be Lowered?

Once the decision to lower a patient's blood pressure acutely is made, the next step should be to establish a safe therapeutic target for the blood pressure reduction. The goals for treating hypertensive emergencies are to lower blood pressure to a level that prevents ongoing acute end-organ damage and at the same time to avoid iatrogenic damage caused by precipitous falls in blood pressure causing hypoperfusion to organs. Understanding the autoregulation of blood pressure in normal states and in patients with chronic hypertension is essential to achieve these goals.

Different organs can autoregulate and maintain a constant blood flow through a range of mean arterial pressures (MAPs). Under normal conditions cerebral autoregulation keeps blood flow constant between MAPs of 60 to 150 mm Hg.[8] When the MAP drops, cerebral arteries dilate, and if the MAP rises, they constrict to maintain a constant blood flow to the brain. Drops in the MAP below the lower limit of autoregulation lead to hypoperfusion resulting in brain ischemia. Rises in the MAP above the higher limit of autoregulation lead to acute end-organ damage from hypertension (hypertensive emergency). In the case of the brain, this may result in hypertensive encephalopathy. With chronic hypertension, compensatory functional and structural changes occur in the vasculature.[9,10] These changes will shift the autoregulatory curve to the right.[11] The autoregulatory curve for cerebral blood flow in healthy individuals and in patients with chronic hypertension is shown in Fig. 32.4. Hence, patients with chronic hypertension have a higher tolerance to elevated blood pressures, as their autoregulatory curve is shifted to the right. This explains why many patients present with severely elevated blood pressure and no evidence of acute end-organ damage. However, rapid reductions of blood pressure to "normal" levels can fall below the lower autoregulatory capacity of the circulation in a chronically hypertensive patient. This phenomenon explains the hypoperfusion of vital organs and the development of renal failure or cerebral



• **Fig. 32.4** Autoregulation of cerebral blood flow. Cerebral blood flow autoregulation curves are depicted for normotensive *(solid purple line)* and chronic hypertensive *(dashed blue line)* states.

ischemia often seen when blood pressure is lowered too far or too fast.[12] Based on these principles, most experts would recommend that for most hypertensive emergencies the goal should be to lower MAP by 15% to 25% over a period of several minutes to hours, depending on the clinical situation.[13] Reduction of blood pressure to normal levels may be warranted in special situations such as those involving patients with aortic dissection or previously normotensive patients with a postoperative hypertensive emergency.

Which Medication Should Be Used to Lower the Blood Pressure?

The ideal medication to treat a hypertensive emergency should have a rapid onset of action, high potency, immediate reversibility, no tachyphylaxis, and minimal or no adverse effects. Although there is no perfect medication, several agents with some of these characteristics are summarized in Table 32.1. There are a limited number of studies comparing agents in terms of clinical outcomes. With no clear outcome data, the selection of an agent is based on the clinical scenario, pharmacologic characteristics of the drug, and availability. Parenteral agents that are useful in treating hypertensive emergencies are further discussed (in alphabetical order).

Clevidipine

Clevidipine is an ultra–short-acting dihydropyridine calcium channel antagonist that is approved for IV use to treat severe hypertension. Clevidipine has vasoselective properties with a rapid onset of action and a very short half-life (<1 minute).[14] Clevidipine is metabolized by red blood cell esterases; therefore its use is not affected in patients with renal and/or hepatic failure. Clevidipine reduces blood pressure by a direct and selective effect on arterioles. It does not produce reflex tachycardia, and its effect on reducing afterload is often associated with increased cardiac output. Clevidipine is administered intravenously as a continuous drip. The initial dose is usually 1 to 2 mg/h with adjustments as needed to obtain the desired response in blood pressure. The maintenance dose is usually 4 to 6 mg/h; however, higher doses may be required in certain clinical situations. Small studies have compared clevidipine to nitroprusside for the treatment of severe hypertension in anesthetized patients undergoing surgery.[15,16] These studies showed that clevidipine had similar effects on blood pressure control with less effect on cardiac filling and heart rate. Although clevidipine has not been studied extensively in other clinical situations, its characteristics make it an attractive option for the treatment of hypertensive emergencies outside the operating room. In addition to its intraoperative use it has received increased attention in neurologic hypertensive emergencies.[17,18] Clevidipine is not recommended in patients with severe aortic stenosis (owing to the high risk of severe hypotension) or in patients with disordered lipid metabolism (because it is administered in a lipid-laden emulsion). Clevidipine's emulsion contains soy and eggs and it is contraindicated in patients with documented allergies to these substances.

Esmolol

Esmolol is an ultra–short-acting cardioselective, β-adrenergic agent that can be administered intravenously for the treatment of hypertensive emergencies.[19] Esmolol has a rapid onset of action

TABLE 32.1 Pharmacologic Agents Used in Treating Hypertensive Emergencies

Drug	Dosing	Elimination Half-Life	Onset of Action	Duration of Effect	Advantages	Disadvantages
Clevidipine	Initial dose 1–2 mg/h with titration Maintenance dose 4–6 mg/h	Initial half-life 1 min	2–4 min	15 min	Rapid action, titratable, not metabolized by liver or kidney	Rapidly metabolized in pseudocholinesterase-deficient patients
Esmolol	200–500 μg/kg over 1–4 min, then 50 μg/kg per minute for 4 min, and titer, then infuse 50–300 μg/kg per minute	9 min	2 min	18–30 min	Easily titratable; cardioselectivity	Use with caution in patients with heart failure or asthma
Fenoldopam	Initial dose, 0.1 μg/kg per minute with titration every 15 min, no bolus	5–10 min	5 min	30–60 min	Induces both a diuresis and natriuresis	Use with caution in patients with glaucoma
Labetalol	Bolus 20 mg, then 20–80 mg every 10 min for maximum dose 300 mg. Infuse at 0.52–2 mg/min	5 h	2–5 min	2–4 h	No reflex tachycardia	Use with caution is patients with asthma, heart failure, or bradycardia
Nicardipine	Initial dose, 5 mg/h to maximum of 15 mg/h	40–60 min	10–20 min	1–4 h	Minimal cardiodepressant effects; minimal dose adjustments required	Possible adverse effects include hypotension, headache, and flushing
Nitroprusside	Initial dose, 0.25 μg/kg per minute, maximum dose 8–10 μg/kg per minute	14 min	Within seconds	3–4 min	Immediate onset of effect	Hypotension; coronary steal; cyanide toxicity; light sensitivity; requires frequent monitoring

(within 2 minutes), a short elimination half-life (approximately 9 minutes), and a rapid offset of action (within 15 to 30 minutes after stopping infusion).[20] Esmolol is rapidly metabolized by red blood cells and is not dependent on renal or hepatic function.[20] These properties enable easy titration of the drug and make it attractive in situations of a hypertensive emergency associated with intense adrenergic responses or tachycardia. This agent is available for IV use, both as a bolus and as a continuous infusion. The usual dose is 0.5 mg/kg as a loading dose, followed by a maintenance infusion of 25 to 300 μg/kg per minute titrated to the patient's individual response.[20] Esmolol has been found effective in controlling postoperative hypertension and tachycardia in several clinical studies.[21–23] Esmolol has also been used successfully to treat hypertensive emergencies under other various clinical situations.[24,25] Esmolol seems to be more effective in situations when both blood pressure and tachycardia are present and there are no problematic issues with β-blockade (severe systolic cardiac dysfunction or asthma). It is often used in conjunction with other agents to achieve a better response.

Fenoldopam

Fenoldopam is a selective dopamine agonist that causes systemic and renal vasodilation by stimulating dopamine-1 adrenergic receptors.[26,27] Fenoldopam is administered intravenously and has a rapid onset of action (5 minutes) and a short duration of action (30 to 60 minutes).[27] It is rapidly metabolized by conjugation in the liver to inactive metabolites that are excreted by the kidney. The plasma elimination half-life is approximately 5 to 10 minutes.[27] Fenoldopam is administered as a continuous infusion (without a bolus dose), at an initial dose of 0.1 μg/kg per minute; this dose is titrated by 0.05 to μg/kg per minute based on desired effect up to a maximum dose of 1.6 g/kg per minute.[26] The most common adverse effects of the drug are related to its vasodilator properties and include hypotension, headache, reflex tachycardia, and flushing.[26] Fenoldopam also increases intraocular pressure and should be used with caution in patients with glaucoma.[28] Fenoldopam has been demonstrated to be safe and effective in postoperative hypertension.[29] Two clinical studies in severely hypertensive patients found fenoldopam to be comparable in efficacy to sodium nitroprusside.[30,31] Because of its effects on the renal vasculature and its ability to increase urine output, fenoldopam has been proposed as a renal protective drug.[32] In the setting of a hypertensive emergency, protective effects of fenoldopam on renal function have not been confirmed. However, because it does not affect renal function adversely and does not have increased toxicity in patients with renal failure, it may be a useful alternative to sodium nitroprusside in patients with hypertensive emergency and renal failure.

Labetalol

Labetalol is a combined α- and β-adrenergic receptor blocker that is approved for both oral and IV use in the treatment of hypertension. Labetalol lowers blood pressure by decreasing systemic vascular resistance by α_1-blockade and at the same time counteracts the reflex tachycardia from vasodilation through its β-blocker effect.[33,34] Labetalol reduces peripheral vascular resistance while maintaining cerebral, renal, and coronary blood flow. Unlike other β-blockers, labetalol does not reduce cardiac output. When administered intravenously it has a rapid onset of action (2–5 minutes) with peak hypotensive effect occurring within 5 to 10 minutes and lasting 2 to 4 hours.[35] The drug is primarily metabolized by the liver and has a plasma elimination half-life of about 5 hours.[33] Labetalol is usually administered intravenously at a loading dose of 20 mg, followed by incremental doses of 20 to 80 mg every 10 minutes until the target blood pressure is achieved or a maximal dose of 300 mg has been reached. An alternative regimen is a continuous infusion starting at 1 to 2 mg/min and titrated upward to achieve a desired blood pressure endpoint. Adverse effects of labetalol include orthostatic hypotension, bronchospasm (should be avoided in asthma patients), heart failure, and significant bradycardia (should be avoided in the presence of sinus bradycardia or heart block greater than first degree). Labetalol has been shown to be effective in a wide range of clinical situations associated with hypertensive emergencies.[33,34,36–39]

Nicardipine

Nicardipine is a short-acting calcium channel antagonist that produces selective arteriolar dilation. Nicardipine decreases systemic vascular resistance, without producing reflex tachycardia while maintaining or increasing cardiac output.[40] IV nicardipine has a rapid onset offset of action (the major effect lasts 10–15 minutes, and the plasma elimination half-life is 40–60 minutes), making it easily titratable when treating hypertensive emergencies.[41,42] An initial dose of 5 mg/h is recommended, increasing the infusion rate by 2.5 mg/h every 5 to 15 minutes (to a maximum rate of 15 mg/h) until the desired hemodynamic response is achieved. Once the target blood pressure is achieved, the infusion rate can be reduced to 3 mg/h and adjusted to maintain the desired endpoint. The drug is rapidly distributed throughout the body and is metabolized by the liver into inactive metabolites. Nicardipine should be avoided or used cautiously in patients with aortic stenosis, in patients with cardiomyopathy receiving β-blockers, and in patients with impaired hepatic function. Several studies have documented the utility and safety of nicardipine in patients with hypertensive emergencies. Randomized studies have demonstrated that nicardipine has similar efficacy when compared to nitroprusside in the management of postoperative hypertension.[41,43]

Nitroprusside

For many years sodium nitroprusside was the standard IV drug administered for hypertensive emergencies. Because of its potential side effects and the appearance of safer and easier to use alternatives it has fallen in disfavor in the view of many experts. However, it is still available and remains a viable alternative today in many settings. Nitroprusside is a potent balanced arterial and venous vasodilator that decreases both cardiac afterload and preload. Nitroprusside has a rapid onset of action (2–3 minutes) and a short serum half-life (1–2 minutes) and may be easily titrated.[44] Because of its potent effects on blood pressure, use of nitroprusside requires invasive hemodynamic monitoring (arterial line for continuous blood pressure monitoring). Nitroprusside is typically begun at 0.3 μg/kg per minute and increased by 0.2 to 1 μg/kg per minute every 3 to 5 minutes as needed until a maximum of 8–10 μg/kg per minute. Cyanide and thiocyanate are metabolites of nitroprusside with potential toxic effects. Cyanide is released nonenzymatically from nitroprusside. Cyanide is converted to thiocyanate by the liver. Finally, the kidney excretes thiocyanate. The total dose of nitroprusside and the presence of liver or renal dysfunction increase the risk of toxicity. Cyanide toxicity can be associated with lactic acidosis, mental status changes, and hypotension. Signs of thiocyanate toxicity include delirium, headaches, nausea, abdominal pain, and muscular spasms.[45] To reduce possible toxicity, the duration of treatment with nitroprusside should be limited and the maintenance rate of infusion should not exceed 2 μg/kg per minute. In patients requiring higher doses of

nitroprusside, an infusion of thiosulfate is recommended to decrease the risk of toxicity.[46] Hydroxocobalamin has also been demonstrated to prevent and treat possible cyanide toxicity associated with the use of nitroprusside. Patients taking nitroprusside should be carefully monitored with special attention focused on unexplained acidosis or dropping serum bicarbonate concentrations. Despite these concerns, nitroprusside has been used successfully in the treatment of hypertensive emergencies for many years and with proper precautions toxicity is seldom encountered.

Other Agents

Several other agents have been used to treat severely elevated blood pressure. Many of them have been abandoned secondary to the emergence of safer and more efficacious alternatives. However, there are a few agents that despite some limitations compared to the drugs previously discussed may be useful in particular situations. Nitroglycerin directly interacts with nitrate receptors producing predominantly venous dilation. Because of its favorable effects on coronary perfusion and its ability to reduce preload, it is a drug well suited for treating hypertensive emergencies associated with myocardial ischemia or acute left ventricular failure.[47] Several clinical studies have shown the safety and efficacy of nitroglycerin for the treatment of hypertension after cardiac surgery.[48–50] Nitroglycerin is administered as a continuous infusion. The starting dose is 5 μg/min, and this dose can be titrated until a maximum of 200 μg/min is reached.

Phentolamine is an α-adrenergic blocking agent that may be used for the management of catecholamine-induced hypertensive emergencies, such as pheocromocytoma.[51] Phentolamine is administered intravenously in 1- to 5-mg boluses. The effects are immediate and may last up to 15 minutes. This drug may cause arrhythmias and angina. Once the blood pressure is controlled, a long-acting α-adrenergic blocking agent such as oral phenoxybenzamine can be started.

Enalaprilat is an angiotensin-converting enzyme inhibitor that can be administered intravenously. Its onset of action is within 15 minutes and its duration of action is 12 to 24 hours.[52,53] The usual dose is of 1.25 mg IV every 6 hours, titrated by increments of 1.25 mg at 12- to 24-hour intervals to a maximum dose of 5 mg every 6 hours.[54] The degree of blood pressure reduction with enalaprilat correlates directly with the pretreatment levels of angiotensin II and plasma renin activity.[55] Enalaprilat is especially useful in hypertensive emergencies associated with scleroderma crises.[56]

Hydralazine is a vasodilator that has been used in pregnancy-related hypertensive crises for many years. However, it has unpredictable effects on blood pressure and a long half-life. Nicardipine and labetalol are better choices for treating pregnant patients with hypertensive emergencies in the ICU.

Specific Clinical Considerations

Hypertensive Encephalopathy

When rises in MAP exceed the upper limits of the cerebral blood flow, autoregulatory curve endothelial damage with extravasation of plasma proteins can lead to cerebral edema.[57] Hypertensive encephalopathy, the clinical manifestation of this phenomenon, is characterized by headache, visual disturbances, confusion, and focal or generalized weakness. If untreated, hypertensive encephalopathy can lead to coma and death.[58] Magnetic resonance imaging has demonstrated that the majority of the cases involve the cortical regions of the brain.[59] However, hypertensive encephalopathy with brainstem involvement has also been described.[60,61] The differential diagnosis of hypertensive encephalopathy includes several neurologic syndromes (Box 32.2). These should be quickly ruled out by imaging of the brain and other pertinent diagnostic tests. Treatment should be instituted immediately. The goal is to reduce the MAP by 15% to 20% within the first 1 to 2 hours.[62] The hallmark of hypertensive encephalopathy is improvement of symptoms once the blood pressure is controlled. Caution should be taken not to cause worsening neurologic symptoms from hypoperfusion caused by lowering the MAP. Drugs suitable for treating hypertensive encephalopathy include nicardipine, labetalol, fenoldopam, and nitroprusside.

• BOX 32.2 Differential Diagnosis of Hypertensive Encephalopathy

Ischemic stroke
Intracerebral hemorrhage
Subarachnoid hemorrhage
Subdural hematoma
Epidural hematoma
Central nervous vasculitis
Brain mass
Seizure disorder
Central nervous system infection
Drug toxicity
Withdrawal syndrome

Hypertensive Crisis in Cerebrovascular Accidents

Hypertension is common after both ischemic and hemorrhagic strokes. Extreme elevations in blood pressure have been associated with poor outcomes after ischemic and hemorrhagic stroke.[63,64] Significant elevations in blood pressure after strokes raise concerns for the potential development of reinfarction, cerebral edema, increased hemorrhage size, or hemorrhagic transformation of ischemic lesions. However, after acute stroke the cerebral vasculature's ability to autoregulate blood flow is impaired.[65] During this time, flow to the brain is highly dependent on MAP. Even modest reductions in blood pressure can compromise blood flow to the brain during this period with the potential for increased secondary neurologic damage. Optimal treatment of blood pressure during stroke is still not a settled debate. Based on available evidence the approach to the acute management of high blood pressure in the setting of acute strokes differs for ischemic and hemorrhagic strokes. In ischemic strokes, current guidelines recommend withholding therapy for hypertension in the acute phase unless the patient will receive thrombolysis, there is evidence of concomitant acute end-organ damage, or excessive elevations in blood pressure are present (arbitrarily selected as systolic blood pressure [SBP] >220 mm Hg or diastolic blood pressure >120 mm Hg).[66] Acute blood pressure management for patients with ischemic stroke who are candidates for reperfusion therapy is summarized in Box 32.3. For hemorrhagic strokes, the concerns over lowering cerebral perfusion pressure need to be balanced by potential hematoma growth with elevated blood pressure. Two recent clinical trials randomly assigned patients with acute spontaneous intracerebral hemorrhage to an SBP target of <140 mm Hg or <180 mm Hg. The first study, INTERACT2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage

• BOX 32.3 Guidelines for Treatment of Hypertension in Ischemic Cerebrovascular Accidents in Patients Who Are Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:
- Labetalol 10–20 mg IV over 1–2 min; may repeat ×1; or
- Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min to desired effect (maximum 15 mg/min)

If BP is not maintained at or below 185/110 mm Hg; do not administer rtPA

Management of BP during and after rtPA or another reperfusion therapy to maintain BP at or below 180/105 mm Hg:
- Monitor BP every 15 min for 2 h from initiation of rtPA therapy, then every 30 min for 6 h, and then every hour for 16 h

If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:
- Labetalol 10 mg IV followed by continuous IV infusion 208 mg/min; or
- Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min to desired effect (maximum 15 mg/min)

If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

BP, *Blood pressure;* IV, *intravenously;* rtPA, *recombinant tissue-type plasminogen activator.*

Trial 2) suggested that acutely lowering the SBP to 140 mm Hg or lower was safe and associated with nonsignificant benefits on death and major disability.[67] However, the results of ATACH-II (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) cast doubts on the benefits of targeting an SBP of 140 mm Hg or lower.[68] Close examination of these trials reveals that the achieved blood pressures in the first 24 hours were lower in ATACH-II compared with INTERACT2. Both trials support the safety of SBP lowering to 140 mm Hg. Current guidelines state that in patients with intracerebral hemorrhage and SBP between 150 and 220 mm Hg who do not have contraindication to acute blood pressure treatment, lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome.[69] IV labetalol or nicardipine are most commonly used as first-line therapies.

Acute Aortic Dissection

Aortic dissection is a life-threatening complication of hypertension caused by a tear in the intima of the aorta. This tear is then propagated by the aortic pulse wave. The aortic pulse wave (first derivative of pressure measured over time [dP/dt]) is dependent on myocardial contractility, heart rate, and blood pressure. The presenting symptom is usually severe, sharp chest pain of abrupt onset. Chest x-ray may be associated with a widened mediastinum. The diagnosis is best made with contrast-enhanced computed tomography or transesophageal echocardiography.[70,71] Aortic dissections are classified as type A (proximal to the left subclavian artery, involving the ascending aorta) or type B (distal to the left subclavian artery, involving the descending aorta).[71] The goal of treatment is rapid reduction of the pulsatile wave (dP/dt) and aortic stress. Both MAP and cardiac output must be controlled to achieve this goal and prevent further propagation of the dissection in the aorta. In patients with aortic dissection, the MAP and heart rate should be reduced to normal values as quickly as possible. Combining a vasodilator (nitroprusside, nicardipine, fenoldopam) with a β-blocker (esmolol, metoprolol) is recommended.[72] All patients with aortic dissection need emergent cardiovascular surgical evaluation. Type A dissections usually require emergent surgery to prevent serious complications such as acute aortic insufficiency, hemopericardium, and cardiac tamponade.[73] Type B dissection is often managed medically. Indications for surgery in type B dissections include complications such as leak, rupture, and impaired flow to vital organs (see Chapter 33).

Hypertensive Crises in Pregnancy

Hypertension is a common complication of pregnancy and is responsible for 18% of maternal deaths in the United States.[74] The spectrum of disease varies from mild increases in blood pressure to severe pregnancy-related syndromes with hypertensive emergencies such as preeclampsia and eclampsia.[75] Hypertension in pregnancy is defined as an SBP of 140 mm Hg or higher or diastolic pressure 90 mm Hg or higher. Preeclampsia is a pregnancy-specific condition defined by new-onset hypertension, proteinuria (>300 mg/24 h) and pathologic edema during gestation. Eclampsia is defined by the development of seizures or coma in a pregnant patient with preeclampsia. The challenge in pregnant patients with hypertensive crises is to lower the blood pressure to prevent maternal end-organ damage while minimizing acute changes in placental perfusion that could negatively affect the well-being of the fetus. Treatment of severe preeclampsia and eclampsia includes delivery of the fetus, magnesium sulfate for the prevention and treatment of seizures, and appropriate blood pressure control. The goal is to reduce the diastolic blood pressure to 100 mm Hg or the MAP by 20%. Historically, hydralazine has been preferred in pregnant patients for its safety profile from a fetal perspective. However, data suggest it may not be the most effective or safe agent for this patient population.[76] For pregnant patients in need of acute lowering of blood pressure in the ICU, drugs such as labetalol and nicardipine are probably better options.[77,78] Nitroprusside is reserved for refractory cases, as a last resort, and for short periods because of concerns for potential fetal cyanide toxicity. Finally, angiotensin-converting enzyme inhibitors such as enalaprilat are contraindicated in the second and third trimesters because of the increase in fetal and neonatal morbidity and mortality.

Postoperative Hypertension

Postoperative hypertension deserving of immediate IV treatment consideration has been arbitrarily defined as an SBP greater than 190 mm Hg or a diastolic blood pressure greater than 100 mm Hg on two consecutive readings after surgery. Previous history of hypertension, high body mass index, age, and the grade of surgical stress are recognized risk factors for developing postoperative hypertension.[79] Severe increases in arterial blood pressure in the immediate postoperative period can result in serious complications, such as heart failure, arrhythmia, myocardial ischemia, wound hemorrhage, and cerebral hemorrhage.[80] Considering the deleterious effects of prolonged postoperative hypertension, many authors have recommended aggressive treatment.[80] The goal of treatment is similar to other hypertensive emergencies: decrease blood pressure to safe levels and at the same time avoid complications related to hypotension. Although some clinicians believe that postoperative hypertension should be treated aggressively based on the potential for acute end-organ damage, others recommend evaluating for possible causes of hypertension, such as pain, hypercarbia, hypoxemia, and urinary retention, before initiating antihypertensive drugs. As most patients in the postoperative period are unable to take oral medications, even patients with no clear evidence of

acute end-organ damage will receive IV medications. In patients with a previous history of hypertension a reasonable goal is to reduce MAP by 20%. In patients with no previous history of hypertension, the goal is to reduce blood pressure to normal levels. Clevidipine, nitroprusside, labetalol, and nicardipine have all been extensively studied in cardiac, vascular, and neurosurgical settings. Nitroglycerin is commonly used in postcoronary bypass surgery, and fenoldopam has been proposed for clinical settings with increased risk of renal ischemia.

Catecholamine-Associated Hypertensive Crisis

A hypertensive crisis related to excess catecholamines can result from several causes. Consumption of sympathomimetic agents (amphetamines, cocaine, phencyclidine, and certain diet pills), decongestants (ephedrine, pseudoephedrine), and other agents (atropine, alkaloids) can result in excessive catecholamine release and hypertension. Withdrawal from β-blockers or α-blocking agents can cause a rapid surge in catecholamines and hypertension. In these cases, reinitiating of the particular drug may be sufficient to treat the elevated blood pressure. Additional causes include pheochromocytoma, autonomic dysfunction (i.e., Guillain-Barré syndrome), and ingestion of tyramine in conjunction with monoamine oxidase inhibitor therapy. As a rule, in catecholamine-related hypertension the use of β-blockers as initial therapy should be avoided. Loss of β-adrenergically mediated vasodilation leaves α-mediated vasoconstriction unopposed and may cause further elevation in blood pressure. Pheochromocytoma is a rare tumor that produces excess catecholamine and can cause severe hypertension. Symptoms commonly associated with pheochromocytoma include headache, palpitations, diaphoresis, abdominal pain, anxiety, and hypertension. Some patients may present with orthostatic symptoms. For patients with a hypertensive emergency associated with pheochromocytoma, the drug of choice is phentolamine. Once blood pressure is controlled a β-blocker can be added to control tachycardia. For less critical situations or after acute hypertension is controlled, the oral agent phenoxybenzamine can be used.

Conclusions

Hypertension is a common disease among patients admitted to the ICU. Severe elevations in blood pressure most often are associated with no symptoms and no evidence of acute end-organ damage. However, a subset of patient with severe elevations in blood pressure will incur acute end-organ damage and require immediate treatment to prevent ongoing and potentially irreversible organ damage. The hallmark of a hypertensive emergency is the occurrence of acute end-organ damage in the presence of elevated blood pressure. As discussed previously, there are no specific blood pressure values to define this clinical situation. Intensivists must be adept at quickly and systematically evaluating patients with elevated blood pressures for evidence of acute end-organ damage. When present, they should act quickly to reduce blood pressure to safe levels. In the absence of acute end-organ damage, intensivists should exercise caution and not fall into the trap of treating numbers with the potential risk of causing more harm to patients owing to abrupt drops in blood pressure. True hypertensive emergencies require rapid reductions of blood pressure with IV drugs, close blood pressure monitoring, and should occur in a high-acuity setting. Once the blood pressure has been stabilized, it is important to initiate a transition to an oral regimen for long-term control of blood pressure.

Key Points

- Hypertension is a common clinical disorder in patients admitted to the ICU. Severe elevations in blood pressure most often are not associated with symptoms or evidence of acute end-organ damage.
- A *hypertensive emergency* is a severe elevation in blood pressure associated with the presence of acute end-organ damage. Hypertensive emergencies require rapid reductions of blood pressure to safe levels.
- The treatment of a hypertensive crisis is guided by (1) whether the blood pressure should be lowered acutely, (2) how much it should be lowered, and (3) what medication should be used.
- The ideal medication to treat a hypertensive emergency would have a rapid onset of action, high potency, immediate reversibility, no risk of tachyphylaxis, and minimal or no adverse effects.
- Parenteral agents with specific indications in the treatment of hypertensive crises include clevidipine, esmolol, fenoldopam, labetalol, nicardipine, and nitroprusside.

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Review Questions

1. Which of the following factors is most important in determining if a patient has a hypertensive emergency?
   a. Systolic blood pressure 200 mm Hg or higher
   b. Diastolic blood pressure 110 mm Hg or higher
   c. Mean arterial pressure ≥120 mm Hg or higher
   d. Presence of acute end-organ damage
   e. Presence of severe headache
   Answer: d. Hypertensive emergencies are defined by the presence of acute organ damage. Key organs that can be affected by an acute elevation of blood pressure resulting in a hypertensive emergency include the brain, heart, and kidneys. It is important to understand that blood pressure numbers in isolation cannot be used to diagnose a hypertensive emergency. Previously normotensive patients may have acute organ damage at lower blood pressures and, conversely, chronically hypertensive patients may tolerate very elevated blood pressure without evidence of acute organ damage.
2. Patients who are chronically hypertensive and poorly controlled will usually exhibit changes in capacity to autoregulate cerebral blood flow in relation to MAP (relationship between blood flow and mean arterial pressure = autoregulation curve). Which of the following statements is *most* correct with respect to the autoregulation curve in a chronically hypertensive patient?
   a. The curve changes to a linear relationship (i.e., changes in flow are directly proportional to changes in MAP).
   b. Changes in the autoregulation curve are important only if the patient develops shock or severe hypotension.
   c. The curve shifts to the right, which means that the patient is more likely to suffer cerebral ischemia with rapid correction of blood pressure to "normal levels."
   d. The curve shifts to the left, which means patients are more capable of tolerating high MAP without developing acute organ damage.
   Answer: c. Under normal conditions cerebral autoregulation will keep cerebral blood flow between MAP of 60 and 150 mm Hg. In chronically hypertensive patients this relationship is changed so that the autoregulation curve shifts to the right. This means that chronically hypertensive patients are better prepared to tolerate higher MAPs without developing acute organ damage or a hypertensive emergency. Conversely, owing to this shift chronically hypertensive patients are much more likely to develop ischemia/hypoperfusion with rapid correction of blood pressure to normal levels. This concept is very important and it informs our therapeutic conduct at the bedside. This is why most experts recommend a target reduction of 15% to 25% of the MAP for most hypertensive emergencies.
3. Which of the following statements is *most* correct regarding use of antihypertensive agents for the therapy of a hypertensive crisis?
   a. Intravenous therapy is mandatory for the therapy of hypertensive urgencies.
   b. The antihypertensive therapy should rapidly reduce the patient's blood pressure to the normotensive range.
   c. A short-acting intravenous drug is the optimal agent for lowering the patient's blood pressure.
   d. Nitroprusside alone is the therapeutic agent of choice for lowering the blood pressure in an acute aortic dissection.
   Answer: c. With a short-acting intravenous drug, the clinician has the ultimate control on achieving a precise blood pressure target. Oral therapy can be used to treat some hypertensive urgencies such as postoperative hypertension with a functioning gut. Reduction of the blood pressure to less than 90 mm Hg systolic, or even by as little as 35% of the initial mean arterial pressure, has been associated with major organ dysfunction, coma, and death. In hypertensive crises the mean blood pressure should be initially reduced by 15% to 20%. Nitroprusside, when used to treat hypertension associated with a dissecting aortic aneurysm, should be used in combination with an intravenous β-blocker.
4. Which of the following factors is most important in determining the need to immediately decrease the blood pressure in a patient presenting with an ischemic stroke?
   a. Presence of altered mental status
   b. Extent of infarct on computed tomography scan
   c. Systolic blood pressure 200 mm Hg or higher
   d. Decision to use systemic thrombolytic
   Answer: d. Management of hypertension in the setting of an acute ischemic stroke is based on an understanding of changes that occur in the capacity to autoregulate blood flow in the injured brain. During an acute ischemic stroke the autoregulation curve for cerebral blood flow in relation to MAP becomes linear. In other words, perfusion becomes directly dependent on MAP owing to loss of autoregulation. Normally the body will compensate by increasing MAP to preserve flow to the areas of the brain surrounding the infarct. Decreases in blood pressure can cause secondary neurologic injury be expanding the infarct size. Based on this concept, current recommendations are to tolerate high blood pressures in the setting of an acute ischemic stroke. The main factor to change this approach would be the use of systemic thrombolytics. In patients receiving thrombolytics the systolic blood pressure must be keep below 180 mm Hg to decrease the risk of hemorrhage.
5. Which of the following is *most* correct concerning treatment of hypertension associated with aortic dissection?
   a. Blood pressure target with aortic dissection is a 25% reduction in mean arterial pressure.
   b. Blood pressure lowering target with aortic dissection should be achieved within first hour.
   c. Combination of a β-blocker and a vasodilator is optimum therapy.
   d. Avoiding dropping blood pressure below the autoregulatory range is paramount in the therapy of aortic dissection.
   Answer: c. Rationale:
   Reducing the shearing force characterizes the rate of change of pressure with respect to time (or dP/dt, the aortic pulse wave [first derivative of pressure measured over time]) to minimize the impact of each cardiac cycle on dissection and is one of the most important principles of therapy of elevated blood pressure with aortic dissection. Blood pressure should be lowered to normal and should be accomplished within 15 to 30 minutes, even at the expense of going below the autoregulatory range for blood pressure. Drug choices include nitroprusside plus esmolol; fenoldolpam plus esmolol; nicardipine plus esmolol; or intravenous labetalol.

33

Acute (Thoracic) Aortic Dissection

FRANK BOWEN AND R. PHILLIP DELLINGER

CHAPTER OUTLINE

History
Types of Thoracic Aortic Dissection
Risk Factors for Thoracic Aortic Dissection
Pathophysiology
Diagnosis
  Symptoms
  Physical Examination
  Imaging
Perioperative Management
  General Principles
Operative Approach
  Ascending Aortic Dissections
  Descending Aortic Dissection and Endovascular Therapy
  Treatment of Aortic Intramural Hematoma and Atherosclerotic Aortic Ulcer
Outcomes and Prognosis
Summary

Thoracic aortic dissection (TAD) occurs with communication between the thoracic aorta lumen and wall with a separation of the thoracic aortic wall layers. TAD is to be contrasted with thoracic aortic aneurysm (TAA), which is defined as dilation of the thoracic aorta to a diameter of 1.5 times normal or larger. TAA is a risk factor for TAD. TAA, although an important morbidity that may be associated with acute catastrophic leakage and death, is in and of itself not the acute emergency signified by a TAD. TAD is a cause of sudden cardiac death (unexpected cardiac death within an hour after onset of symptoms).[1] After acute type A dissection the mortality is 1% to 3% per hour for the first 24 hours following diagnosis. The International Registry of Acute Aortic Dissection reported an overall mortality of 27.4% with this condition. Surgical mortality was 26% for proximal (type A dissection) versus 58% for medical management, and for distal (type B dissection) mortality was 10.7% for medical management and 31% for surgical management.[2]

History

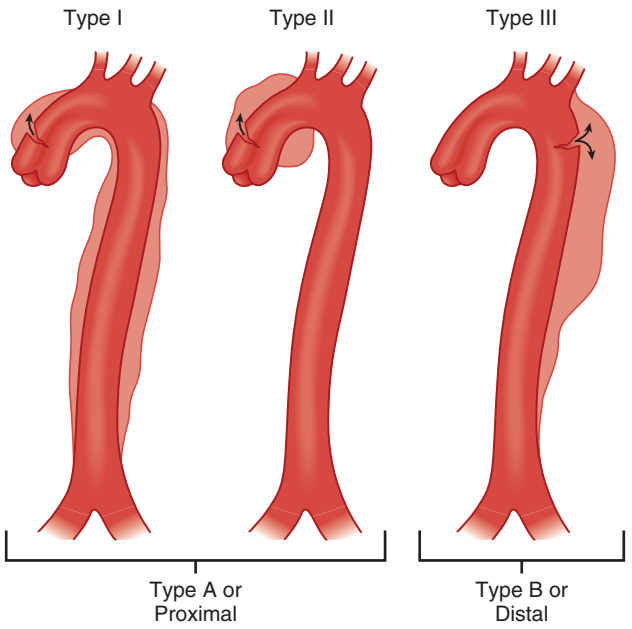
In 1819, Laenec introduced "aortic dissection" into the medical literature when he described an intimal tear distal to the aortic valve associated with a longitudinal space in the aortic wall postmortem.[3] An report in 1761 described aortic dissection and pericardial tamponade as the causes of death of King George II.[4] In 1863, Peacock reported a summary of findings in 80 patients with aortic dissection and classified the disease into three stages: intimal tear, propagation of the dissection with the potential for rupture, and recanalization of the lumen.[5] In 1896, Marfan described the aortic connective tissue abnormality now known to be associated with this entity.[6] In 1952 DeBakey was the first to repair an aortic aneurysm using a cadaver graft.[7] In 1955, DeBakey and colleagues treated a descending TAD with resection and reapproximation of dissected layers with graph interposition.[8]

Types of Thoracic Aortic Dissection

The thoracic aorta is divided anatomically into the ascending portion, the transverse portion, and the descending portion.[9] The ascending aorta has two sections: the aortic root (valvular annulus and sinuses) and the tubular portion extending to the origin of the innominate artery. The transverse portion of the aorta is a short segment, and the brachiocephalic arteries come off this portion of the aorta. The descending thoracic aorta begins immediately distal to the left subclavian artery and extends to the diaphragm. The anatomic location of the TAD has important clinical and prognostic implications. The most commonly used classification scheme for TAD is the Stanford system (Fig. 33.1), which has mostly replaced the first classification system, the DeBakey system (see Fig. 33.1). An advantage of the DeBakey system is that it does distinguish between dissections that are confined only to the ascending aorta (DeBakey type II) and dissections that involve the entire aorta (DeBakey type I). Using the Stanford system, which is more simplistic, any involvement of the ascending aorta classifies the dissection as a Stanford A, whereas lack of ascending aorta involvement classifies the dissection as a Stanford type B.

Risk Factors for Thoracic Aortic Dissection

Multiple risk factors for TAD have been identified.[9] Men are at greater risk for developing TAD than women; approximately two-thirds of patients with TAD are male.[10] The sex distribution is consistent across different classifications of aortic dissection. Women with TAD are more likely than men to have a history of hypertension. Women are older at the time of diagnosis of TAD compared with men. The average age at diagnosis of TAD is 65 years and is younger for type A TAD than for type B TAD.[9] Specific risk factors for TAD are shown in Table 33.1. It is thought that the higher the blood pressure, the greater the probability of



• **Fig. 33.1** Pictorial representation of DeBakey 1, 2, and 3 as well as Stanford A and B classification of thoracic aortic aneurysms. (From Braunwald E. *Heart Disease: Textbook of Cardiovascular Medicine.* 9th ed. Philadelphia: WB Saunders; 2011.)

TABLE 33.1 Specific Risk Factors for Thoracic Aortic Dissection

Age and gender	Smoking	Trauma
Atherosclerosis	Aortitis	Pregnancy
Hypertension	Diabetes mellitus	Drug use[a]
Congenital cardiovascular defects[b]	Connective tissue syndromes[c]	Aortic dilatation

[a]Cocaine, amphetamine, sildenafil.
[b]Biaortic value, aortic coarctation.
[c]Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, familial TAD.

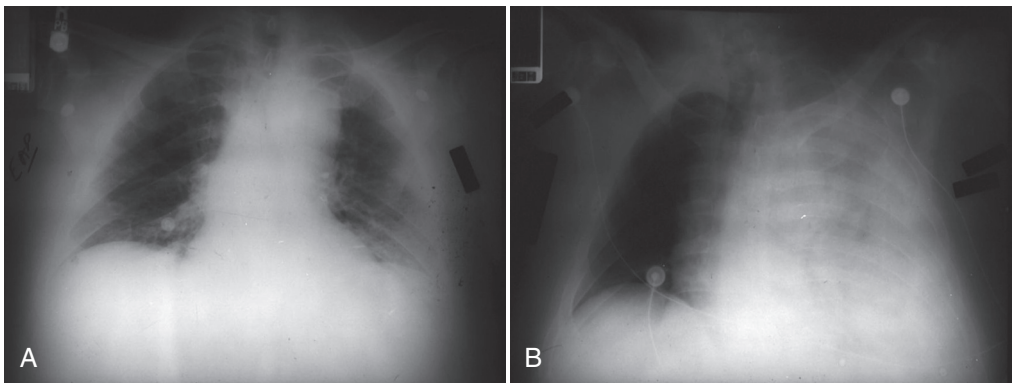
aortic dissection. In the presence of coarctation of the aorta, acute dissection typically occurs proximally rather than distal to the coarctation. The majority of patients with aortic dissection have hypertensive disease at the time of diagnosis.[11] Ascending aortic aneurysm is an independent risk factor for the development of aortic dissection. As the aortic diameter increases, the propensity for developing TAD increases. In patients without connective tissue disorder, a diameter above 5 cm is used as the surgical indication for elective ascending aortic repair. It is thought that blood pressure control decreases the occurrence of aortic dissection. However, hypertension is not thought to be the sole cause of dissection in a given patient. Many think that pregnancy is an independent risk factor for aortic dissection, although analysis of the available data and the conclusions from these data are hampered by the small number of patients affected and coexisting additional predisposing factors such as hypertension.[12–14] In addition to blunt trauma, TAD may be induced after establishing antegrade or retrograde arterial perfusion during cardiopulmonary bypass. Intraaortic balloon counterpulsation use may also trigger aortic dissection. There is increased risk of type A TAD after aortic valve replacement, especially with larger aortic diameters.[15] Finally, diagnostic angiography and cardiac catheterization may be complicated by aortic dissection (see Table 33.1).[15]

Pathophysiology

The aortic wall is composed of three layers: the innermost intima, the media (smooth muscle and elastic connective tissue), and the outermost adventitia. Hemodynamic stresses to the aortic inner walls can result from risk factors such as prolonged hypertension or inherently weakened connective tissue walls as seen in some connective tissue syndromes or a bicuspid aortic valve that alters the flow pattern of blood ejected out of the aorta. A dissection may be initiated by an intimal tear or ulceration with entry of blood into the medial layer facilitated by degeneration from normal aging or compounded by the risk factors listed in Table 33.1. A classic aortic dissection is classified by an intimal tear into the media of the aortic wall, resulting in separation of the medial layer and formation of a false channel, allowing blood to flow into this channel. An intramural hematoma (IMH) caused by rupture of the vasorum can also be the trigger for a dissection when an accumulation of blood separates the medial layers; in this circumstance, the inciting entrance tear is initially lacking. IMH can also occur if the is no distal exit tear in the media. In this situation blood is stagnant within the aortic wall with thrombosis leading to the hematoma. IMH can progress to an aortic dissection if the distal intimal layer ruptures and a true false channel forms.[16] IMH is more common in the elderly hypertensive patient's descending aorta. Aortic atheromatous plaque rupture or penetrating atheromatous ulcers can also disrupt the aortic wall and result in aortic IMH dissection.[17] Aortic rupture may occur in the setting of aortic dissection if the adventitia of the false lumen tears. This may cause extravasation of blood into the pericardium (tamponade), the chest (hemothorax), or retroperitoneum (Fig. 33.2).

Patients with aortic ulcers are older than those with IMH. TAD has been reported after heart transplation.[18] Inflammatory diseases of the aorta such as giant cell arteritis (large vessel or Behçet's disease vasculitis) may also lead to dissection.[19] Once aortic dissection has occurred, a true and false lumen are typically created. The false lumen of a TAD has the potential to extend both distally and proximally. There are usually fenestrations between the true and false lumen, and distal branch vessels may arise from either lumen. Frequently the false lumen can compress the ostium of the true lumen and cause malperfusion syndrome, depending on the distribution of the occluded vessel. Sequelae of malperfusion syndromes can include myocardial infarction, cerebral vascular accident, spinal cord ischemia (paralysis), renal or mesenteric infarct, or lower extremity ischemia (see Fig. 33.2).

Rupture is the most common cause of death during the early acute phase of TAD. The most frequent rupture route leading to death is into the pericardium causing tamponade. Compromise of arch vessels may lead to neurologic symptoms and injury. Death may also occur with involvement of the aortic root, producing primary ostial compromise and acute myocardial infarction or severe aortic regurgitation. Rarely, fistulas and high-degree heart block may be produced. The thin wall of any residual pseudoaneurysm after TAD tends to enlarge and over time is at high risk of rupture. Total thrombosis of the false lumen is rare, whereas distal reentry into the true lumen may help decompress the false lumen and increase the chance of survival. Postoperative false lumen patency is a predictor of late mortality.[20]



• **Fig. 33.2** Chest radiograph with a widened mediastinum (A) with subsequent rupture of the thoracic aortic aneurysm into the left pleural space (B).

Diagnosis

Symptoms

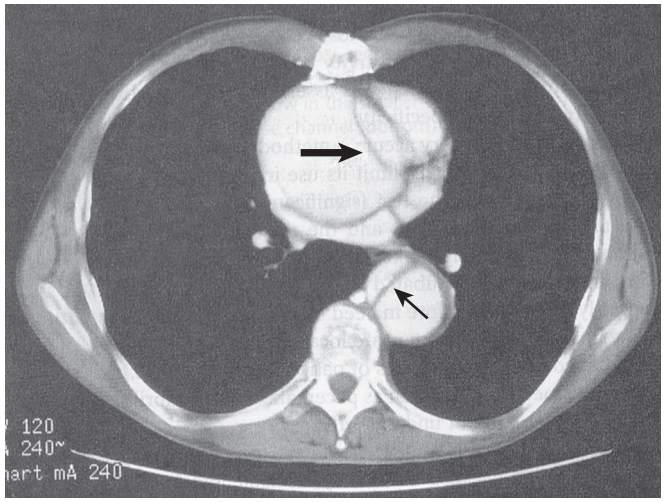
The diagnosis of acute TAD is complicated by the infrequent occurrence of this clinical condition as well as the diagnostic difficulty and is particularly problematic because of the potential catastrophic outcome.[21] Typical symptoms of TAD are excruciating, severe at onset, pain of a sharp and tearing nature. The location of the pain (anterior chest, neck, jaw, inner scapular, and lumbar/abdominal) is linked to the location of the dissection. Symptoms, other than pain, include visceral symptoms (vomiting, diaphoresis, and syncope). Chronicity is defined as presentation later than 2 weeks from the onset of symptoms.

Physical Examination

Although physical examination findings may be absent, if present, they are useful in directing the clinician's attention to this diagnosis.[21] Inequality of pulses in the upper extremity and a blood pressure differential of 20 to 30 mm Hg between the two extremities may be seen based on the location of the dissection. A new aortic regurgitation murmur occurs in a significant number of patients. Proximal dissection may also interfere with coronary artery blood flow. Most commonly the right coronary artery is affected and patients may present with an inferior myocardial infarct and evidence of ischemia in the inferior leads. Echocardiogram may demonstrate severe right ventricular failure. Rupture into the pericardium typically results in pericardial tamponade. Pericardial tamponade is supported by findings of jugular venous distention, muffled heart tones, tachycardia, and hypotension. Mass compression effects can produce findings such as superior vena cava syndrome, Horner syndrome, hoarseness, dyspnea, or dysphagia. Syncope is seen in 1 of 10 cases of TAD and likely results from cerebral malperfusion or hypotension secondary to cardiogenic shock or tamponade. Vasovagal pain response may also be a potential etiology of syncope. When syncope is related to hypovolemic shock from rupture through the adventitia into the pleural space, the prognosis is grave.

Laboratory Findings

Laboratory evaluation is usually not helpful in the diagnosis of acute aortic dissection. A meta-analysis demonstrated that cardiac troponin was elevated in 26.6% of acute aortic dissection (range 23%–33%) and was significantly associated with short-term mortality.[22] A normal D-dimer level combined with a low aortic dissection score (≤1) supports ruling out acute aortic dissection.[23]



• **Fig. 33.3** Computed tomographic angiogram demonstrating a thoracic aortic dissection. This Stanford type A dissection extends from the ascending aorta (*large arrow* pointing to the intimal flap) to the descending aorta (*smaller arrow* pointing to the intimal flap).

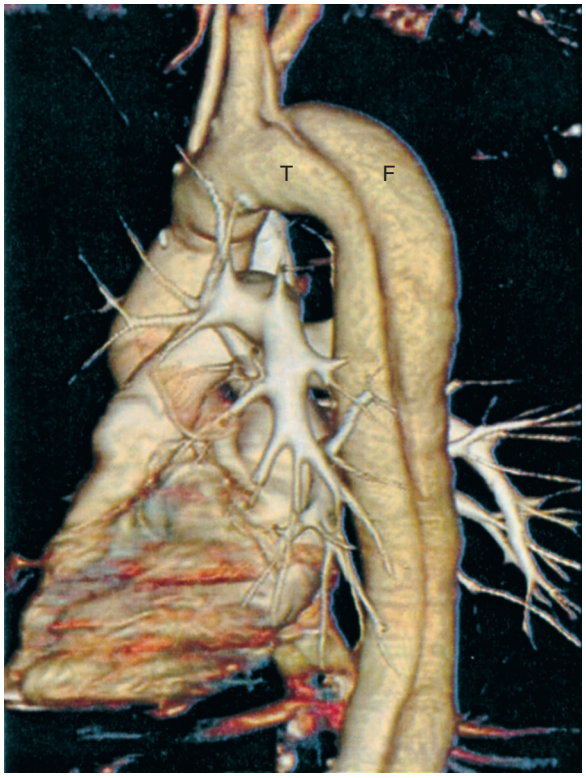
Imaging

Chest Radiograph

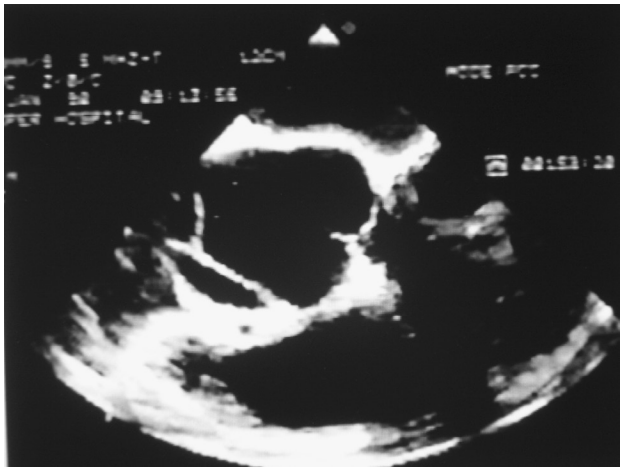
The great majority of patients with TAD have abnormalities on the chest radiograph. A normal chest radiograph may therefore help in decreasing the likelihood of aortic dissection. A study by Klompas looked at 1337 chest radiographs in patients with TAD and reported abnormalities in 90% of patients.[24] The most common changes associated with dissection are abnormal aortic contour, widening of the mediastinum, pleural effusion, displacement of intimal calcification, abnormalities of the aortic knob, and displacement of the trachea or nasogastric tube to the right. In the absence of an abnormal aortic contour or mediastinal widening, a diagnosis of dissection is less likely.

Computed Tomography

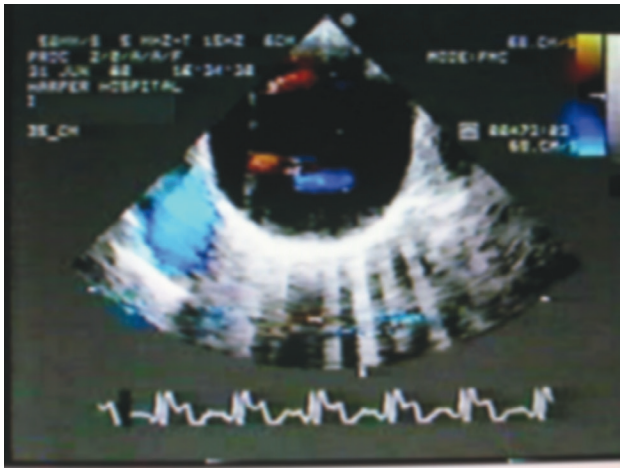
The most common diagnostic modality used for diagnosis of TAD is computed tomography (CT) (Fig. 33.3). A CT angiogram shows high sensitivity and specificity in diagnosis and exclusion of TAD.



• **Fig. 33.4** Volume-rendered enhanced image from computed tomographic angiography study showing true *(T)* and false *(F)* lumens in the descending thoracic aorta. (From Kapustin AJ, Litt HI. Diagnostic imaging for aortic dissection. *Semin Thorac Cardiovasc. Surg.* 2005;17:219–213.)



• **Fig. 33.5** Transesophageal echocardiogram image showing intimal flap in the ascending aorta extending to the aortic annulus. (Courtesy Priscilla Peters, Cooper University Hospital, Camden, NJ.)



• **Fig. 33.6** Image from a transesophageal echocardiogram revealing an intimal flap in the descending aorta. Color Doppler shows flow through two fenestrations in the flap. (Courtesy Priscilla Peters, Cooper University Hospital, Camden, NJ.)

It is the optimal imaging modality for ruling out aortic dissection in patients with low clinical pretest probability. Limitations of this technique include use of ionizing radiation and contrast media, the need for transfer to the imaging station, and limited ability to access the aortic valve. Advantages are ready availability, turnaround time, delineation of entire aorta, and diagnosis of other disorders causing the patient's symptoms. Advances in CT angiographic techniques—such as spiral multidetection scanner technology that allows volume-rendered, three-dimensional reconstruction of a CT angiogram—are likely superior to magnetic resonance images (Fig. 33.4 provides an example of the technology).

Echocardiography

Transthoracic echocardiography (TTE) should be performed early in the evaluation of any patient in whom the diagnosis of ascending aortic dissection is entertained. If a pericardial effusion is present, signs of tamponade can be identified. TTE can help identify aortic dissection if multiple views are obtained—specifically, suprasternal, subcostal, and right parasternal views. The intimal flap may be identified within the lumen with motion that is not synchronized with the surrounding structures. To minimize the chance of a false-positive result, the flap should be visualized in more than one view. The addition of color Doppler helps to identify flow artifacts (as opposed to an intimal flap) within the ascending aorta by demonstrating flow between the true and false channels at the site of an intimal tear and by showing a difference in the timing or direction of flow within the two lumens.[25] Color Doppler permits detection and quantification of aortic regurgitation. TTE is especially useful for diagnosing dissections involving the ascending aorta but is much less sensitive for descending dissections. If a dissection is not visualized in the patient with chest pain, finding regional wall motion abnormalities may suggest the alternative diagnosis of coronary ischemia.

Transthoracic echocardiography (TEE) (Fig. 33.5) can be performed safely on most critically ill patients in a monitored setting.[26,27] To avoid precipitating hypertension, tachycardia, or gagging (straining) in a patient with suspected dissection, conscious sedation should be administered. Nearly all of the thoracic aorta can be visualized, including most of the arch. The area from the distal ascending aorta to the midarch, however, is difficult to evaluate with TEE because of interposition of the airway between the esophagus and the aorta.[28] The sensitivity of TEE for TAD is close to 100%, but specificity is lower, owing primarily to reverberation artifacts that may be visualized within the ascending aorta, simulating an intimal flap.[29] Color flow Doppler with TEE may demonstrate flow through or on either side of the suspected intimal flap (Fig. 33.6). TEE is helpful for evaluating involvement of the coronary ostia and aortic valve. As with TTE, regional and overall

ventricular wall motion can be evaluated and the presence of pericardial effusion can be determined.

Aortography

Once the gold standard for diagnosis of TAD, aortography fell into disfavor as the diagnostic study of choice owing to its invasive nature and a relatively high false-negative rate.[30] The sensitivity of aortography is lower than that of CT, and its specificity is no better. Reliance on iodinated contrast does not ensure direct visualization of a thrombosed lumen or intramural hematoma, or occasionally even to confirm the presence of a second, false lumen.[31] Although it is not a first-line diagnostic technique, early aortography with endovascular stent graft intervention as a treatment for distal malperfusion syndrome in type B dissections has become more common. These interventions are directed at stenting across intimal tears to reduce false lumen flow, stenting open an occluded true lumen, fenestration of intimal flaps, and opening occluded branch vessels.[32,33]

Magnetic Resonance Imaging

The most reliable diagnostic finding with magnetic resonance imaging (MRI) is demonstration of two lumens separated by an intimal flap. Gadolinium-enhanced magnetic resonance angiography allows the visualization of blood flow, which can be used to detect the presence and magnitude of aortic regurgitation or to demonstrate communication between the true and false lumens at the site of an intimal tear. An intimal flap can be identified in most cases, except when the false lumen is completely thrombosed. The diagnostic accuracy of MRI for aortic dissection approaches 100%.[34] Problems with MRI include (1) that it cannot be performed in patients with pacemakers or defibrillators, aneurysm clips, or ferrous metal implants; (2) claustrophobia; and (3) life support equipment (ventilators, monitors, intravenous [IV] infusion pumps) with associated logistical issues. Image acquisition, despite advances in the technology, is more time-consuming than with CT. Because it entails no radiation exposure, MRI may be an appropriate initial study in the stable patient[29] and for long-term follow-up evaluation.[29,35]

Summary

Table 33.1 shows a comparison of diagnostic imaging modalities for evaluation of TAD. The 2010 American Heart Association guidelines for diagnosis of dissection give a Class I recommendation for using urgent TEE, MRI, or CT angiogram to determine a definitive diagnosis in patients with high clinical suspicion.[36] If the initial diagnostic test result is negative in patients with high clinical suspicion, a second imaging modality should be completed. Fig. 33.7 shows the diagnosis algorithm from the 2010 guidelines for the diagnosis and management of TAD.

Perioperative Management

General Principles

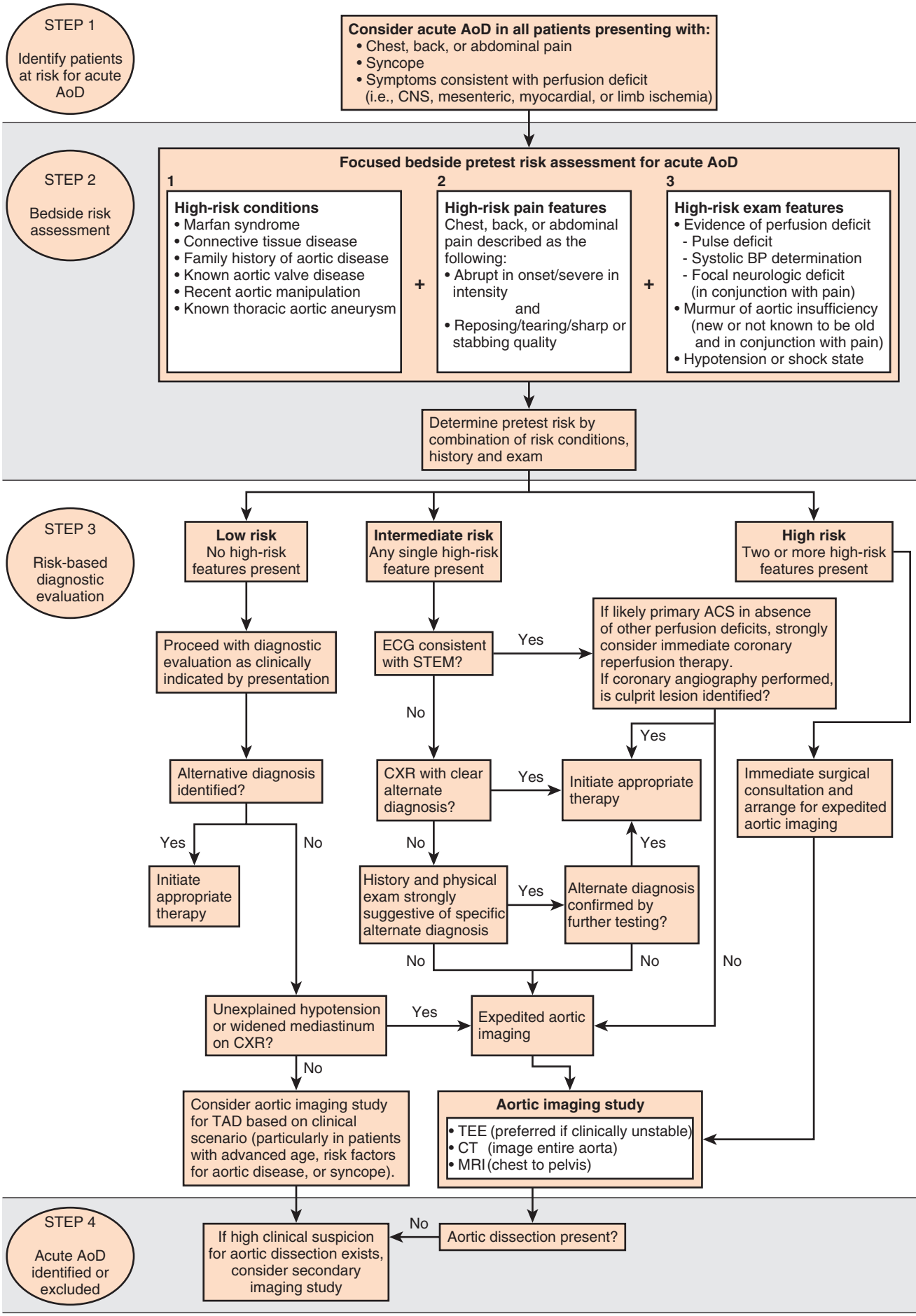
Medical therapy is critical for survival with both type A and type B TAD.[37–40] Immediate initiation of medical therapy is imperative, both before surgical intervention for type A TAD and as definitive therapy for patients with type B TAD that is uncomplicated. The primary objectives of therapy are rapidly normalizing arterial blood pressure in hypertensive patients and reducing the force of left ventricular contractility in all patients. Following admission to the intensive care unit, vital signs are monitored continually; blood pressure should be compared between upper extremities, and the same for carotid pulses. Arterial line insertion is indicated. A radial arterial line on the side of higher blood pressure or a femoral arterial line is placed. For type B dissection, a right radial arterial line is preferred. IV drugs are indicated for medical therapy. To limit shear force, which is propagating the dissection, it is important to control the rapidity of the rise of the systole, which is done by avoiding tachycardia (goal heart rate is 60–75 beats/min), depressing contractility, and decreasing blood pressure. Because blood pressure is maintained at low normal, a Foley catheter is recommended to judge adequate tissue perfusion. Pain is a marker of continued dissection of a TAD, and subsiding of pain can be assumed to be a marker of halting of dissection. Medical therapy is the treatment of choice for uncomplicated type B TAD. It may also be successfully used in patients who are poor surgical candidates or in select patients who have been diagnosed with subacute dissections who are awaiting surgical intervention.

The mortality of nonoperative management of type A dissection may be up to 1% to 2% per hour in the early phase after symptom onset.[41] The goals of medical management should be stabilization, management of hypertension, and evaluation of neurologic and metabolic function while the operating room is being prepared for the patient. Most centers favor transport directly to the operating room after the surgical team has been mobilized to avoid any delay that would increase mortality. Exceptions to this rule are patients who may present with severe malperfusion that may preclude operative intervention (severe cerebral or visceral ischemia). These exceptions need to be thoroughly evaluated with CT scan and neurologic consultation if central nervous system issues are present. In patients presenting with severe acidosis and elevated lactate levels, CT scan of the abdomen to evaluate for bowel infarction, which if present may make the patient inoperable, is indicated.

Initial postoperative management is heralded by the need to prevent hypertension. Because of multiple suture lines used during the reconstruction, hypertension can result in excessive postoperative bleeding from the mediastinum or cause aortic suture lines to disrupt. Most patients have hypertrophic ventricles from long-standing hypertension, and control of blood pressure in the initial postoperative period can be difficult and requires IV vasodilators, β-blockers, or calcium channel blockers. Lifelong control of hypertension will be required. Most patients who undergo type A dissection repair have evidence of residual dissection within the arch and descending aorta and a 15% risk for progressive aneurysmal dilatation. Many patients have a history of malignant or refractory hypertension and will require multiple oral agents in the outpatient setting to keep them normotensive. Blood pressure control over time is important to reduce the incidence of late false channel aneurysm development and decreases the risk of rupture. Periodic evaluation of the status of the aorta over time after successful therapeutic intervention is needed and is typically done with CT scan. After repair of a type A dissection, Signs of persistent back pain, new left pleural effusion, or organ hypoperfusion may indicate that the residual type B dissection is unstable and that the patient may require a second endovascular procedure to stabilize the residual descending aorta.

Specific Medications

Control of blood pressure and heart rate in the presence of TAD is essential.[42] IV β-blockers are the first line of therapy for aortic dissection and are immediately initiated to avoid tachycardia, which may occur with some medications chosen to lower blood pressure.[43] β-Blockers, in addition to controlling heart rate, also depress


STEP 1
Identify patients at risk for acute AoD
Consider acute AoD in all patients presenting with:
• Chest, back, or abdominal pain
• Syncope
• Symptoms consistent with perfusion deficit (i.e., CNS, mesenteric, myocardial, or limb ischemia)
STEP 2
Bedside risk assessment
Focused bedside pretest risk assessment for acute AoD
1
High-risk conditions
• Marfan syndrome
• Connective tissue disease
• Family history of aortic disease
• Known aortic valve disease
• Recent aortic manipulation
• Known thoracic aortic aneurysm
+
2
High-risk pain features
Chest, back, or abdominal pain described as the following:
• Abrupt in onset/severe in intensity
and
• Reposing/tearing/sharp or stabbing quality
+
3
High-risk exam features
• Evidence of perfusion deficit
- Pulse deficit
- Systolic BP determination
- Focal neurologic deficit (in conjunction with pain)
• Murmur of aortic insufficiency (new or not known to be old and in conjunction with pain)
• Hypotension or shock state
Determine pretest risk by combination of risk conditions, history and exam
STEP 3
Risk-based diagnostic evaluation
Low risk
No high-risk features present
Intermediate risk
Any single high-risk feature present
High risk
Two or more high-risk features present
Proceed with diagnostic evaluation as clinically indicated by presentation
ECG consistent with STEM?
Yes
If likely primary ACS in absence of other perfusion deficits, strongly consider immediate coronary reperfusion therapy.
If coronary angiography performed, is culprit lesion identified?
No
Yes
Alternative diagnosis identified?
CXR with clear alternate diagnosis?
Yes
Initiate appropriate therapy
Immediate surgical consultation and arrange for expedited aortic imaging
Yes
No
No
Yes
Initiate appropriate therapy
History and physical exam strongly suggestive of specific alternate diagnosis
Yes
Alternate diagnosis confirmed by further testing?
No
No
No
Unexplained hypotension or widened mediastinum on CXR?
Yes
Expedited aortic imaging
No
Consider aortic imaging study for TAD based on clinical scenario (particularly in patients with advanced age, risk factors for aortic disease, or syncope).
Aortic imaging study
• TEE (preferred if clinically unstable)
• CT (image entire aorta)
• MRI (chest to pelvis)
STEP 4
Acute AoD identified or excluded
If high clinical suspicion for aortic dissection exists, consider secondary imaging study
No
Aortic dissection present?

• **Fig. 33.7** Algorithmic flow diagram approach to diagnosis or exclusion of aortic dissection. *ACS,* Acute coronary syndrome; *AoD,* aortic dissection; *BP,* blood pressure; *CNS,* central nervous system; *CT,* computed tomography; *CXR,* chest x-ray; *ECG,* electrocardiogram; *MRI,* magnetic resonance imaging; *TAD,* thoracic aortic dissection; *TEE,* transesophageal echocardiography; *STEM,* ST segment elevation myocardial infarction. (Modified with permission from Hiratka LF, Bakris, GL, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic dissection. *Circulation.* 2010;121:e266–e369.)

contractility and lower blood pressure, both goals of therapy. IV esmolol is the ideal drug as it is a quick-onset and short-acting agent and can be titrated to effect. IV diltiazem is an alternative to esmolol for decreasing contractility and avoiding tachycardia when there are contraindications to the use of β-blockers, such as in the active asthmatic. This target blood pressure will then be anticipated to persist for 6 to 8 hours.

Nitroprusside is the vasodilator of choice for blood pressure control and is begun after the initiation of esmolol when blood pressure lowering is required. Nitroprusside acts by decreasing both preload and afterload. Because it may be associated with reflex tachycardia, it is added only after a β-blockade is in place. Tachycardia should always be avoided in the presence of aortic dissection. Labetalol is an alternative choice to esmolol plus nitroprusside and is given as a loading dose of 10- to 40-mg boluses (based on degree of blood pressure response) every 10 to 15 minutes until target blood pressure is reached or 300 mg is delivered. Duration of action for IV labetalol is approximately 4 hours. Table 32.1 reviews drugs used in the medical therapy of acute TAD.

Operative Approach

Ascending Aortic Dissections

Surgical intervention is indicated in all patients with proximal dissections, with the exception of patients with serious concomitant conditions that preclude surgery.[44] Stroke is the most common contraindication to surgery because there is real concern that anticoagulation (cardiopulmonary bypass) as well as reperfusion can result in further neurologic deterioration by converting the ischemic stroke to a hemorrhagic stroke. Every attempt must be made to perform a careful neurologic assessment before undertaking surgical intervention. Additional evidence of severe malperfusion (bowel ischemia) is also a contraindication to surgery. In certain instances inoperable patients may be managed with a stent graft to the ascending aorta via retrograde approach or transapical approach.[45]

Preoperative evaluation is essential to assess for the presence of aortic regurgitation, pericardial effusion, the extension of the dissection into the major aortic branches, and the localization of entry and reentry sites. CT angiography helps to delineate visceral and renal vessel involvement and end-organ perfusion. The presence of thrombosis in the false lumen yields information that can be helpful in planning the surgical approach.[46]

The operative mortality rate for patients with aortic dissections ranges from 5% to 10% and may approach 70% in cases with complications. The independent predictors of operative mortality include the presence of cardiac tamponade, the site of the tear, the time to operation, the presence of renal/visceral ischemia, renal dysfunction, and the presence of pulmonary disease.[47]

Once the diagnosis of ascending aortic dissection is made, cardiac surgical consultation should be obtained and the patient transported directly to the operating room. There is no indication for preoperative cardiac catheterization. Not infrequently patients present with inferior cardiac ischemic changes (electrocardiogram leads II, III, aVF). Proximal disruption of the right sinus of Valsalva is very common and can result in right main coronary malperfusion. This also becomes evident as right ventricular failure or inferior wall ischemia and is identified on intraoperative TEE. Left main coronary malperfusion is almost uniformly fatal and is infrequently encountered.

Intraoperatively general anesthesia is induced. If cardiac tamponade is suspected, care must be taken to avoid cardiovascular collapse secondary to a loss of adequate preload when general anesthesia is induced. A TEE probe is then placed and a careful examination is performed. This should include evaluation of right and left ventricular function; extent of the intimal dissection from the sinus of Valsalva to the descending aorta; evaluation of aortic, mitral, and tricuspid valve function; and presence of a pericardial effusion.

Intraoperative planning should involve focus on two key elements: (1) restoration of competent aortic valvular function and (2) resection and reconstruction of all areas of disease in the ascending aorta.

Standard techniques for surgical reconstruction involve cardiopulmonary bypass with circulatory arrest. Arterial cannulation is performed in the femoral artery, innominate artery, or axillary artery. Venous cannulation is usually performed in the right atrium, and cardiopulmonary bypass is then initiated. A cross clamp is then applied across the ascending aorta, and the heart is arrested with retrograde cardioplegia. During this time the patient is then cooled for a period of circulatory arrest. During the cooling period, the ascending aorta is resected down to the sinotubular junction and the extent of dissection is evaluated.

At this time the aortic valve is evaluated for leaflet pathology, and the sinus of Valsalva must be inspected to determine if this is the origin of the initial intimal tear. The right coronary ostium can frequently be disrupted from the intimal dissection, and if it cannot be reconstructed, coronary artery bypass grafting must be undertaken to prevent ischemia and myocardial infarction.

If there is no primary tear site in the sinus of Valsalva, most surgeons favor reconstruction of the aortic root with glue aortoplasty and valve resuspension.[48] Indications for performing a full aortic root replacement with a valved conduit and a left and right coronary artery reimplantation (Bentall operation) include a tear through the sinus of Valsalva or an aortic valve that cannot be reconstructed. This can be performed with a mechanical valved conduit, pericardial conduit, or porcine heterograft.[48–52] Valve-sparing aortic root replacement may be also performed in patients who have a long life expectancy. This complex procedure requires resection of all aorta distal to the annulus, creation of neosinuses, and coronary artery reimplantation with reconstitution of aortic lumen continuity.[53]

Reconstruction of the distal aortic arch is performed during circulatory arrest with the patient cooled to 15°C to 25°C. Cerebral

perfusion is often maintained during the circulatory arrest period and may be accomplished either antegrade (flow maintained in the axillary or innominate artery) or retrograde (flow through the superior vena cava). Current surgical practice favors the use of the antegrade techniques, as they improve cerebral oxygenation and increase the length that circulatory arrest can safely be performed without neurologic or systemic sequelae.

The distal aortic arch is frequently reconstructed with a glue aortoplasty (such as a hemiarch) or a total arch reconstruction with branch graft reconstruction if there is severe disruption at the level of the cerebral vasculature.

In addition, stent grafting of the distal thoracic aorta may be performed in an antegrade fashion during a period of circulatory arrest (stented elephant trunk technique). This may stabilize the distal aorta, prevent future aneurysmal dilation, or facilitate a proximal endovascular landing zone for future endovascular therapy should that become necessary.[54]

After reconstruction of the aortic arch, a Dacron graft is sewn to the distal arch and full cardiopulmonary bypass is reinitiated. The Dacron graft is then anastomosed to the sinus of Valsalva (or valve conduit), thus restoring continuity from the heart to the aortic arch. The patient is then rewarmed and weaned from cardiopulmonary bypass.

Descending Aortic Dissection and Endovascular Therapy

Uncomplicated acute type B dissection is best managed medically. Approximately 15% of patients with this type of dissection develop aneurysmal degeneration and require surgical intervention within 5 years of the initial event. The indications for performing early surgery in patients with distal dissections are the rapid expansion of a dissecting aneurysm, rupture into the left chest, impending rupture, persistent and uncontrollable pain, or impairment of the blood flow to an organ or limb.[44,55–57] Open surgical repair carries extremely high morbidity and mortality, and endovascular stent grafting is the currently favored approach for the acute treatment of malperfusion.[58,59]

Organ malperfusion and ischemia in patients with aortic dissections are caused by encroachment on the aortic lumen (true) that provides the blood supply to a branch vessel. The lumen supplying blood to the branch vessel may be the true lumen or the false lumen. A stent is deployed through the percutaneous approach within the lumen supplying the branch vessel to hold the lumen open by displacing the intimal flap toward and overcoming the pressure from the other lumen. To overcome the high pressures in the other lumen, a balloon fenestration procedure may be combined with the stent procedure.

The clinical success of endovascular stent placement for aortic dissection ranges from 76% to 100% with a reported 30-day mortality rate of up to 25%.[59–64] Data on the long-term follow-up of these patients are scarce.

The goals of treatment are coverage of the primary tear site, exclusion of the false lumen, restoration of blood flow to the true lumen, and restoration of organ perfusion and limb perfusion. Covered thoracic stent grafts are usually deployed from the left subclavian artery to the middle descending aorta. If the initial tear site begins at the origin of the subclavian artery, the proximal landing zone is advanced across the subclavian artery to the left common carotid. If there is evidence of a dominant vertebral system on CT scan, or clinical concern for left arm ischemia, a subclavian to carotid bypass graft can be performed via a separate neck incision. The use of intravascular ultrasound has also gained favor to ascertain that the graft is deployed correctly in the true lumen of the dissection.

About 13% of patients with aortic dissections receive stent-graft treatment and this proportion is steadily increasing. With more data available and more advancement in operator expertise, stent graft placement may, in the future, become the standard treatment for most cases of distal aortic dissection, because waiting for the complications to occur may not be prudent given that the operative mortality rate in these situations approaches 70%.[62]

Treatment of Aortic Intramural Hematoma and Atherosclerotic Aortic Ulcer

The treatment of patients with both aortic intramural hematomas and atherosclerotic aortic ulcers is similar to that for patients with classic aortic dissections and depends on the aortic site involved. Both aortic IMH and atherosclerotic aortic ulcer are more common in the descending aorta and therefore are treated with aggressive medical therapy. Medical therapy should consist of the optimal control of blood pressure, a maximum rate of aorta pressure rise over time (dp/dt max or "shearing force"), as well as close long-term follow-up. Surgery is preferred for the treatment of patients with intramural hematomas and atherosclerotic aortic ulcers in the ascending aorta and aortic arch, and for patients with progressive dilatation and aneurysm formation of the aorta, irrespective of the site of involvement.[65–69] In a meta-analysis of 143 patients with aortic intramural hematomas, of whom 30 patients (21%) died, 20 deaths (67%) were due to aortic dissection or rupture.[70]

Interest has also grown in the use of endovascular treatment of type A aortic dissection with short segment stent grafting in high-risk nonoperable patients.[71] Use of short segment grafts to cover an ascending tear is possible if the dissection is limited to the aorta just above the sinotubular junction and there is no associated valvular compromise. Placement may be performed retrograde or antegrade through the apex of the left ventricle.

Outcomes and Prognosis

The rationale for surgical treatment of acute type A TAD is universally recognized. Patients with acute ascending aortic dissection treated medically fare far worse than those with dissection involving the descending aorta. Little controversy exists over the treatment of choice for the acute type B variety. For most patients, unless life- or limb-threatening vascular compromise is present, medical therapy is considered superior to surgical treatment.[72,73] If a complication such as rupture necessitating emergency surgery arises, however, the mortality rate is very high. Fortunately, this occurs infrequently. If operation is required for type B TAD within the first 2 weeks, mortality remains high.[74] Analysis of all early postoperative complications shows a much lower stroke rate for descending aorta repairs compared with repair of ascending dissections, although the incidence of pulmonary complications and spinal cord injury is higher.

Summary

Aortic dissection is caused by a tear in the intima of the aorta that is propagated by the aortic pulse wave. The aortic pulse wave, or "shearing force," depends on a combination of myocardial contractility, heart rate, and blood pressure. The risk factors for aortic dissection include advanced atherosclerosis, connective tissue diseases, and aortic coarctation. Dissections involving the area proximal to the left subclavian artery are considered to be type A, and when this area is not involved they are considered to be type B (involving the descending aorta only). Chest pain is the typical presenting symptom, and the classic chest radiographic finding is a widened mediastinum. Diagnosis is best made either with a contrast-enhanced CT scan or TEE. Dissection is usually diagnosed using CT scanning with and without contrast enhancement, which demonstrates a gray-white false lumen predominantly filled with a clot alongside a bright white, dye-filled true aortic channel. Dissecting thoracic aortic aneurysms involving the arch and descending aorta that do not interfere with major vessel outflow are typically managed medically with blood pressure control. Aneurysms involving the ascending aorta are typically surgically treated. Aneurysms of the ascending aorta may dissect proximally, producing a murmur of aortic insufficiency or acute pericardial tamponade. Distal migration may produce an obstruction of the major vascular outflow vessels or a rupture into the thorax. Occasionally, a leak may occur into the thorax, which on occasion is diagnosed in time to allow lifesaving surgery. The propagating force for a dissection is the change in pulse over the change in time or the maximum shearing force. This shearing force is minimized by a combination therapy of keeping the pulse in the low normal range, normalizing blood pressure, and decreasing inotropy. Dissection of the aorta is a hypertensive emergency in which normalization of blood pressure is indicated.

Key Points

- Men are at greater risk for developing TAD than are women; approximately two-thirds of patients with TAD are male.
- There is an increased risk of type A TAD after aortic valve replacement, especially with larger aortic diameters.
- Rupture is the most common cause of death during the early acute phase of TAD.
- The most common diagnostic modality used to diagnose TAD is CT.
- Advances in CT angiographic techniques—such as spiral multidetection scanner technology that allows volume-rendered, three-dimensional reconstruction of the CT angiogram—are likely superior to magnetic resonance images.
- The primary objectives of therapy are rapidly normalizing arterial blood pressure in hypertensive patients and reducing the force of left ventricular contractility in all patients.
- Once the diagnosis of ascending aortic dissection is made, cardiac surgical consultation should be obtained and the patient should be transported directly to the operating room.
- If cardiac tamponade is suspected, care must be taken to avoid cardiovascular collapse secondary to a loss of adequate preload when general anesthesia is induced.
- If there is no primary tear site in the sinus of Valsalva, most surgeons favor reconstruction of the aortic root with glue aortoplasty and valve resuspension.

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Review Questions

1. Which one of the following is *most correct* concerning acute aortic dissection?

a. Dissections of the descending aorta mandate surgical treatment.

b. In the presence of hypertension, blood pressure lowering should be targeted for a 15% reduction.

c. Pain is considered a marker for ongoing dissection.

d. Compression of aortic valvular ring may produce a murmur of aortic stenosis.

Answer: c. Unless a descending aortic dissection compromises a vessel coming off of the aorta, surgery is typically not indicated and medical management (blood pressure control) is the sole therapy. Normalization of the blood pressure is indicated. Pain implies continued dissection with wall separation. Proximal dissection into the aortic ring may lead to aortic insufficiency, not aortic stenosis.

2. Which one of the following antihypertensive regimens would be most appropriate for normalizing blood pressure in the presence of an aortic dissection?

a. Intravenous hydralazine

b. Intravenous esmolol and intravenous nitroglycerin

c. Oral clonidine

d. Intravenous esmolol and intravenous nitroprusside

Answer: d. The approach to blood pressure management with an aortic dissection is to rapidly normalize blood pressure while controlling rate to avoid tachycardia and bradycardia. An intravenous β-blocker (initiated first) plus a balanced vasodilator is the preferred regimen. Nitroprusside is a balanced vasodilator and has a rapid onset and offset of action.

3. Which one of the following is the preferred diagnostic method for acute thoracic aortic dissection?

a. Computed tomographic angiogram

b. Magnetic resonance angiography (MRA)

c. Aortography

d. Transthoracic echocardiography

Answer: a. Volume-rendered, three-dimensional reconstruction-capable computed tomographic angiography is the preferred initial diagnostic test for aortic dissection showing high sensitivity and specificity. Aortography is less desirable because of its invasiveness and false-negative rate. Diagnostic accuracy of MRA is high, approaching 100% in technically adequate studies. MRA is handicapped by exclusions for study such as pacemakers, metal implants, and supportive devices. Transthoracic echocardiography is an important diagnostic test to look for pericardial effusion (proximal dissection), aortic insufficiency, or compromise of coronary artery blood flow as complications of dissection but not for diagnosis itself. Transesophageal echocardiography is highly diagnostic for ascending aorta dissections.

34

General Principles of Postoperative Intensive Care Unit Care

DAMON H. CLARK AND HEIDI L. FRANKEL

CHAPTER OUTLINE

General Principles
- Admission Criteria
- Discharge Criteria
- Structure and Staffing of Surgical Intensive Care Unit
- Intraoperative History

Best Practices: General Postoperative Care
- Pain, Agitation, and Delirium
- Recovery From General Anesthesia
- Mechanical Ventilation
- Ventilator Liberation
- Ambulation
- Prophylaxis
- Nutrition
- Glucose
- Drains

Surgical Complications
- Hemorrhage
- Anastomotic Leak
- Abdominal Compartment Syndrome
- Necrotizing Soft Tissue Infection/Wound Complications
- Pulmonary Embolism
- Acute Coronary Syndrome
- Acute Kidney Insufficiency
- Chronic Critical Illness

Specific Surgical Specialty Operations
- Noncardiac Thoracic Surgery Care
- Vascular Surgery
- Abdominal Surgery
- Abdominal Organ Transplantation
- Trauma

General Principles

Admission Criteria

A predictable number of patients (15%) undergoing elective, urgent, or emergent surgical procedures can be expected to require care in an intensive care unit (ICU).[1] ICU beds should be reserved for patients with a reversible condition and reasonable prospect of substantial recovery and admission criteria should reflect this principle.[2] Established procedures, clinical judgment, and recognition of local resources and limitations should guide development and use of ICU admission criteria.[3,4]

Admission to an ICU is a decision that can be made by the surgeon and anesthesiologist in the preoperative phase in patients undergoing elective surgery. Elderly patients and/or those with significant comorbidities may require ICU admission for postoperative monitoring and care. The type of surgical procedure and the anticipated duration of surgery may also lead to a preoperative plan of ICU admission in the postoperative period. Patients undergoing liver transplantation or open abdominal aortic aneurysm repair, for example, traditionally require planned ICU admission for access to physicians and/or advanced care providers and bedside nurses unencumbered by other responsibilities. However, other patients may merely require more intensive bedside nursing that cannot be provided on a typical surgical ward. For example, this might include vascular surgery patients after distal arterial bypass for frequent neurovascular checks. In some settings, step-down units or extended-stay postanesthesia care units might be the appropriate setting to provide this care.

Patients, particularly after emergent operations, with unanticipated intraoperative complications, such as significant hemorrhage, shock, and respiratory failure, may also require ICU admission. Significant intraoperative hemorrhage may require ongoing blood product resuscitation and frequent analysis of complete blood cell counts, clotting factors, and lactic acid levels to monitor for continued hemorrhage. Patients in whom intraoperative shock develops require determination of etiology to guide therapy. Those with acute respiratory failure and/or inability to liberate from mechanical ventilation generally require ICU admission. These patients warrant examination and evaluation of radiologic data to evaluate for pneumothorax, hemothorax, lobe collapse, and/or malposition of the endotracheal tube. Obtaining an arterial blood gas (ABG) sample to determine hypercapnic versus hypoxic respiratory failure will afford appropriate ventilator adjustments. Measuring

intraabdominal compartment pressure and monitoring ventilator peak airway pressure may be key to evaluating those at risk for abdominal compartment syndrome.

Discharge Criteria

Patients admitted to ICUs should have constant evaluation and review of their clinical status to determine when such care is no longer necessary or beneficial. ICUs may benefit from a baseline set of objective criteria that can be used as a guide to determine which patients are ready for transfer (Table 34.1). These guidelines should be developed in concert with downstream units in consideration of available resources, particularly regarding nursing capability. Further, those who are deemed to no longer benefit from ICU care because of a deterioration in clinical status can also transfer.[3]

TABLE 34.1 Intensive Care Unit Discharge Criteria

Respiratory	
Stable oxygen requirement for 24 h (unchanged or improved)	Y/N
Acceptable ABG (or patient's baseline ABG)	Y/N
Adequate work of breathing	Y/N
On chronic but stable ventilator settings without need for frequent changes	Y/N
Sepsis	
Hemodynamic/respiratory system stable with fluid resuscitation completed	Y/N
Vasoactive infusions off (excluding a single (1) fixed-dose vasopressor)	Y/N
No evidence of end-organ hypoperfusion (lactate ≤2.5 mmol/L)	Y/N
Cardiovascular	
No ECG/cardiac enzyme evidence of active ischemia	Y/N
Stable hemodynamics with no chest pain	Y/N
Gastrointestinal	
No evidence of active GI bleed with hemostasis achieved and stable hemoglobin for 24 h	Y/N
Endocrine	
DKA resolved with: 1. HCO_3^- ≥18 mg/dL for two consecutive electrolyte panels at least 4 h apart 2. No evidence of anion gap acidosis 3. Blood glucose levels stabilized without insulin drip 4. Not requiring frequent electrolyte replacement	Y/N
Diabetes insipidus being managed with PO intake alone?	Y/N
Electrolytes normalized	Y/N
Neurologic	
Resolving neurologic status requiring less frequent neuro checks (≥every 4 h)	Y/N
No evidence of new focal deficit	Y/N
Surgical	
PACU recovery complete?	Y/N
Meets above criteria and fluid, respiratory, cardiac, and bleeding risks resolved, not requiring intense monitoring/intervention	Y/N

ABG, Arterial blood gases; *DKA*, diabetic ketoacidosis; *ECG*, electrocardiogram; *GI*, gastrointestinal; *HCO_3^-*, bicarbonate; *PACU*, postanesthesia care unit; *PO*, oral; *N*, no; *Y*, yes.

Structure and Staffing of Surgical ICU

Structure

ICUs are currently structured to have a designated geographic location in the hospital, specialized monitoring devices, and advanced therapeutic capabilities. Surgical ICUs (SICUs) can be general and admit patients from all surgical subspecialties, or they may be superspecialized (trauma, transplant, and cardiac). There are no compelling data to support the superiority of superspecialized surgical ICUs over general ones.

The basic ICU organizational structure of an open versus closed format is particularly germane in the care of a surgical patient. In an open ICU format the primary surgeon is responsible for patient care, order entry, and family communication. In a closed ICU format the patient's care is transferred to an intensivist who cares only for patients admitted to the ICU. There has been evidence that shows the benefit of decreased mortality and morbidity in the closed ICU format.[5,6] This would be particularly true in settings where a busy operative surgeon would have great difficulty responding rapidly to a patient with an emergency in the ICU. On the other hand, most surgical ICU patients are admitted in an elective fashion, so the ICU team should be fully cognizant of surgeon preferences, care paradigms, and desire for communication. In practicality, even in fully closed ICUs, the operative surgeon must be notified of patient status as recognition of and therapy for specific issues might require further surgery.

Whether in an open, closed, or hybrid ICU, a multidisciplinary team approach led by an intensivist is best practice to care for the critically ill patient. This team includes the critical care physician, nurse, registered dietician, pharmacy, physical therapist, respiratory therapist, and social worker. Multidisciplinary ICU teams optimally use extensively researched evidence-based guidelines to develop institutional protocols and guidelines. For example, guidelines for the management of sepsis, ventilator management, sedation, nutrition, and bedside ultrasound have improved patient outcomes and care.[7,8] Additionally, SICU teams benefit from the use of checklists and bundles of care. Checklists ensure that important aspects of critically ill patients care are addressed daily. Use of checklists to review daily goals dramatically improves understanding of the plan and may decrease the ICU length of stay.[9] Bundling evidence-based care practices in a more easily remembered format allows ICU teams to provide and keep up with the most up-to-date critical care practices. Bundles addressing ventilator-associated events, central line bloodstream infections, catheter-associated urinary tract infections, pressure ulcer prevention, and sepsis management have been shown to improve patient outcomes.[10]

Staff

The ICU provides close monitoring and care of patients by experienced physicians, nurses, respiratory therapists, dieticians, pharmacists, social workers, and other ancillary staff. The appropriate intensivist/patient ratio should be 1 intensivist to 14 patients to complete rounds in a timely fashion and provide high-quality patient care and education of trainees.[11] ICU nurse/patient ratios range from 1:3 to 2:1, depending on the complexity of the patients and interventions they require such as extracorporeal membrane oxygenation, continuous renal replacement therapy, and prone positioning. Nurse practitioners, physician assistants, dieticians, pharmacists, respiratory therapists, and physical therapists dedicated to the ICU improve compliance with evidence-based care and patient outcomes.[12–15]

Ideally, the ICU should be covered 24/7 with an attending intensivist. Several studies show that a 24/7 intensivist model improves morbidity and resource utilization but does not improve mortality.[16,17] This is particularly true in academic institutions with fellow coverage. Community and nonacademic ICUs may see a decrease in mortality with a 24/7 staffing model.

Intraoperative History

Efficient and effective communication among the surgeon, anesthesiologist, and intensivist should occur routinely after surgery. Studies have shown that postoperative handovers are typically informal, brief, and often incomplete.[18] Incomplete transfer of patient information between the teams can lead to medical errors and patient harm.[19] Using standardized checklists for patient handover from the operating room (OR) to the ICU improves quantity and quality of transmitted medical information[20] (Fig. 34.1).

During the transfer of the patient from the OR and/or postanesthesia care unit, a detailed sign-out to the ICU physician, nurse, and respiratory therapist should be conducted. This should commence with a discussion of the patient's past medical/surgical history, medications, allergies, and comorbidities. A detailed description of the surgical procedure, patient positioning, unexpected events, and anticipated course should occur. The patient's airway (standard vs. difficult requiring advanced intubation techniques), type of endotracheal tube used and/or currently in place, and the intraoperative mechanical ventilation settings, unexpected ventilator changes, ABG results, and patient current oxygenation requirement should be conveyed to the ICU team. The patient's estimated blood loss, quantity of intravenous fluid, number of blood products transfused, vasopressor use, and urine output should be strictly recorded and discussed with the ICU team. The insertion of invasive monitoring/resuscitation lines, transesophageal echocardiography, urinary catheter, enteric tubes, and postsurgical drains should be communicated to the ICU team. Intraoperative and postoperative medications, including antibiotics, analgesia, antiemetics, steroids, and the patient's home medications, require acknowledgment.

Certain preoperative medications should be continued in the perioperative period. Glucocorticoids should be administered at the traditional preoperative dose, without a need for superphysiologic "stress" dosing.[21] The use of unnecessary high-dose glucocorticoids can lead to hyperglycemia, increased risk of infection, and wound complications. Patients taking β-blockers should continue their preoperative regimen in the postoperative period if hemodynamically stable.[22] Other antihypertension medications such as calcium channel blockers, diuretics, and angiotensin-converting enzyme inhibitors should be held until the patient is observed to be hemodynamically stable postoperatively. Antiseizure medications, bronchodilators, and thyroid replacement therapy should be given preoperatively and continued in the postoperative period. Long-acting hyperglycemia medications such as lantus insulin, metformin, and glyburide should be withheld until the patient is stable in the postoperative period and can tolerate a consistent, uninterrupted diet to prevent episodes of hypoglycemia.

Best Practices: General Postoperative Care

Pain, Agitation, and Delirium

Most ICU patients who require mechanical ventilation benefit from pain control, light sedation, early mobility, and screening/treatment of delirium. The use of a narcotic analgesic as a first-line

Date of Surgery:_____ Weight:_____ Allergies:_____
Mental Status:_____ Antibiotic:_____ Code Status:_____
Urine Output:_____

SURGICAL

Pre-op Diagnosis:
Surgery Performed:
X-Clamp Time (min): ICPB time (min):
Intraop Complications:
Estimated Blood Loss:

DRIPS

Inotropes (dose):
Vasodilators (dose):
Muscle Relaxant:
Reversal Agents:
Diuretics:
Other Meds:

AIRWAY

ET Size:	Position:
Cuff Volume:	Depth (cm):
Method of Intubation:	
Difficult Intubation: Y/N	
Extubated Post Op: Y/N	
Tracheostomy: Y/N	
Vent Settings:	
Airway Comments:	

FLUID-BLOOD

Product	Volume (mL)
Crystalloid	
Colloid	
PRBCs	
Ultrafiltrated lood	
FFP	
Platelets	
Cryoprecipitate	
Other	

LINES

1.
2.
3.
4.

LABS

Labs	Result	Time
ABG		
H/H		
PT/PTT/INR		
Other		

PAIN MANAGEMENT

Epidural:
PCA:
Other:
Name/Last Dose:

COMMENTS: (Pending Labs, Imaging Studies, Plans)

Anesthesia CareTeam: _____ _____ _____ _____
Print Name Signature Date Time
Intensive Care Team: _____ _____ _____ _____
Print Name Signature Date Time

• **Fig. 34.1** Anesthesia handoff communication tool.

agent for the treatment of pain and agitation should be attempted. Fentanyl is typically the narcotic of choice in mechanically ventilated patients because of its excellent analgesia properties, rapid onset and short duration of effect, and lack of active metabolites during its metabolism. The use of nonopioid pain medications such as ketamine, acetaminophen, and gabapentin may lead to decreased opioid use in perioperative SICU patients.[23–25] When sedative medications are required for discomfort and agitation, the choice of agent should be easy to titrate, be of rapid onset and short-acting, and have a low incidence of hemodynamic instability and depressed respiratory drive. Historically, propofol and benzodiazepines have been used for sedation. However, benzodiazepines have also been shown to increase the incidence of delirium and ventilator time and propofol may be associated with a syndrome of acidosis and cardiac instability that may be greater in young patients.[26] An alternative sedative to consider is dexmedetomidine, an α_2-adrenoreceptor agonist with analgesic and sedative properties. Compared with the use of benzodiazepines, dexmedetomidine may decrease episodes of delirium and decreased duration of mechanical ventilation.[27,28] Patients may also be treated with dexmedetomidine after liberation from mechanical ventilation to improve sleep hygiene and prevent delirium in the ICU.[29] Patients who are treated with dexmedetomidine should be closely monitored for hypotension and bradycardia.

ICU patients who require significant analgesia and/or sedation owing to significant surgery or injury should be monitored and treated with analgesia and sedation scores. Analgesia and sedation scores provide a universal numerical score that allows communication between the multidisciplinary teams caring for these critically ill patients. The Richmond Agitation-Sedation Scale (RASS) allows the physicians to communicate in a universal language with team members the goal and actual sedation level of ICU patients[30] (Table 34.2). The Critical Care Pain Observation Tool uses facial expression, body movements, muscle tension, and compliance with the ventilator to develop a pain level score that allows the multidisciplinary team to know if the current analgesia plan is effective or needs to be altered. The Confusion Assessment Method for the ICU (CAM-ICU) can be used to monitor ICU patients for delirium, which is common in critically ill patients owing to their underlying illness, surgical history, and medications used for analgesia and sedation. With reduction in the targeted level of sedation and lightened RASS scores, assessment with the CAM-ICU leads to decreased burden of delirium, duration of mechanical ventilation, and decreased duration of ICU and hospital stay.[30,31] Updated ICU analgesia, sedation, and delirium protocols using RASS and CAM-ICU documentation result in decreased benzodiazepine dose, delirium, and duration of mechanical ventilation, ICU, and hospital stay.[32]

ICU-acquired dependence, possible addiction, and withdrawal should be a focus of ICU physicians when caring for patients requiring opioids. Patients in the ICU receiving opioids for more than 7 days may develop significant dependence, risk for withdrawal, and signs/symptoms similar to opioid-addicted patients' withdrawal when the opioids are discontinued.[33] The use of multimodality analgesia (α_2-antagonists, acetaminophen, nonsteroidal antiinflammatory drugs, and slow weaning of opioids in the ICU patient should be used to prevent withdrawal/dependence.[34] Currently there is no evidence that ICU opioid use leads to outpatient opioid use, but more investigation is needed.[35] In addition to the possibility of dependence and addiction, opioid analgesia produces side effects of somnolence, depressed respiratory effort, vomiting, and ileus. The use of neuraxial and peripheral nerve blocks can achieve adequate pain control, improve outcomes, and decrease the amount of opioid use and its side effects.[36,37]

TABLE 34.2 Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative and violent; danger to staff
+3	Very agitated	Pulls on/removes tubes or catheters; aggressive toward staff
+2	Agitated	Frequent nonpurposeful movement; patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but without aggressive vigorous movements
0	Alert and calm	
–1	Drowsy	Not fully alert but with >10-second awakening with eye contact
–2	Light sedation	<10-second awakening with eye contact to voice
–3	Moderate sedation	Any movement but without eye contact to voice
–4	Deep sedation	No response to voice but movement with physical stimulation
–5	Unarousable	No response to voice or physical stimulation

From Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166:1338–1344. Reproduced with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

Recovery From General Anesthesia

Approximately one-third of patients admitted to the SICU require mechanical ventilation,[38] exposing them to the effects of medications administered for analgesia and sedation. Inadequate sedation can lead to patient-ventilator asynchrony, patient agitation/discomfort, and self-extubation. Excess sedation can lead to longer duration of mechanical ventilation, longer ICU/hospital length of stay, and increased risk of delirium.[39,40] Patients requiring sedation may benefit from sedation holidays, Spontaneous Awakening Trials (SAT) and the pairing of these with ventilator liberation protocols, Spontaneous Breathing Trials (SBT).[41,42] Daily multidisciplinary rounds and/or standardized ICU protocols should be used to identify patients eligible for sedation holidays or administration of light or no sedation. Patients to be excluded from SAT include those with active neurologic pathology (i.e., active seizures, ethanol withdrawal, or intracranial hypertension) and severe respiratory failure with no plan to wean the ventilator and extubate. SATs have resulted in decreased sedation and increased RASS scores.[43]

Postoperative patients admitted to the ICU may have hypothermia, or core temperature less than 36°C. Hypothermia in postsurgical patients can result in coagulopathy and consequent hemorrhage. Patients with mild hypothermia (32°C–36°C) can undergo passive external rewarming with coverage with warm

blankets and increasing the temperature of the ICU room. Moderate hypothermia (28°C–32°C) in patients should be treated with active external rewarming with forced-air warming systems, heated blankets, and radiant heat. For severe hypothermia (<28°C), active core rewarming with intravenous warmed crystalloid and blood products, warm fluid irrigation into the pleural/peritoneal cavity, and/or endovascular warming devices should be used. In the OR most patients are treated with a combination of forced-air warming, intravenous fluid warmers, and increased temperature of the OR.

An assessment of volume status should be undertaken by reviewing the anesthesia records for fluids/blood products given, estimated blood loss, duration of surgery, and urine output. The use of isotonic crystalloid (0.9% normal saline solution, or balanced solutions such as lactated Ringer solution and Plasma-Lyte [Baxter Healthcare, Deerfield, IL]) should be used in increments of 500 to 1000 mL for depleted volume status in the absence of anemia and hemorrhage. Isotonic crystalloid bolus should be used until the patient's mean arterial pressure is more than 65 mm Hg, urine output is 0.5 mg/kg per hour, and perfusion of vital organs is demonstrated by normalization of serum lactic acid. The use of focused echocardiography in the ICU may be used to monitor resuscitation efforts versus the use of invasive monitoring devices.[44] Once the patient has been determined to achieve adequate resuscitation, the patient should be transitioned to a maintenance fluid of 0.45% normal saline solution with 5% dextrose to prevent catabolism.

Mechanical Ventilation

Postoperative patients admitted to the ICU may be mechanically ventilated or develop de novo acute respiratory failure. If the latter is true, the first step is to establish a patent and protected airway. This may not necessarily entail endotracheal intubation; a nasopharyngeal or oropharyngeal airway may suffice. Physical examination, bedside ultrasound, chest radiograph, ABG, and other laboratory values should be obtained immediately in both groups. For patients admitted to the ICU without an endotracheal tube, diagnostic studies may discover a pneumothorax, pleural effusion, or pulmonary edema that can be managed acutely and prevent intubation and mechanical ventilation. Inadequate awakening or rebound from general anesthesia may also be identified and treated.

Mechanical ventilation is typically set at respiratory rate (RR) of 12 to 16 breaths/min, positive end-expiratory pressure (PEEP) of 5 cm H_2O, and fraction of inspired oxygen (F_{IO_2}) of 1.0, unless more modest settings have been used successfully in the OR. To prevent the development of barotrauma and worsening lung injury, tidal volumes of 6 mL/kg are appropriate.[45] Frequent monitoring of ABG and oxygen saturation of arterial blood (Sa_{O_2}) should be used to wean F_{IO_2} below 0.4 to prevent oxygen toxicity. If the patient is still under the effect of general anesthesia and is not overbreathing the ventilator, it generally does not matter which mode of ventilation is selected. Intermittent mandatory ventilation, with or without pressure support, is used more frequently in surgical than in medical ICU patients as patients emerge from general anesthesia. Once fully awakened and physiologically stable, rapid assessment of readiness for extubation is appropriate. Unlike with patients in the medical ICU, it might be entirely appropriate to extubate those in the SICU without a trial SBT period, much as in the OR—once awake and able to lift the head as a gauge of strength.

Adult respiratory distress syndrome (ARDS) is defined by acute onset hypoxemia, bilateral infiltrates on CXR and absence of left heart failure. Common causes of ARDS include sepsis, trauma, aspiration event and inhalation injuries, all of which are common in patients admitted to the ICU postoperatively. ARDS is categorized as mild (partial pressure of arterial oxygen [Pa_{O_2})]/F_{IO_2} ratio <300), moderate (<200), and severe (<100).[46] The gold standard for managing ARDS with conventional ventilator mode settings is with low tidal volume (6 mL/kg) to decrease the incidence of ventilator-associated barotrauma.[47] However, most data from ARDS studies have been acquired in patients in medical ICUs. Surgical patients may be at a greater risk for damage from atelectasis, and those with large abdominal incisions and packing may require use of higher tidal volumes. Measurement of transpulmonary pressure through esophageal monitoring may be of benefit.[48] Other therapies may be added in patients with ARDS who continue to have significant hypoxia while using low-tidal ventilation. Prone positioning therapy and sedation with short-term neuromuscular blockade have both been shown to decrease mortality in ARDS patients.[49,50] Prone positioning can be used in surgical patients with so-called open abdomens and spine immobilization, although greater care is required. Other ventilator strategies such as high levels of PEEP, inversed inspiratory/expiratory (I:E) ratio, high-frequency oscillator ventilation, and airway pressure release ventilation (APRV) can be considered. These rescue modes use different methods to achieve the same goal of increasing mean airway pressure while preventing increased peak airway pressures. APRV uses a very high I:E ratio and short pressure release time, allowing the buildup of intrinsic PEEP and the use of spontaneous breathing. Studies have shown APRV to be at least equivalent to low–tidal volume ventilation in safety and outcomes in SICU patients.[51–53] Extracorporeal membrane oxygenation can be used as a last resort in the management of ARDS and has shown some promise in improving mortality in ARDS; however, the risk of postoperative bleeding must be considered.[54]

Ventilator Liberation

In postoperative ICU patients with improved/resolved hypoxia, hemodynamic stability, and no neurologic pathology, who have been ventilated for several days, formal assessment for the readiness to be extubated is appropriate. SBTs are performed during spontaneous breathing with or without low pressure support (<5 mm Hg). SBTs are typically 30 minutes in duration and include close monitoring for tachypnea, hypoxia, hypercapnia, distress, and other signs of respiratory distress. A rapid shallow breathing index (RSBI), which is the tidal volume/respiratory rate, is the one proven numerical parameter to predict successful extubation during an SBT. A rapid shallow breathing index below 105 is predictive of a successful and sustained extubation.[55] Standardized weaning protocols in ICUs reduce the duration of mechanical ventilation, weaning duration, and ICU length of stay.[56]

Ambulation

ICU-acquired weakness and neuropsychiatric disease (delirium) are long-term complications of critical illness. Immobilization, analgesia, sedation, and physiologic stress from critical illness may contribute to these complications. ICU care that minimizes sedation and encourages early mobilization of mechanically ventilated patients early to the course of a patient's critical illness can result in improved patient outcome, including ICU and hospital length of stay.[57–60]

Prophylaxis

Stress gastrointestinal bleeding in ICU patients may occur as a result of impaired mucosal barrier protection. Risk factors for stress ulcer bleeding in ICU patients include 48 hours of mechanical ventilation and coagulopathy. In these high-risk patients proton pump inhibitor or histamine-2–blocker therapy should be started to decrease the incidence of gastrointestinal bleeding. Patients receiving enteral nutrition may not require additional stress ulcer prophylaxis.[61]

The postoperative SICU patient is at high risk for venous thromboembolism (VTE) via the Virchow triad of stasis, endothelial injury and hypercoagulability. VTE is a common cause of morbidity and mortality in postoperative critically ill patients. The incidence can range from 10% in low-risk patients to 80% in high-risk patients such as those with multitrauma. The Caprini score is a point-based system used to quantify VTE risk, and it is recommended that perioperative patients with a score greater than or equal to 7 should receive chemical prophylaxis[62,63] (Table 34.3). Mechanical prophylaxis for VTE includes intermittent compression devices that are used independently in low-risk patients and in concert with chemical prophylaxis in high-risk patients.[64] ICU patients at high risk for VTE, including multitrauma and major surgery patients, should receive low–molecular-weight heparin (LMWH).[65] Unfractionated heparin (UFH) should be used in moderate risk ICU patients for VTE prophylaxis. Even for ICU patients at high risk of bleeding there may be a benefit of early chemical VTE prophylaxis without increased risk of bleeding complications.[66]

Stopping anticoagulation during the perioperative period may increase thromboembolic risk, whereas initiating or continuing anticoagulation increases the risk of hemorrhage with surgical procedures. The risks of thromboembolic events, hemorrhage, and the specific medication used must be taken into account when determining stop and start times of anticoagulation in surgical patients.[67] Patients receiving anticoagulation for major risk factors such as prosthetic cardiac valves and recent venous and/or arterial thromboembolism should have medication withheld for as short a time as possible. Resumption of anticoagulation can occur once hemostasis has been achieved in postoperative patients. Warfarin typically is resumed within 12 to 24 hours after surgery; if the patient is tolerating an oral diet, hemostasis is achieved and no further planned procedures are planned.[68] Warfarin is resumed at the preoperative dose and may require 5 to 10 days to reach therapeutic levels. Because of this, patients at high risk of thromboembolic events should be treated with bridging LMWH or UFH until the international normalized ratio becomes therapeutic. Direct oral anticoagulants (DOACs) are a relatively new generation of anticoagulants that include a direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). DOACs have rapid onset of action and do not require bridging anticoagulation with LMWH and UFH. Because of the rapid onset of action, resumption of DOAC therapy is delayed for 2 to 3 days after adequate hemostasis is achieved in postoperative patients. Although expensive, agents to reverse DOAC action now are available.

Ventilator-associated pneumonia (VAP) is a hospital-acquired infection that develops in 10% of mechanically ventilated patients after 48 to 72 hours of endotracheal intubation.[69] VAP prevention is achieved through routine ICU hygiene practices and several special approaches and techniques. Noninvasive positive-pressure ventilation can be used in select patients who have an easily treated cause of their respiratory failure and can maintain adequate protection of their airway. Prevention of VAP also includes the routine use of SAT and SBT with extubation as soon as feasible,[70] early mobility, and head of bed elevation to 30 to 45 degrees.[70] Subglottic secretion drainage ports should be used for patients who require intubation longer than 48 hours.[70] Oral care with chlorhexidine, oral/digestive decontamination, and prophylactic probiotics are

TABLE 34.3 Caprini Scores

RISK FACTORS			
1 Point	2 Points	3 Points	5 Points
Age 41–60 years	Age 60–74 years	Age >75 years	Major lower extremity arthroplasty
Minor surgery	Arthroscopic surgery	History of venous thromboembolism	Hip, pelvis, leg fracture
Previous surgery	Malignancy	Family history of thrombosis	Stroke
Varicose veins	Major surgery	Heparin-induced thrombocytopenia	Multiple trauma
History of inflammatory bowel disease	Laparoscopic surgery	Congenital/acquired thrombotic disorders	Paralysis
Edematous legs	Bed rest (>72 h)		
Body mass index >25	Immobilizing cast		
Acute myocardial infarction	Central venous catheter		
Congestive heart failure			
Sepsis (<1 month)			
Pneumonia (<1 month)			
Chronic obstructive pulmonary disease			

From Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon.* 2005;51:70–78.

special approaches that have been shown to reduce VAP.[70] Critically ill patients who require emergent intubation in the prehospital setting or emergency department have higher risks of VAP.[71,72] While these critically ill patients are in the emergency department, they should undergo VAP preventive measures such as chlorhexidine oral care, subglottic secretion drainage, and head of bed elevation to 30 degrees if feasible. In centers with high rates of VAP in SICU patients, the use of silver-coated endotracheal tubes should be considered.

Nutrition

Critically ill patients are in a catabolic stress state and malnutrition leads to worse outcome. Well-nourished patients can be managed without supplemental nutrition for a week or so if critical illness or features of the surgical procedure prevent its use. In other patients, early enteral nutrition results in decreased morbidity, mortality, and ICU costs.[73] ICU patients require 25 to 30 kcal/kg per day and 1.2 to 2.5 g/kg per day of protein based on ideal body weight. In most patients, enteral nutrition can be begun within 24 to 48 hours of ICU admission and critical illness. Initiating nutrition that delivers 8 to 10 kcal/kg per day within 7 days is optimal.[74] Early initiation of enteral nutrition in critically ill postoperative patients can be considered in those managed with an open abdomen, frequent trips to the OR, and a stable dose of vasopressor therapy.[75–77]

Provision of enteral nutrition in the critically ill patient may require placement of an oral or nasal gastric tube. Gastrically placed tubes with continuous feeding is typical as postpyloric enteral nutrition does not necessarily lower rates of aspiration or improve food tolerance.[78] The risk of aspiration can be decreased by elevating the head of bed 35 to 40 degrees and use of continuous infusion and prokinetic agents. Frequent checking of gastric residuals should not be part of routine care in patients receiving enteral nutrition. Evaluating patients for abdominal distention, nausea, and worsening abdominal pain should be used to assess the patient's tolerance of gastric feeds. If gastric residuals are checked, then volumes of 500 mL or less should not prompt stopping enteral nutrition.[79,80] Patients at high risk for aspiration may benefit from postpyloric enteral access.[79]

Parenteral nutrition may be required in critically ill patients who are not tolerating enteral nutrition, with intolerance expected to last at least 7 days. Historically, parenteral nutrition has been found to have complications associated with central venous access placement, infectious complications, and hyperglycemia. The current literature supports the use of parenteral nutrition in patients unable to tolerate enteral nutrition. Patients receiving parenteral compared to enteral nutrition may have similar infection rates, complications, lengths of stay, and mortality if assiduous care is taken to avoid central line infections.[81,82]

Providing adequate nutrition has been shown to improve outcomes in patients with severe acute pancreatitis. The use of enteral nutrition in these patients is safe and decreases mortality, hospital length of stay, and systemic infections.[83]

Glucose

Hyperglycemia in the perioperative patient admitted to the ICU may be due to a history of diabetes, stress response to critical illness, nutritional therapy, and/or sepsis. Hyperglycemia in this patient population has been shown to increase mortality and risk of wound and infectious complications. The use of subcutaneous or intravenous continuous insulin therapy with a target glucose level of less than 180 mg/dL leads to decreased perioperative complications and fewer episodes of hypoglycemia[84] compared with more aggressive targets.

Drains

Prophylactic drains are placed postoperatively to monitor bleeding and anastomotic leak (AL) and to decrease the accumulation of soft tissue edema. Drains also may be useful to decrease intra-abdominal pressure from ascites and to detect bile leaks after liver resection.[85] In general, drains used to monitor bleeding should be removed 1 to 2 days after surgery when the risk of bleeding has decreased. Drains placed to monitor ALs leaks are typically removed within 3 to 5 days of the operation or after adequate enteral nutrition is initiated. Drains left in place to decrease postoperative edema and seroma formation are often left for longer durations. The SICU team should closely monitor the volume of drain output, the appearance of the drain output, and any acute changes in the output. Surgical drains have their own complications, including intraabdominal and wound infections, increased abdominal pain, decreased pulmonary function, and bowel injury.[86,87]

Surgical Complications

Hemorrhage

Perioperative hemorrhage after elective, emergent, or urgent procedures is a frequent cause for or feature of ICU admission. Persistent postoperative hypotension is most commonly due to bleeding and the ICU team should be scrupulous about surveillance. Rapid identification and appropriate management of perioperative hemorrhage can prevent shock and multisystem organ failure. It is ideal to diagnose hemorrhage before hypotension develops.[88] The use of hemodynamic monitoring, physical examination, and monitoring laboratory values such as hemoglobin and lactate are useful clues to identify hemorrhage.

Before most operations that warrant ICU admission, baseline laboratory values such as hemoglobin, hematocrit, coagulation panel, and blood type and cross-match should be available for the patient.[89] Perioperative communication among the surgeon, anesthesiologist, and critical care team should be ongoing during the surgery and during transition to the ICU to manage operative hemorrhage. If significant and major bleeding occurs perioperatively, transfusing patients with a high ratio of plasma to platelets to red blood cells leads to improved survival, decreased hemorrhage, and improved hemostasis.[90,91] In ICU patients when blood products are not readily available, resuscitation with isotonic crystalloids with a goal of mean arterial pressure (MAP) above 65 mm Hg and normalization of lactic acid. Avoidance of excess infusion of crystalloid in patients with hemorrhage compared with transfusion of blood products is also beneficial.[92] In patients with hypovolemic shock caused by sepsis, trauma, or following surgery the use of colloid versus crystalloid resuscitation shows no difference in mortality or renal failure.[93,94] Colloids are more expensive and some (hydroxyethyl starches) may increase the risk of death or acute kidney injury; we therefore preferentially use crystalloid for resuscitation.

Careful inspection of the surgical field before closure is the best method for prevention of postoperative hemorrhage. In the postoperative phase, the patient should be monitored for signs of hemorrhage: tachycardia, shock, oliguria, altered mental status, and increasing surgical site pain and distention. Patients with

hemodynamic instability and signs of hemorrhage should have immediate surgical reexploration. Postoperative ICU patients with progressive anemia but hemodynamic stability may be managed more conservatively. Conservative management includes ICU monitoring of hemodynamics, hemoglobin, and urine output with transfusions as necessary. Patients with intraluminal sources of hemorrhage may be treated with endoscopic and endovascular techniques to stop the bleeding. Extraluminal sources of bleeding may be treated with angioembolization.

Anastomotic Leak

Anastomotic leak (AL) is one of the most devastating surgical complications resulting in significant morbidity and mortality. AL occurs in 3% to 21% of patients with an associated mortality of 3T to 22%.[95–97] The wide variation in the rates of AL may be due to the presentation of early and dramatic leaks versus late and subtle leaks. Historically, AL occurs by postoperative day 5, but studies have shown mean days to AL of 12 days.[96] Postoperative patients may present with signs of AL with fever, elevated white blood cell count (WBC), tachycardia, hypotension and enteric contents in the perianastomotic drain. The diagnosis of AL may be difficult with relevant studies showing low sensitivity. Computed tomography (CT) scanning with oral contrast has a sensitivity of 50% in diagnosing AL, contrast swallow 21%, and 14.4% via perianastomotic drain examination.[98] CT scanning with oral contrast may be the modality of choice for assisting in the diagnosis of AL, because it also allows for the detection of associated pathology such as intraabdominal abscess.[99] Endoscopy may be more sensitive and is used to diagnose ALs in critically ill patients.[99]

Typically the management of AL has been surgical, with revision of the anastomosis, diversion, and wide local drainage. However, in hemodynamically stable patients, small ALs may be managed with intravenous antibiotics, percutaneous drainage, and close monitoring.[96,97] Patients who are able to undergo nonoperative management are typically diagnosed late in the postoperative course because of a more indolent presentation of the AL.[97] Further, minimally invasive management using endoscopically deployed stents may be possible.[100] Surgical management should be used for patients in septic shock and with generalized peritonitis.

Abdominal Compartment Syndrome

Intraabdominal hypertension (IAH) is defined as intraabdominal pressure (IAP) greater than 12 mm Hg. Abdominal compartment syndrome (ACS) is defined as IAP greater than 20 mm Hg with new and/or worsening end-organ dysfunction.[101] Intraabdominal pressures are measured via the bladder pressure. Measurement of bladder pressure steps include placement of 50 mL of saline solution into the bladder via the Foley catheter and clamping the catheter, and insertion of a needle attached to the manometer into the collecting port of the Foley catheter tubing, where the patient lying flat the pubis symphysis is the zero mark. Alternatively, ACS may be defined by an abdominal perfusion pressure (APP). APP is the difference between MAP and IAP. A target goal APP of more than 60 mm Hg has been shown to improve outcomes in patients with IAH/ACS. Hypotensive patients with some level of IAH/ACS may have even more decreased perfusion of abdominal viscera. ACS can be caused by severe abdominal trauma, intraabdominal and retroperitoneal hemorrhage, and excessive crystalloid and blood product administration. Diminished abdominal wall compliance after abdominal wall reconstruction, deep burns to the abdominal wall, and elevated body mass index increase the risk for ACS.

In addition to elevated IAP, patients with ACS will present with a tense and distended abdomen on physical examination. There may be an increased peak airway pressure and/or decreased tidal volumes on mechanical ventilation. Patients with ACS may develop oliguria, elevated serum creatinine, and elevated serum potassium. ACS may also lead to shock and decreased cardiac output owing to caval compression.

Patients with abdominal hypertension or early ACS without physiologic compromise may be managed nonsurgically. This approach involves decreasing the resuscitation volume and administration of sedation and neuromuscular blockade. If ACS is secondary to a large volume of intraabdominal ascites, various catheters can be used for percutaneous drainage. The standard approach to the treatment of ACS is through surgical decompression of the abdomen via celiotomy.[101,102] After celiotomy, a temporary negative-pressure dressing may be placed, but ACP may still develop in these patients who should be closely monitored.

Necrotizing Soft Tissue Infection/Wound Complications

Necrotizing soft tissue infection (NSTI) may occur at a recent surgical site or from a primary infection. NSTI is an aggressive infection that may involve the skin, subcutaneous tissues, fascia, and/or muscles. NSTI causes extensive morbidity and mortality rates of 25% to 35%.[103] Postoperative patients in whom fever, cellulitis, and surgical site drainage develops should be assessed for NSTI. NSTI may be difficult to diagnose early and differentiate from other soft tissue infections. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is a point system of laboratory values developed to assist with the diagnosis of NSTI (Table 34.4). An LRINEC score of 6 or greater has a positive predictive value of 92%; a score of less than 6 has a negative predictive value of 96%.[104] Radiographs and CT scans may show NSTI by visualizing soft tissue gas with or without an associated abscess. CT scanning has been shown to be more sensitive than conventional radiology and should be used in patients in stable condition with any question of the diagnosis.[105] These infections are caused most commonly by group A *Streptococcus*, *Clostridium perfringens,* and polymicrobial bacteria that include methicillin-resistant *Staphylococcal aureus*. During the evaluation of a patient for possible NSTI, if there is any question of the diagnosis, management requires surgical exploration of the soft tissue site in question.

Treatment of these infections requires, prompt surgical debridement, administration of broad-spectrum antibiotics, isotonic crystalloid resuscitation with an initial bolus of 30 mL/kg to achieve an MAP above 65 mm Hg, lactate level normalization, and supportive care in the ICU.[7] Early operative debridement is a major determining factor in the outcomes of these patients. The operative debridement should be aggressive and may require limb amputation.[106] Once in the ICU these patients require significant supportive care, including analgesia and dressing changes. NSTI patients will require multiple trips to the operating room for aggressive debridement.

Surgical site infections (SSIs) consist of superficial infections (skin and subcutaneous tissue) and deep infections (fascia and muscle). Patients are at high risk of developing SSIs during emergency surgery with colon injury, perioperative hypothermia, and after receiving large-volume blood transfusions perioperatively.[107] SSIs are typically caused by normal skin flora such as *S. aureus* or by common enteric

TABLE 34.4 LRINEC Score

Variable	Value	Score
C-reactive protein (mg/L)	≥150	4
White blood cell count (10,000/uL)	<15	0
	15–25	1
	>25	2
Hemoglobin (g/dL)	>13.5	0
	11–13.5	1
	<11	2
Sodium (mmol/L)	<135	2
Creatinine	<1.6 mg/dL	0
	>1.6 mg/dL	2
Glucose	≤180 mg/dL	0
	>180 mg/dL	1

From Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med.* 2004;32:1535–1541.

organisms such as *Enterococcus* strains and *Escherichia coli*. Administering perioperative antibiotics for 24 hours to target common bacterial pathogens decreases the rates of SSIs. SSIs are diagnosed by physical examination targeted at identifying cellulitis, swelling, and purulent drainage from the surgical wound. Treatment consists of intravenous antibiotics, opening of the surgical wound, and possible debridement in the operating room. Fascial dehiscence is a surgical complication that often occurs along with SSIs and perioperative intraabdominal infections. Patients in whom fascial dehiscence develops must undergo repeat surgical exploration, evaluation for underlying surgical infection, and reclosure of the fascia.

Enterocutaneous fistulas may result from inflammatory bowel disease or as a complication of a surgical procedure and can result in significant morbidity and mortality (7%).[108] In patients in whom the abdomen has been left open as part of a damage control operation, the fistulas may communicate directly with the environment, so-called enteroatmospheric fistulas.[109] The management of fistulas must address the presence of an intraabdominal collection, including abscess, and control of accompanying systemic signs of sepsis. Further, high-output fistulas (>500 mL/day) may require electrolyte correction and rehydration with isotonic crystalloids.[109] Nutritional support typically uses parenteral nutrition to afford closure of the fistula. In select patients with distal, low-output (<200 mL/day) fistulas, the use of enteric nutrition may be appropriate. Local wound care and negative-pressure dressings are used to protect the skin and control the fistula effluent. Octreotide may decrease the volume of effluent from a high-output fistula but generally will not assist in its closure, particularly in the presence of factors hostile to healing—foreign bodies, previous radiation, active infection, epithelialization, neoplasm, and obstruction distal to the fistula.[108]

Pulmonary Embolism

Pulmonary embolism (PE) is the obstruction of the pulmonary artery by thrombus, air, or fat. PE leads to significant morbidity with a 30-day mortality of 3.9% and a 1 year rate of 9.2%.[110] Patients in the SICU are at high risk of PE owing to recent major surgery, immobilization, trauma, and comorbidities such as obesity and tobacco use.[111] In a majority of patients with PE, the thrombus originates from iliac, femoral, and popliteal veins. Patients with PE can present with signs and symptoms of chest pain, shortness of breath, tachycardia, and symptoms of extremity deep vein thrombosis. PEs can lead to alterations in the ventilation-perfusion ratio and acute lung inflammation, resulting in hypoxia. Massive PE or PE in a patient already critically ill with compromise may cause significant hemodynamic instability. Hemodynamic compromise develops as the result of blockage of a main or major branch of the pulmonary artery with resultant increased pulmonary vascular resistance. This elevated pulmonary vascular resistance leads to right heart dilation. The right heart dilation compresses the left heart and leads to decreased preload and cardiac output.

Diagnostic modalities such as D-dimer testing and ventilation-perfusion scanning are not reliable or feasible in critically ill surgical patients. D-dimers are normally elevated in perioperative patients. CT pulmonary angiography is diagnostic in stable patients with concern for a PE.[112] Hemodynamically unstable patients should undergo bedside echocardiography to assess for right heart dilation and functional compromise. Once the diagnosis of PE is made, the treatment is therapeutic anticoagulation. Patients who have hypoxia and hypotension resulting from PE require supplemental oxygen, possible mechanical ventilation, resuscitation, and vasopressor treatment as needed. Hemodynamically unstable patients with PE should be considered for thrombolysis therapy or surgical versus endovascular embolectomy. In SICU patients with recent surgery, active hemorrhage, or intracranial hemorrhage, it may not be safe to consider anticoagulation or thrombolysis. These patients should undergo inferior vena cava filter placement to prevent additional PE and possible embolectomy.

Acute Coronary Syndrome

Critically ill patients are at high risk of myocardial injury/acute coronary syndrome after emergent surgery, long procedures with excessive blood loss, postoperative acute kidney insufficiency, and vasopressor administration.[113] Acute coronary syndrome in the SICU may not present typically (i.e., with substernal chest pain) owing to the administration of analgesia, mechanical ventilation, and other medications and support devices that may mask signs and symptoms. Critically ill patients may present with cardiac arrhythmias and unexplained shock without concomitant chest pain and dyspnea. Diagnosis of acute coronary syndrome requires an electrocardiogram, cardiac biomarker evaluation, and bedside echocardiography to evaluate kinetic and cardiac wall abnormalities. Treatment in SICU patients often requires the use of supplemental oxygen, pain control with narcotic analgesia, β-blockers for the prevention of ventricular arrhythmias, and statin therapy. The use of antiplatelet therapy and anticoagulation must be balanced with the patients risk for hemorrhage. A cardiologist should be consulted for percutaneous coronary diagnosis and intervention specifically for ST-elevation myocardial infarctions. A restrictive blood transfusion threshold may not be safe in the face of acute coronary syndrome.[114]

Acute Kidney Insufficiency

The development of acute kidney insufficiency (AKI) in the perioperative period can lead to increased morbidity and mortality. Older patients with ischemic heart disease and congestive heart failure who undergo emergency or high-risk surgery are at increased

risk of developing AKI.[115] AKI develops in 25% of SICU patients and leads to a threefold increase in hospital death.[116] The Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) criteria are three methodologies to classify the severity of renal failure.[117–119] Prerenal AKI in the SICU is typically caused by hypovolemia and often is the result of bleeding. Patients with impaired cardiac function and euvolemia/hypervolemia may also develop prerenal AKI. Acute tubular necrosis that leads to AKI is caused by hypovolemia, shock, and nephrotoxic agents. Evaluating serum and urine electrolytes and osmolality can be used to distinguish between these two types of AKI. Postrenal AKI is the result of obstruction to urine flow. The potential etiology of AKI in SICU patients includes damage to ureters and obstruction of urinary drainage, as seen when the urinary catheter is kinked or clotted.

Prevention of AKI in the SICU requires adequate volume repletion and maintaining MAP goals above 65 mm Hg. Other therapies, such as administration of bicarbonate, N-acetyl cysteine, colloid volume replacement, and dopamine, have not been shown to prevent AKI.[120–122] The initial treatment of patients with AKI is correction of severe electrolyte abnormalities and management of symptomatic volume overload. Patients with hyperkalemia should receive calcium to decrease cardiac irritability; insulin and bicarbonate both provide temporary correction. Renal replacement therapy and potassium binders provide more long-term correction of hyperkalemia; however, use of the latter may not be possible in the face of an ileus of fresh intestinal anastomosis or discontinuity of gastrointestinal tract. The use of diuretics has not been shown to prevent or improve AKI; however, they may assist with fluid balance.[123] Renal replacement therapy is indicated in ICU patients with severe fluid overload, hyperkalemia, uremic encephalopathy, and severe metabolic acidosis. Patients in the ICU may require continuous renal replacement therapy for severe hemodynamic instability and persistent metabolic acidosis; however, the data do not consistently show a benefit over intermittent or hybrid methods of dialysis.

Chronic Critical Illness

Most patients improve and return to baseline status after appropriate surgical care. Others have persistent critical illness, develop repeated bouts of sepsis, and continue to require mechanical ventilation and other forms of support. Patients with chronic critical illness have prolonged mechanical ventilation, profound weakness, neuroendocrine dysfunction, impaired anabolism, delirium, and skin breakdown.[124] Prolonged mechanical ventilation (PMV) has been defined as undergoing mechanical ventilation in the ICU for longer than 21 days.[125,126] Patients requiring PMV have higher mortality rates (40%), increased readmission rates, and increased total health care costs.[126] Patients who typically require PMV are older, sicker, and have more frequent diagnosis of pancreatitis, acute respiratory distress syndrome, pneumonia, and septic shock.[126]

Patients who survive chronic critical illness typically are functionally dependent owing to physical impairments, pain, and significant psychosocial issues.[124,127,128] A multidisciplinary approach to care is required for patients with chronic critical illness. Patients with PMV may be sent to centers that specialize in weaning from mechanical ventilation and rehabilitation. The most important role of the ICU in chronic critical illness is prevention by following protocols for decreased sedation, early mobility, and physical therapy.[58] Adequate nutrition and protein without underfeeding or overfeeding patients leads to decreased ICU complications, costs, and mortality.[129] Neurorehabilitation and close monitoring and treatment for posttraumatic stress disorder should be used in these patients. Frequent meetings between the ICU and surgical teams and the patient's family should occur to understand goals and define prognosis and expectations. Formal palliative care consults should be considered for patients with chronic critical illness to discuss achievable goals of treatment and alternatives to continued critical care.[130]

Specific Surgical Specialty Operations

Noncardiac Thoracic Surgery Care

Thoracic surgery cases requiring ICU admission postoperative include pulmonary resection, treatment of pleural disease (empyema, pneumothorax), diaphragm hernia repair, esophagectomy, and chest wall tumor resection. Many of these patients have pulmonary dysfunction and require pulmonary function testing to identify those at high risk for postoperative hypoxia and complications. Thoracic surgery patients are typically older, have cardiovascular comorbidities, are active smokers, and have chronic obstructive pulmonary disease.[131,132] Typical complications, as discussed earlier, are common and should be monitored for and treated accordingly. Patients may have prolonged ICU stays after thoracic surgery if there is difficulty controlling pain, and in the face of debility, cardiac arrhythmias and prolonged air leaks after pulmonary resection.[133]

Intravenous fluids are typically administered in reduced amounts to decrease the risk of postoperative respiratory distress and failure in patients after thoracic surgery. Patients who undergo pulmonary resection may be high risk for persistent hypoxia based on their pulmonary function test results and may require prolonged mechanical ventilation and oxygen therapy. High-flow nasal cannula can be used as an adjunct to prevent intubation in hypoxic thoracic surgery patients.[134] Prolonged air leak (>5 days) after pulmonary resection may lead to increased risk of pneumonia and empyema.[135] Most air leaks resolve on their own with continued tube thoracostomy, but patients with persistent air leak may require pleurodesis or reoperation to repair the lung parenchyma/bronchus leak. Atrial fibrillation is the most common cardiac-related complication after thoracic surgery. Because atrial fibrillation in this patient population is usually temporary and self-limiting, the initial treatment is with β-blockers or calcium channel blockers for rate control.[136] All patients who develop cardiac arrhythmias do require electrocardiogram and cardiac enzyme monitoring to evaluate for acute coronary syndrome. New-onset atrial fibrillation after esophagectomy may occur because of anastomotic leak and should prompt investigation, particularly if it occurs after the first 24 hours postoperatively.[137] Postoperative pain from thoracotomy is significant and can lead to noncompliance with chest physiotherapy and early mobility. The use of epidural catheters for this patient population can improve pain control and improve respiratory function and mobility.[138,139] Early postoperative mobility and chest physiotherapy is key to prevent atelectasis and pneumonia. With the development of minimally invasive thoracic surgery/video-assisted thoracoscopic surgery, thoracic surgery patients have decreased pain, early mobility, and decreased incidence of atrial fibrillation, pneumonia, and prolonged air leak.[140,141] Chest tubes that are placed after lung resection, pleurodesis, or any type of thoracic pleura violation are typically kept at −20-mm Hg wall suction for 24 to 48 hours; and if no persistent leak the chest tube is placed to water seal and removed if follow-up chest x-ray shows no significant pneumothorax or pleural effusion.

Vascular Surgery

Patients undergoing vascular surgical procedures for arterial disease have a high incidence of concomitant coronary artery disease; 50% to 70% of vascular surgery patients have ischemic heart disease and 30% to 50% have had a previous myocardial infarction.[142] Perioperative myocardial ischemia is the primary cause of death of patients after major vascular procedures.[143] Increased oxygen demand owing to the stress of surgery, pain, hypotension, and perioperative tachycardia in this high-risk group can lead to myocardial ischemia and plaque rupture.[144] Perioperative vascular surgery patients require adequate pain control, hemodynamic monitoring, and continuation of home doses of β-blocker and statins. Currently there are insufficient data to support initiating β-blocker therapy de novo. AKI is another significant complication of vascular surgery and leads to increased mortality rates of 60% to 80%.[145] AKI develops in vascular surgery patients as the result of preexisting renal disease, radiologic contrast administration, suprarenal aortic clamping, acute blood loss anemia, and vasopressor use. AKI treatment in these patients requires crystalloid resuscitation, blood product transfusion for anemia, and avoidance of nephrotoxic agents. Thoracotomy and celiotomy for aortic aneurysm repair puts patients at risk for PMV, pneumonia, and ARDS. These patients are best treated with low lung volume ventilation strategies. Vascular surgery patients undergoing celiotomy for aortic aneurysms are at risk for abdominal compartment syndrome and bowel ischemia. Postoperative persistent metabolic acidosis and shock is suggestive of bowel ischemia requiring CT scan, endoscopy, and surgical exploration for diagnosis. Neurovascular checks, blood and mucous per rectum, and severe abdominal pain with or without peritonitis are relevant features of the physical examination after major aortic procedures.

Abdominal Surgery

Patients who undergo abdominal surgery require critical care for continued resuscitation, monitoring, and management of sepsis, hemorrhage, and respiratory failure. Resuscitation entails administration of isotonic crystalloid and blood products to achieve adequate circulating volume, MAP above 65 mm Hg, urine output to 0.5 mL/kg per hour, and clearance of serum lactate levels. Recently there has been a shift away from invasive monitoring to achieve resuscitation goals to assessing volume responsiveness via noninvasive means, and to restricting crystalloid volume administration with consideration of earlier use of vasopressors.[146] In postoperative patients with tenuous enteric anastomoses, the use of vasopressor therapy may be ill advised.

Many ICU patients require close monitoring for sepsis owing to surgical site infection and AL after abdominal operations. Prophylactic intravenous antibiotics should be given for less than 24 hours to prevent surgical site infection. Patients in the ICU with intraabdominal sepsis require surgical source control and therapeutic intravenous antibiotics to prevent local and hematogenous spread. Most common organisms involved in intraabdominal sepsis are gram-negative species such as *E. coli* and gram-positive species such as *Enterococcus*. Patients most common begin a combination of vancomycin, extended-spectrum penicillins, metronidazole, and higher-generation cephalosporins with escalation or de-escalation based on culture results.[147] The recommended duration of intravenous antibiotics for intraabdominal infections with source control and associated bacteremia is 7 days.[148] Procalcitonin levels can be measured to guide the duration of antibiotics with cessation at procalcitonin levels of less than 0.5 ng/mL.[149]

Staged procedures in which the abdomen is left open and/or bowel is left in discontinuity after resection may be appropriate for those in extremis or too unstable for definitive surgery. After the initial procedure, patients require ICU resuscitation, metabolic corrections, administration of blood products for anemia and coagulopathy correction, and warming to achieve normothermia. After these goals are achieved, typically within 24 to 48 hours, the patient is returned to the operating room for a definitive procedure and possible celiotomy closure. Therapy after definitive surgical treatment requires prevention of ICU-related complications by early mobility and extubation, VTE prophylaxis, stress ulcer prophylaxis, and early enteral nutrition. Patients with an open abdomen who receive early enteral nutrition have better outcomes compared with those who have enteral nutrition delayed until abdominal closure.[75] After patients have definitive abdominal closure, they should undergo frequent measurements of abdominal compartment pressures and monitoring of urinary output and mechanical ventilation requirements to watch for ACS. Typically the skin and subcutaneous tissues remain open after fascia closure and are treated with serial dressing changes and negative-pressure wound therapy.

Abdominal Organ Transplantation

Patients undergoing liver transplantation require ICU admission because of long operative time, significant intraoperative and postoperative blood transfusion requirements, and postoperative respiratory failure. Those with renal failure may require renal replacement therapy. The use of fast-track extubation and other care protocols results in improved outcomes and decreased mortality.[150,151] Liver transplant patients frequently have postoperative hemorrhage owing to significant perioperative coagulopathy and thrombocytopenia. The correction of coagulopathy and thrombocytopenia should be achieved before reexploration if patients are hemodynamically stable and without ACS.

Early liver transplantation dysfunction may be diagnosed in the first few days after transplantation through elevated liver serum tests. Technical errors during surgery may lead to hepatic artery thrombosis, biliary duct anastomosis stricture, or leak, which can be evaluated by Doppler ultrasound of the liver. Hyperacute rejection (HAR) after liver transplantation is rare and due to ABO cross-match issues. HAR presents as elevated bilirubin, encephalopathy, weakness, thrombocytopenia, coagulopathy, fever, and hypotension within a few hours of transplantation. Doppler ultrasound displays thrombosis of the portal vein and absence of biliary duct obstruction in patients with HAR. Treatment of HAR is supportive therapy with retransplantation. Acute rejection after liver transplantation may also occur over the first 6 to 8 weeks after liver transplantation and is due to cell-mediated attacks on the liver, and thus is rarely a feature of the initial postoperative ICU stay. Patients with acute rejection typically present with fatigue, low-grade fever, and elevated transaminase levels, but rarely is the patient critically ill. Prevention and treatment of acute rejection entails the use of prednisone, calcineurin inhibitors, and antimetabolite drugs. These immunosuppression regimens can cause complications, such as diabetes, renal failure, hypertension seizures, and increased susceptibility to infection. Most of these symptoms are dose dependent and can be limited by dose adjustments.

The most common cause of mortality in these patients after liver transplantation is infection. Infection-based mortalities account

for more than 60% of the deaths in liver transplant recipients.[152] Signs and symptoms of fever, leukocytosis, cellulitis, and pain may be absent owing to immunosuppression, making the diagnosis of infection difficult. Prolonged surgical time and large amounts of fresh frozen plasma transfusion lead to an increased risk of infectious complications in transplant patients.[153] Infections that occur early in the patient's posttransplant period (first 6 weeks) typically are the result of bacterial infections related to the surgical procedure, invasive monitors, ventilator, or other iatrogenic causes. Perioperative antibiotic regimens should include broad-spectrum antibiotics to cover methicillin-resistant *S. aureus* and other multidrug-resistant bacteria and fungus. Intraabdominal infections are most commonly due to leak from the biliary anastomosis. Intraabdominal infections are best treated with intravenous antibiotics, percutaneous drainage, and reexploration if the patient is in septic shock or symptoms do not improve. Invasive critical care devices such as central venous catheters, endotracheal tubes, and urinary catheters should be removed as early in the ICU course as possible to prevent hospital-acquired infections. During the first 6 months of immunosuppression transplant patients are at high risk of opportunistic infections. A regimen of trimethoprim-sulfamethoxazole and ganciclovir is used to prevent the opportunistic infections with *Pneumocystis carinii* and cytomegalovirus.

Trauma

The tertiary trauma survey usually occurs after initial resuscitation and surgical treatment and may be initiated once the patient has arrived in the ICU. A tertiary trauma survey includes a full physical examination to look for missed injuries, a review of laboratory values and radiographic data, and a detailed medical history of the patient. Trauma patients who require admission to the ICU often require continued resuscitation for hemorrhagic shock. These patients should have blood product resuscitation with a high ratio of red blood cells to plasma to platelet transfusion ratio.[90,154] Trauma patients with major hemorrhage have improved mortality rates with these high transfusion ratios. The use of tranexamic acid in trauma patients with hemorrhagic shock may also provide some mortality benefit, especially if delivered rapidly after bleeding.[155,156] Damage control resuscitation involves early control of hemorrhage and gross contamination, permissive hypotension, avoidance of crystalloids, and early use of blood components (plasma and platelets) in a high ratio in patients requiring greater than 10 units of red blood cells leads to improved hemostasis and reduces deaths caused by hemorrhage.[90,154,157] Reversing metabolic acidosis and hypothermia with the use of fluid/blood product warmers and body-warming devices also aids in correction of coagulopathy in trauma patients. Trauma hospitals using protocols for blood product resuscitation (massive transfusion protocol) will improve the mortality rate, decrease the amount of blood products used, and decrease the amount of crystalloid used.[158]

Damage control laparotomy uses the surgical technique of rapid control of hemorrhage and contamination; postoperative resuscitation with correction of coagulopathy, hypothermia, and acidosis; and subsequent definitive repair of injuries.[159] Damage control laparotomy is used in concert with damage control resuscitation to improve mortality rates in trauma patients. Patients undergoing damage control laparotomy present to the ICU with negative-pressure abdominal dressings used to remove toxic intraperitoneal fluid, reduce the risk of fistula formation, and prevent evisceration of intraabdominal contents. Negative-pressure dressings may also allow the visualization of continued hemorrhage or enteric content leak. Negative-pressure dressings do not completely eliminate the risk of ACS, leading to the need for frequent evaluation of bladder pressure, hemodynamic monitoring, and evaluation of the mechanical ventilator peak airway pressures. When the patient's hemodynamic and physiologic status has improved, typically within 24 to 48 hours, a return to the operating room for definitive treatment can be undertaken.

Traumatic brain injury (TBI) is a leading cause of death after a major traumatic injury. The role of ICU management of TBIs is to prevent secondary brain injury caused by hypotension, hypoxia, and seizures. Hypotension at any point during hospitalization of patients with TBI increases their risk of death.[160] Blood product resuscitation and emergent control of hemorrhage are key to preventing hypotension. Endotracheal intubation and appropriate oxygenation with mechanical ventilation is required in patients with Glasgow Coma Scale scores less than 8. Temporary hyperventilation may be used to reduce carbon dioxide levels to reduce intracranial pressures until surgical decompression of intracranial mass lesions. Platelet levels below 100,000 μL and international normalized ratio higher than 1.5 may lead to progression of intracranial hemorrhage.[161,162] Treating these patients with plasma and platelet transfusions and/or administration of factor VII and prothrombin complex concentrate may decrease progression of intracranial hemorrhage.[163] Seizures after TBI can lead to elevated intracranial pressures, increased metabolism, and increased secondary brain injury. The use of phenytoin or levetiracetam for 7 days will decrease the number of TBI-associated seizures.[164]

Pain control in trauma patients is key to improving patient's early mobility and pulmonary toilet, which have been shown to decrease the incidence of pneumonia, delirium, duration of mechanical ventilation, and ICU length of stay. In patients who have no contraindications and especially in patients with thoracic trauma, epidural analgesia has been shown to improve pain control and overall outcome.[165] Trauma patients with intact intestinal continuity should have early (24 hours) enteral nutrition started even in the face of stable levels of vasopressors or an open abdomen.[75,79] VTE chemical prophylaxis should be started immediately because of the high risk of VTE formation in trauma patients. Patients with active hemorrhage or significant TBI should have initiation of chemical VTE prophylaxis delayed until these injuries are stabilized.[66]

Key Points

- ICU beds are a limited resource and should be reserved for patients with medical needs requiring ICU-level care, a reversible disease, and a reasonable prospect of a meaningful recovery.
- A multidisciplinary team approach with evidence-based guidelines, checklist, and bundles should be used to provide best practice care for ICU patients.
- The use of universal pain and sedation scores such as RASS, the Critical Care Pain Observation Tool, and CAM ICU allows for communication between the teams caring for the patient. Light sedation, early mobility, and delirium screening can improve ICU patient outcomes.

- ARDS is best managed with low tidal volumes of 6 mL/kg and assisted with prone positioning and neuromuscular blockade.
- Mechanically ventilated patients who are assigned weaning protocols. treated with minimal sedation, and achieve early mobility have decreased time of mechanical ventilation and ICU length of stay.
- Patients with a Caprini score higher than 7 and/or after major surgery and trauma should receive chemical VTE prophylaxis when clinical risk of hemorrhage is minimal to reduce the risk of increased morbidity and mortality related to VTE.
- Enteral nutrition goals of critically ill patients include provision of 25 to 30 kcal/day and 1.2 to 2.5 g/kg of protein per day. Early initiation of nutrition has been shown to decrease morbidity and mortality.
- Patients with hemorrhagic shock should be treated with a high ratio of plasma to platelets to red blood cells to decrease hemorrhage and improve hemostasis.
- AKI leads to a significant risk of in-hospital mortality with prevention of AKI with adequate volume repletion and MAP above 65 mm Hg.
- Surgical specialties have a variety of treatments and complications specific to their specialty. These complications often depend on their patients' comorbidities before surgery and the specific surgery they have undergone.

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Review Questions

1. Which of the following preoperative medications should be continued in the immediate perioperative period for patients undergoing a major general surgery procedure?
   a. Diuretics
   b. Calcium channel blockers
   c. Glucocorticoids
   d. Metformin
   Answer: c. Glucocorticoids should be continued at their standard dose for major general surgery procedures to prevent hypotension caused by adrenal suppression. Calcium channel blockers and diuretics should be held perioperatively to prevent hypotension and possibly worsening hypotension associated with hemorrhage or sepsis. Metformin should be held perioperatively until the patient is tolerating uninterrupted nutritional intact to avoid hypoglycemia if diet is interrupted.
2. Which of the following medications may lead to a decrease in the episodes of delirium when used as sedation in mechanically ventilated patients?
   a. Dexmedetomidine
   b. Benzodiazepines
   c. Gabapentin
   d. Morphine
   Answer: a. Dexmedetomidine is an α_2-adrenoreceptor agonist that has been shown to decrease anxiety, duration of hyperactive delirium, and time of mechanical ventilation in patients with delirium. Benzodiazepines have been shown to increase rates of delirium and increase duration of mechanical ventilation and ICU length of stay. Morphine (opioid) and gabapentin (nonopioid) analgesia medications typically are not used for sedation.
3. The patient with the following diagnosis should be excluded from daily spontaneous awakening trials (SAT)?
   a. Septic shock
   b. Active seizures
   c. Open abdomen
   d. Deep venous thrombosis
   Answer: b. Patients with active seizures often require significant sedation to break and prevent seizure activity, and an SAT may lead to recurrence and worsening of seizures. Septic shock, open abdomen, and deep vein thromboses do not prevent decreasing sedation and attempting to get the patient to follow commands and perform a spontaneous breathing test/trial.
4. Mortality can be improved in patients with adult respiratory distress syndrome (ARDS) with which of the following techniques?
   a. Tidal volume of 10 mL/kg
   b. Inversed inspiratory/expiratory ratio
   c. Prone positioning
   d. High-frequency oscillator ventilation
   Answer: c. Prone positioning has been shown in peer-reviewed medical literature to improve mortality and oxygenation by improving ventilation-perfusion matching and decreasing shunt flow. Low tidal volume (6 mL/kg) ventilation with supplemental positive end-expiratory pressure and fraction of inspired oxygen has been shown to improve mortality in ARDS. Inversed inspiratory/expiratory ratio and high-frequency oscillator ventilation have not been shown to improve mortality in peer-reviewed medical literature.
5. Which of the following techniques does not decrease the incidence of ventilator-associated pneumonia (VAP)?
   a. Emergent intubation in prehospital setting to protect airway
   b. Elevating the head of the bed 30 to 45 degrees
   c. Chlorhexidine oral care
   d. Subglottic secretion drainage
   Answer: a. Emergent intubation has been shown to increase the risk of VAP. Elevation of the head of the bed, chlorhexidine oral care, and subglottic secretion drainage have all been shown to decrease VAP rates in ICU patients.
6. Which of the following patients will likely require parenteral nutrition?
   a. A patient requiring stable low-dose vasopressors
   b. A patient with high-output proximal enterocutaneous fistula
   c. A patient with open abdomen
   d. A patients with gastric residuals of 300 mL
   Answer: b**.** Patients with high-output proximal enterocutaneous fistulas require total parenteral nutrition owing to the lack of absorption of enteral nutrients and worsening of the fistula output. Patients receiving low-dose vasopressors and with open abdomens can tolerate enteral nutrition without complications. Gastric residuals should not be checked on a routine basis, and if they are enteral nutrition should only be held in patients with volumes higher than 500 mL.
7. Optimal resuscitation strategy in patients with hemorrhagic shock includes which of the following?
   a. Transfusion of red blood cells (RBCs)
   b. Infusion of isotonic crystalloids
   c. Infusion of colloids
   d. Transfusion with a high ratio of plasma to platelets to red blood cells
   Answer: d. High-ratio transfusions replace lost clotting factors and decrease the amount of RBCs given in patients with hemorrhage. Isotonic crystalloids, colloids, and RBCs given to patients with active hemorrhage do not replace clotting factors, cause dilution, and lead to an increased number of RBCs transfused.
8. The most sensitive study to diagnose an anastomotic leak after esophagectomy is
   a. Contrast swallow study
   b. Endoscopy
   c. Computed tomography (CT) scan with oral contrast
   d. Examination of perianastomotic drain content
   Answer: b. Endoscopy has a higher sensitivity than the other studies to detect anastomotic leak and also allows possible minimally invasive management of leaks with stent deployment. Contrast swallow, CT scan, with oral contrast and drain content all have low sensitivities of 7% to 50%.

9. The next step in management in a patient with an extremity wound causing concern for necrotizing soft tissue infection and hemodynamic instability would be which of the following?
a. Obtaining plain films
b. Obtaining a CT scan
c. Admission to the ICU for antibiotics and resuscitation
d. Emergent surgery for surgical exploration and debridement
Answer: d. Patients with necrotizing soft tissue infection require emergent operative drainage and debridement and exploration will provide a definitive diagnosis. CT scan, ICU admission for antibiotics and resuscitation, and plain films will only delay definitive management without providing a definitive diagnosis.

10. Prevention of acute kidney injury in ICU patients includes which of the following?
a. Low-dose dopamine
b. N–acetyl cysteine
c. Volume repletion with isotonic crystalloid
d. Administration of bicarbonate
Answer: c. Keeping patients euvolemic with crystalloids to continue adequate renal perfusion has been shown to decrease the incidence of ICU and perioperative acute kidney insufficiency (AKI). N–acetyl cysteine and bicarbonate have not been shown to decrease the incidence of AKI. Low-dose dopamine may increase renal perfusion but has not been shown to decrease the incidence of AKI.

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Postoperative Management of the Cardiac Surgery Patient

EUGENE BUNNELL AND SAMANTHA K. BRENNER

CHAPTER OUTLINE

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Conclusion

Specialized intensive care units (ICUs) are becoming increasingly common. Cardiothoracic critical care has become an emerging subspecialty of critical care focused on ensuring that patients who have undergone major cardiac procedures are closely monitored in an ICU setting. These patients require this level of care during the immediate postoperative period, as they are more likely to be unstable during that critical time during their care. The goal of ICU providers is to identify and address potential problems early to prevent further long-term complications. Although there are many hospital-specific, or even surgeon-specific, protocols used to facilitate care, often the role of the critical care specialist is to identify when a patient's status dictates deviating from routine care to ensure patient safety and prevent complications. This role has become increasingly valued as the population of patients undergoing cardiothoracic surgery becomes sicker, older, and more medically complex with respect to comorbid conditions.[1] This chapter covers the most essential aspects of cardiothoracic critical care starting with immediate postoperative complications followed by organ-system-specific complications that are encountered later in the course of care. For any complications discussed, treatment strategies are provided to readers to mitigate any downstream effects.

Early Postoperative Care

Admission to the ICU

Transport of the patient from the operating room (OR) to the ICU, while seeming routine, can actually engender patient complications. Therefore upon admission to the ICU, both the nursing staff and the providers should conduct a careful check to ensure a safe transition. Common sources of transport and transition-related problems include loss of a secure airway, changes in ventilation and acid/base status from manual bag-valve-mask ventilation, inadvertent medication changes that can lead to loss of sedation, hypotension or hypertension, and arrhythmias. Catheters and monitoring devices can be dislodged, so accurate transduction and monitoring should be confirmed to ensure that any observed disruptions or changes reflect actual patient changes instead of spurious findings.[2]

Another important aspect of admission to the cardiothoracic ICU is direct communication between the ICU and OR staff. Ideally, a verbal handoff should be given from both the surgical and anesthesiology teams. Although automated vital sign capture, electronic health records, and remote telemetry access have all improved transparency between the OR and the postoperative setting, the best practice involves verbal communication. Direct verbal communication between teams ensures questions can be raised, thereby minimizing errors and miscommunications. Although there is no single handoff system or protocol that has been found to be most effective, it is widely held that team-based approaches and standardized handoffs improve patient outcomes.[3,4] As such, the handoff should be conducted as a team, including nursing, respiratory, perfusion, and physician or other providers, spanning multiple disciplines, ICU, OR, and anesthesia. This ensures that all members of the team with essential information or questions will be present during the discussion of the patient's operative course. Some of the basic elements of a standardized handoff from OR to ICU are covered in Box 35.1.[2,5]

• BOX 35.1 Basic Protocol for Admission From the Operating Room to the Intensive Care Unit

- Patient age and name
- Operation performed and preoperative diagnosis necessitating procedure
  - Elective vs. emergent
  - Type of anesthesia used
- Premorbid conditions
  - Relevant medical history, being sure to include renal function preoperatively and allergies
  - Surgical history
  - Social history
- Operative course
  - Blood products utilization
  - Fluids given, urine output recorded
  - Intraoperative pressor support required
  - Intraoperative ventricular function
  - Summary of most recent and salient laboratory findings.
- Location access and drains
  - Lines (pulmonary artery catheter measurement)
  - Drains
  - Tubes (endotracheal tube placement at lips or teeth)
  - Pacing wires (atrial, ventricular, polarity)
- Current medications
  - Drips and rates on arrival
  - Timing of most recent intraoperative antibiotics
- Postoperative treatment plan
  - Blood pressure goals
  - Extubation likelihood (fast-track or not), including a discussion of the airway difficulty or ease

Common Postoperative Management Challenges

Fluid and Line Management

Despite adequate resuscitation and even a positive fluid balance in the OR, patients may still require significant fluid administration postoperatively. Cardiopulmonary bypass can trigger a systemic inflammatory response syndrome (SIRS) in which patients experience significant hypovolemia intravascularly even if total body water levels are significantly elevated. Capillary leak is thought to be the mechanism by which SIRS causes this phenomenon of hypovolemia in the setting of fluid overload. Thus aggressive fluid administration may routinely need to be used after cardiopulmonary bypass. Colloids are generally favored over crystalloid for volume replacement to maintain adequate cardiac output (CO), pulmonary artery catheter (PAC), and central venous pressure (CVP) trends.[2] Although the amount of volume required for any individual patient will vary according to his or her hemodynamics and the operative course, many centers use 2 L as a trigger point to consider causes of hypovolemia other than SIRS alone.

If a patient has been deemed to require fluids based on the CVP, CO, and PAC trends, chest tube output and postoperative laboratory test results should also be taken into consideration. If chest tube output is high or hemoglobin/hematocrit levels are found to be low, blood transfusion should be considered. Conservative transfusion strategies are preferred owing to concern of worse outcomes when blood transfusions are required.[2,6]

Another common postoperative finding is high urine output. In this setting, hemodilution or diuretic administration intraoperatively should be suspected and, in that setting, in addition to fluid administration, potassium levels should be monitored closely and replaced as needed.

Once the capillary leak has resolved, careful consideration should be given to clinician-driven diuresis to promote the elimination of the patient's likely fluid overloaded state. Before diuresis, it is preferable that the patient be hemodynamically stable to tolerate the fluid loss.

In the absence of significant postoperative complications, the instruments used for monitoring perfusion, cardiac function, and bleeding can be removed, particularly to minimize the risk of infections. Foley catheters are commonly removed overnight preceding the second postoperative day if the patient has been mobilized, is not undergoing significant diuresis, and does not have a history of urinary retention. The arterial line can be removed once the postextubation blood gas profile has been reviewed and found to be adequate. The Swan-Ganz catheter should be removed once the patient is hemodynamically stable and no longer receiving ionotropic support. The criterion for chest tube removal is generally drainage of less than 100 mL for the previous 8 hours or less than 50 mL over the previous 4 hours. The chest tube drainage should be serosanguineous (drain-blood hematocrit ratio <0.3)

before removal of the chest tube. The pacing wires should be removed before the removal of mediastinal chest tubes because the main complication of wire removal is bleeding and the first clue may be an increased output from these tubes. A chest x-ray should be used to check for pneumothorax after pleural chest tube removal, but it is not necessary after mediastinal chest tube removal.[7,8]

Hypotension and Hypertension

When evaluating hypotension, the most common cause is venous pooling on transfer from the OR. There are several tests for hypovolemia such as the leg raise test or administering a fluid challenge. However, before evaluating physiologic causes, it is important to rule out iatrogenic causes of hypotension including increased rates of medications that cause hypotension, such as analgesics, sedatives, or vasodilators. Vasopressors that support the blood pressure may have run out, been mixed at the wrong concentration, or disconnected from the patient may be another source of hemodynamic instability. Faulty monitoring, such as an improperly calibrated arterial line or height of arterial transducer relative to the patient, can also cause false indicators of hypotension. If the clinician is confident that there are no iatrogenic causes, then physiologic causes should be considered including bleeding, SIRS, myocardial ischemia possibly as a complication of venous graft dysfunction, arrhythmia, tamponade, tension pneumothorax, and auto–positive end-expiratory pressure.[2] The workup should include analysis of the Swan-Ganz catheter measurements, arterial line measurements and waveform, electrocardiogram (ECG), bedside ultrasound, chest x-ray, laboratory tests including complete blood cell count, and examination of the chest tubes for bleeding.

Similar to hypotension, iatrogenic causes of hypertension—such as inadequate sedation or pain control, hypothermia, increased or incorrect dosing, concentration of vasoconstrictors, arterial monitoring transduction positioning, and calibration errors—are also common and must be ruled out. Other important causes include increased sympathetic tone, hypertrophic left ventricle, and preexisting history of hypertension or stroke. In many cases, a nitroglycerine infusion is sufficient to treat postoperative hypertension. Secondary agents are typically determined by the surgeon or by institutional preference. In general, to protect suture lines, surgeons prefer to err on the side of lower blood pressure, particularly in the first few hours postoperatively, although this may compromise renal perfusion in patients who are hypertensive at baseline.[2]

Warming From Hypothermia

Hypothermia (<36°C) is used intraoperatively to preserve cardiac and neurologic function postoperatively. Unfortunately, hypothermia carries the risk of adverse effects, including increased systemic vascular resistance (SVR), increased risk of arrhythmias, shivering, and coagulopathy. Shivering is of particular concern, as it increases oxygen (O_2) consumption while also increasing carbon dioxide (CO_2) production, sometimes precipitating acidosis. Meperidine and dexmedetomadine have been shown to treat shivering.[9,10] The increase in SVR can mask hypovolemia and increase afterload, which increases myocardial demand. The dangerous combination of increased SVR and coagulopathy can also lead to mediastinal bleeding. Without active rewarming with forced air, hypothermia and its complications, particularly the prolongation of anesthetic time half-life, can also prolong intubation times. There is some evidence that the risk of wound infection also increases with hypothermia as well, likely owing to the immunosuppressive effects of hypothermia.[11–13] Therefore upon arrival to the ICU, steps should be taken to increase core body temperature to normal using forced air, as that has been shown to be more effective at expeditiously increasing core body temperature than radiant heaters or warming blankets. By contrast, heated intravenous fluids and heated ventilator circuits can be used to prevent worsening hypothermia, but they have not been found to improve the rewarming process.[14–16]

Weaning to Extubation

The current trend in cardiothoracic surgery is toward early extubation, variably described as extubation within 6 hours or up to 12 hours. Extubation criteria may differ among cardiothoracic groups, but at a minimum patients should be awake with stimulation and following commands, moving all extremities (i.e., without neuromuscular blockade), minimal chest tube drainage (<50 or 100 mL/h), core temperature above 35.5°C, hemodynamically stable with a CO >2.2 L/min per meter squared, free of arrhythmias, ventilator stability with respiratory rate between 12 and 30 breaths/min, and reassuring arterial blood gas (ABG) levels (partial pressure of arterial oxygen [PaO_2]/fraction of inspired oxygen [FIO_2] >150, partial pressure of carbon dioxide [PCO_2] <50 torr, and pH 7.30–7.50). In some institutions, patients in routine cases are extubated in the OR. The criteria for extubation will likely differ in the OR and be institution-specific.

Using the Society of Thoracic Surgeons (STS) risk models, studies have determined that the following preoperative risk factors predispose patients to longer postoperative intubation times: increasing age, chronic obstructive pulmonary disease, tobacco use, chronic kidney disease, peripheral vascular disease, depressed left ventricular fraction (ejection fraction <30%), myocardial infarction within the past 90 days, preoperative ventilation, prior cardiac surgery, or urgent or emergent surgery.[17] Intraoperative risk factors also exist, such as deep hypothermic circulatory arrest, coagulopathy, and long pump runs (>4 hours). Postoperatively, mediastinal bleeding, hemodynamic instability, respiratory failure, and stroke are the major risk factors for prolonged intubation. It is estimated that about 5% to 10% of patients are unable to be extubated early and remain intubated for 48 hours or longer.[17]

Mediastinal Bleeding and Cardiac Tamponade

The primary mechanism for identifying mediastinal bleeding is chest tube drainage. Mediastinal bleeding can either be "surgical"—meaning it requires repair and revision owing to a technical problem that can result from either arterial or venous bleeding—or it can be "medical" (which will not require surgical intervention). Even in the case of suspected surgical bleeding, control of coagulopathies, blood pressure (maintaining lowest perfusing pressures), and shivering can assist in decreasing bleeding, and its associated harm, until surgical intervention can be obtained. Causes of medical bleeding include preoperative and intraoperative anticoagulant medications, transfusion-associated coagulopathies, hypothermia, low calcium levels from transfusions, and underlying medical conditions predisposing the patient to coagulopathy, such as uremia, hepatic dysfunction, or underlying coagulopathies.

Currently the most accurate and effective measure of bleeding is obtained using a thromboelastogram (TEG). The drawback of even the rapid TEG is that the results take some time. However, it remains the most specific test to identify coagulopathies so that

they can be identified and treated in a more targeted manner.[18] In the absence of a TEG, complete blood cell count, calcium levels, full metabolic panel (to evaluate uremia and hepatic function), prothrombin time, international normalized ratio, and fibrinogen levels can all be useful in identifying sources of bleeding requiring correction.

High chest tube output, while troubling, can be medically managed and temporized awaiting a surgical revision, if that is determined to be required. Immediate laboratory work should, along with clinical judgment and patient history, be used to identify any reversible coagulopathies to assist in temporizing or treating surgical or medical bleeding. A complication of cessation of bleeding using prothrombotic agents is clotting off the chest tubes and promoting cardiac tamponade. By contrast, hemodynamically significant cardiac tamponade usually requires either bedside (if emergent) or operative management for treatment. The mechanism for cardiac tamponade is frequently inadequately drained bleeding into the confined mediastinal space, masked by low chest tube output. If the accumulation of blood is fast enough, the external compression of the heart chambers is not compensated for and the resultant low CO can lead to rapid decline and ultimately death. For this reason, it is important to maintain free draining of the chest tubes and to avoid or break up formation of chest tube clots.

The diagnostic signs of cardiac tamponade include decreased chest tube drainage, equalization of cardiac pressures, increased CVP, pulsus paradoxus, and low-voltage ECG. The best test for cardiac tamponade is a transesophageal echocardiogram (TEE).[2] If bedside transthoracic echocardiogram (TTE) is available, then that can be used as the first confirmatory step when obtaining a TEE may be logistically challenging or require too much time. Unfortunately, although bedside ultrasound is an excellent tool, both ventilatory constraints (e.g., hyperinflated lungs) and chest tube or bandage placement may limit clinicians' ability to perform a diagnostically relevant TTE when cardiac tamponade is suspected in the immediate postoperative period.

Common Low–Cardiac Output Scenarios

In taking care of cardiothoracic surgical patients in the early postoperative period, clinicians need to be able to discern certain useful patterns. Knowing these patterns enables clinicians to anticipate problems rather than reacting to problems. Remaining a step ahead of serious complications is critical to prevent significantly compromised perfusion and avoid the creation of a vicious cycle that is more difficult to treat. Table 35.1 shows the common low CO states and their treatment modalities.[19]

TABLE 35.1 Common Low Cardiac Output States and Their Treatment Modalities

Clinical Syndrome/Scenario	Key Characteristics or Predisposing Factors	Treatment
Vasoconstriction from hypothermia	• Core body temperature <36°C • Often, PAD or PCWP <15 mm Hg	• Active warming of patient with forced air • Fluids during rewarming • Vasodilators to maintain MAP 70–80 mm Hg • Ionotropic support to maintain CI >2.0 L/min per m^2
Vasodilation during rewarming	• Active rewarming • PAD or PCWP <18 mm Hg	• Trial of colloid (or crystalloid) fluid boluses, not to exceed 2 L; goal to maintain PAD or PCWP >18 mm Hg • If fluid fails to raise MAP, then vasopressor support may be considered and selected based on CI and relative need for ionotropic support
Copious urine output with low filling pressures	• Use of mannitol or furosemide in operating room • Hyperglycemia • Normal left ventricular function with a short CPB run	• Discontinue use of tesiritide, fenoldopam, or dopamine • Administration of sufficient fluids to maintain CO and filling pressures but overall negative fluid balance

Impaired left ventricular function	• Ischemia from compromised graft flow or incomplete revascularization
	• Reversible myocardial stunning from cardioplegic arrest
	  • Prolonged CBP (>6 h)
	  • Inadequate myocardial protection
		• ECG and possible re-op or catheterization lab for revascularization
		• Ionotropic support
		• Mechanical support:
		  • IABP
		  • Impella
		  • ECMO
		• TEE or TTE to evaluate function if etiology unclear

Diastolic dysfunction or right ventricular failure	• Elevated filling pressures with normal left ventricular function • Preoperative pulmonary hypertension	• Lusitropic drug administration such as milrinone or nesiritide • Diuresis with concomitant colloid administration to maintain intravascular volume while improving diastolic relaxation • Inhaled nitric oxide for patients with underlying pulmonary hypertension

CI, Cardiac index; *CO*, cardiac output; *CPB*, cardiopulmonary bypass; *ECG*, electrocardiogram; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intraarterial balloon pump; *MAP*, mean arterial pressure; *PAD*, pulmonary artery diastolic pressure; *PCWP*, pulmonary capillary wedge pressure; *TEE*, transesophageal echocardiogram; *TTE*, transthoracic echocardiogram.

Postoperative Resuscitation

Cardiac arrest following cardiothoracic surgery deviates from standard cardiopulmonary resuscitation taught in Advanced Cardiac Life Support (ACLS). Importantly, in the setting of postoperative cardiac arrest it is recommended that the FIO_2 be increased to augment the supply of oxygen available to the patient. In all cases, one of the considerations, which is not a recommendation during standard ACLS protocols, is when to open the chest. For ventricular fibrillation (VF) or ventricular tachycardia (VT), it is recommended that three shocks be delivered before a bedside thoracotomy can be considered. For pulseless electrical activity (PEA) and asystolic arrests, pacing wires should be set to DDD (dual pacing for both chambers, dual chamber activity sensing, and dual response) at 90 beats/min at 10 mV, and 3 mg of atropine may also be given. In all cases, ACLS protocol cardiopulmonary resuscitation and epinephrine can be conducted simultaneously with the other considerations discussed.[20,21] Once shocks have been delivered, amiodarone should be given, or at least considered for VF/VT arrests, and atropine with pacing has been considered in the case of PEA/asystole, then chest reopening within 10 minutes of arrest and 24 hours of initial surgery has been found, to be associated with higher survival rates.[22] Several studies show that the timing of chest reopening is imperative, so standardization and training have been found helpful in ensuring staff are prepared for cardiac arrest. In the right hands, survival of arrest in post–cardiac surgical patients can range from 50% to 79%.[20]

Thoracotomy should include three sterile operators, full drapes, sterile cleaning of chest wall, scalpel for cutdown, wire cutters for wire removal, suction, and sternal retractor. Before cardiac massage, grafts should be visualized and then internal cardiac massage is performed using the two-hand technique for 1 minute before assessing rhythm. Internal cardioversion can be performed in the case of VF/VT or massage can be continued for asystole. In all cases, extracorporeal membrane oxygenator support (ECMO) or other forms of cardiac augmentation, such as intraarterial balloon pump (IABP) or Impella device (Abiomed, Danvers, MA) placement,[20] can be considered.

Late Postoperative Care

Consideration of the immediate issues postoperatively can identify those circumstances that may lead to poorer outcomes, but despite meticulous attention patients can develop various organ system dysfunction. The focus now changes to common conditions that may occur postoperatively based on individual organ systems that may be seen in patients undergoing cardiac surgical procedures.

Cardiology

Arrhythmias

Atrial Fibrillation

Postoperative atrial fibrillation (AF) is one of the most common complications in cardiac surgery and occurs in up to 30% to 50% of patients. Patients are at highest risk in the first 5 days, with a peak incidence on postoperative day 2. The mechanisms of AF are multifactorial and still being identified. Surgical procedures and the stress associated with these procedures increased the incidence, but the inflammatory state induced by cardiopulmonary bypass creates a perfect milieu for this supraventricular tachyarrhythmia.[23]

All postoperative cardiac surgical patients should have electrocardiographic monitoring, which can lead to the initial detection of this arrhythmia. An ECG should be performed for diagnostic purposes when AF is first suspected. Documented AF should have duration of at least 30 seconds, but new-onset AF is a first-time occurrence of any duration. The ventricular rate is usually 90 to 180 beats/min with an irregular R-R interval with the loss of a morphologically consistent P wave.

AF is associated with increased mortality and length of stay. The frequency of occurrence makes it the most costly complication after cardiac surgery.[24] There is also an association with cognitive impairment and treatment with antiarrhythmics add to this cost. Given the increased mortality and cost associated with this complication, many studies have been done looking at the prevention of AF after cardiac surgery. There is some support for carvedilol as being superior to metoprolol for preoperative prophylaxis. Although the effects on the occurrence of supraventricular tachyarrhythmia and hospital length of stay were reduced, the influence on other measures of morbidity and mortality after cardiac surgery were unclear.[25] Sotalol and amiodarone are more effective in prophylaxis postoperatively, but adverse effects associated with these agents limit their use to prophylaxis in patients at high risk for postoperative AF. Statins have been shown to be effective in reducing new-onset AF in postoperative patients naïve to statins and deserves further study.[26] Calcium channel blockers and digoxin have no role in postoperative AF prophylaxis.

The previously mentioned modalities are entities that have been initiated preoperatively or perioperatively. Biatrial pacing can be initiated in the immediate postoperative period and has been shown to be effective at prevention of postoperative AF. The efficacy of single-chamber atrial pacing has not been determined.

Treatment of AF in the postoperative setting depends on two factors: onset and stability. In clinically unstable patients, as defined by acute heart failure, hypertension, or myocardial ischemia, electrical cardioversion may be warranted. For patients who are clinically stable, correction of electrolyte, oxygenation, and perfusion abnormalities as well as volume status should be addressed. The onset of AF allows more options after patient stability has been assessed. New-onset AF makes elective cardioversion either chemical or electrical a safe option. In general, cardioversion within 48 to 72 hours after onset is acceptable without investigation for left atrial appendiceal thrombus. A recent study of rate versus rhythm control for AF after cardiac surgery showed no difference in hospitalization days, persistence of AF at 60 days, or rate of complications.[27]

The equivalence in clinical outcomes between rate and rhythm control leaves the decision in the hands of providers. A rate control strategy is best accomplished using β-blockers. They are more effective than nondihydropyridine calcium channel blockers at controlling heart rate. Digoxin has some role in rate control but usually as an adjuvant therapy because of its narrow therapeutic window. Amiodarone can be used as a rate-controlling agent, but it may also lead to chemical cardioversion and care should be taken to rule out a left atrial appendage thrombus.

Rhythm control can be accomplished with either electrical or pharmacologic cardioversion. The first-line agents for pharmacologic cardioversion are dofetilide, ibutilide, flecainide, and propafenone. Flecainide and propafenone are contraindicated in patients with coronary artery disease or structural heart disease and they should not be considered in postoperative cardiac surgical patients. Amiodarone is very effective in both conversion and maintenance of sinus rhythm, but the side effect profile (specifically pulmonary,

liver, and thyroid toxicity) limits its consideration as first-line therapy.

Patients who have AF of greater than 48-hour duration warrant a transesophageal echocardiogram to rule out left atrial appendage thrombus prior to cardioversion (either electrical or pharmacologic). The presence of the left atrial appendage thrombus necessitates anticoagulation for at least 4 weeks before elective cardioversion. After elective cardioversion anticoagulation is indicated for 4 to 6 weeks because there is a lag between the mechanical function and electrical restoration of sinus rhythm that may allow for thrombus formation.

Anticoagulation decreases the risk of stroke significantly in patients with AF. All patients with AF of greater than 48-hour duration should undergo anticoagulation unless there is a specific contraindication. There are multiple scoring systems for risk assessment when deciding about anticoagulation. The most widely used are CHA_2DS_2-VASc (CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Prior Stroke or TIA or thromboembolism [doubled]) for stroke risk assessment and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio, Elderly [≥65 years], Drugs/alcohol concomitantly) for risk of gastrointestinal (GI) bleeding.[28]

Heparin or enoxaparin as a bridge to full anticoagulation with warfarin is the standard and has applicability across all cardiac procedures. Dual antiplatelet therapy has been used but is less effective in stroke prevention and is associated with an increased risk of bleeding. Novel oral anticoagulants are popular because of efficacy and they have no need for routine monitoring of the coagulation profile. Novel oral anticoagulants are contraindicated in renal failure and valve replacement and are difficult to reverse in the event of bleeding.

Ventricular Tachyarrhythmias[29]

Premature ventricular complexes (PVCs) are commonplace after cardiac surgery and are usually related to electrolyte or other metabolic imbalances. They do not increase the risk of malignant dysrhythmias if they are isolated and infrequent. When PVCs are more frequent, then ventricular function may be affected. The management of simple unifocal PVCs does not require antiarrhythmic therapy but only correction of the aforementioned imbalances.

VT and VF are infrequent after cardiac surgery, with a reported incidence of less than 1.5%. The risk factors are multiple, including hypoxia, hypovolemia, electrolyte imbalances, and hemodynamic instability. Reperfusion after cardiopulmonary bypass is unique in cardiac surgery and the effects are limited. Inotropes and antiarrhythmics are frequently used in cardiac surgical units and may further irritate the recently violated myocardium. The area that needs to be investigated thoroughly when ventricular arrhythmias develop is new myocardial ischemia, specifically acute graft closure. These patients can be refractory to traditional antiarrhythmic therapy and intervention with cardiac catheterization or reoperation may be needed.

The principles of ACLS apply in these patients. Hemodynamic instability and sustained VT require electrical cardioversion but stable patients can undergo synchronized cardioversion or antiarrhythmic therapy. Lidocaine is the first choice and is used first as an intravenous bolus and is then administered via maintenance drip. Procainamide is generally a second-line drug. Significant toxicities from both lidocaine and procainamide can develop, especially in patients with renal insufficiency. As a result, amiodarone has become a more preferred choice as the first-line therapy. Amiodarone can be used in patients with impaired cardiac or renal function and is easily transitioned to an oral equivalent. The toxicities associated with amiodarone are still a consideration but benefit outweighs the risk in this population.

Individuals with impaired ventricular function (less than 40% left ventricular ejection fraction) may benefit from automatic implantable cardioversion defibrillation, but there is a waiting period postoperatively before implantation. This period allows time for left ventricular function to recover, which may lead to a reduced arrhythmic potential. These individuals may be fitted with the life vest or temporary external defibrillator until an automatic implantable cardioversion defibrillator can be appropriately implanted.

Bradyarrhythmias[29]

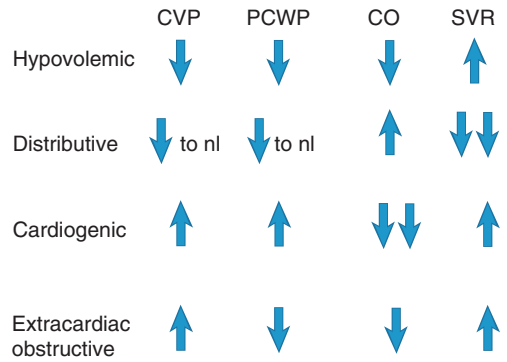
Bradyarrhythmias are common after cardiac surgery, especially after valve surgery. Preoperative sick sinus syndrome (SSS) or atrioventricular block (AVB) should heighten awareness for postoperative rhythm disturbances. Affected individuals will have temporary epicardial wires placed intraoperatively and these bradyarrhythmias may be limited to the immediate postoperative period. Because node recovery in SSS is frequent but unpredictable, recovery from a complete AVB is infrequent. The usual practice is to implant a permanent pacemaker if AVB or severe SSS lasts longer than 5 to 7 days postoperatively.

Shock

Shock is defined as the disruption of perfusion causing cellular injury that is initially reversible but, if left uncorrected, can lead to organ system dysfunctions and ultimately death. The Hinshaw-Cox classification of shock has applicability to the management of postoperative cardiac surgical patients. The basis of this classification is the understanding of cardiac performance variables, preload, afterload, and contractility. There are four categories of shock in this model, each of which has distinct hemodynamic profiles.

1. Hypovolemic shock is a disorder of inadequate preload resulting in impaired cardiac performance based on Starling's law the heart; examples are GI bleeding or dehydration.
2. Distributive shock is a disorder of maldistribution of volume. The issue is not a lack of volume but that the volume has been diverted out of the vascular compartment. There is a vascular dilation that leads to a markedly decreased afterload. An example is septic shock after adequate volume replacement with vasodilation and leaky capillary beds, leading to third spacing of volume or maldistribution of volume out of the vascular space.
3. Cardiogenic shock is the impairment cardiac performance based on a weakness in the muscle or impairment in contractility. An example is an acute myocardial infarction with left ventricular dysfunction.
4. Extracardiac obstructive shock is a disorder of obstruction of blood flow into or out of the heart. Examples are multiple and varied but obstruction is an important component of this disorder. Examples are tamponade, constrictive pericarditis, pulmonary embolism (PE), and tension pneumothorax. To some extent right ventricular (RV) dysfunction can be listed in this category because of its typical hemodynamic profile.

As Fig. 35.1 suggests, hypovolemic shock is a disorder of preload, distributive shock of afterload, and cardiogenic shock of contractility. Extracardiac obstructive shock is the result of a mechanical



• **Fig. 35.1** Hemodynamic profiles in shock. *CO,* Cardiac output; *CVP,* central venous pressure; *nl,* normal; *PCWP,* pulmonary capillary wedge pressure; *SVR,* systemic vascular resistance.

disruption outside of the heart and appears to be a miscellaneous category that does not fall into the confines of this paradigm.

Hypovolemic Shock

Hypovolemic shock is the easiest issue to deal with in the postoperative period. Most cases are optimally monitored intraoperatively with either a transesophageal echocardiogram or PAC and oftentimes both. It is rare for patients to be hypovolemic before their chest is closed. The management of volume is a matter of matching input with output. Drainage from urinary catheter, gastric tubes, and thoracic tubes as well as insensible losses should be accounted for. Most patients will have a CVP monitoring device and sometimes a pulmonary artery catheter. Reasonable goals are a CVP between 8 and 14 mm Hg during positive-pressure ventilation. Pulmonary capillary wedge pressure between 12 and 16 mm Hg should be an adequate preload for most patients. Disorders leading to hypovolemia during the postoperative recovery phase are bleeding, rewarming, diuresis, and on rare occasion, underresuscitation intraoperatively.

Distributive Shock

Cardiopulmonary bypass is an inflammatory-inducing procedure.[30,31] The immune system is activated with an exuberant production of cytokines and other modulators of inflammation. It is not uncommon for a vasoplegic syndrome to develop in patients after cardiopulmonary bypass.[32,33] This may occur in 5% to 25% of patients. This syndrome is manifested by peripheral vasodilation that requires treatment with vasopressors. The hemodynamics in this vasoplegia are consistent with distributive shock and on occasion can be refractory to routine treatment with vasoactive medications. The identified pathways are threefold; (1) activation of adenosine triphosphate–sensitive potassium channels on vascular smooth muscle, (2) activation of an inducible form of nitric oxide synthetase, and (3) a deficiency of vasopressin that may contribute to this vasodilation.[34] Risk factors for developing the vasoplegic syndrome have been identified as preoperative treatment with angiotensin-converting enzyme inhibitors or β-blockers and preoperative requirement of vasopressors. In addition, patients undergoing non–coronary artery bypass grafting surgical procedures were at higher risk for developing the vasoplegic syndrome.[35]

The vasoplegic syndrome carries a poor prognosis, and mortality for individuals with catecholamine refractory vasoplegia for 36 to 48 hours is as high as 25%. The treatment of the vasoplegic syndrome often requires high-dose vasopressors with vasopressin blended in after administration of norepinephrine and phenylephrine. There is no advantage to vasopressin greater than 0.04 units/min and even lower doses may be effective due to vasopressin deficiency. Methylene blue is an intriguing agent that has been used in refractory vasoplegic syndrome.[36] It works by blocking guanylate cyclase, which is the enzyme that catalyzes guanylate triphosphate to cyclic guanylate monophosphate the latter is part of the messenger system that leads to smooth muscle relaxation. Because this vasoplegia is a single insult event, if patients can be supported through the sequela related to this event with minimal organ damage, survival to hospital discharge seems an obtainable goal.

• **BOX 35.2 Causes of Cardiogenic Shock**

Ischemic-Mediated
- ST-elevated myocardial infarction
- Complications from myocardial infarction
  - Ventricular septal rupture
  - Free wall rupture
  - Papillary muscle rupture

Cardiomyopathy
- Acute myocarditis
- Takotsubo
- Hypertrophic

Valvular
- Aortic stenosis
- Mitral regurgitation

Endocrine
- Adrenal insufficiency
- Hypothyroid/myxedema

Right Ventricular Failure
Myocardial Dysfunction After Cardiopulmonary Bypass

Cardiogenic Shock

The diagnosis of cardiogenic shock was initially described as a result of non–ST-elevated myocardial infarction. The territory affected is the anterior wall or the left anterior descending distribution, which leads to a markedly reduced left ventricular ejection fraction, hypotension, and high filling pressures with pulmonary edema. Although this remains the most common cause of cardiogenic shock, many other disorders can present with this picture (Box 35.2).

This broad differential has few clinically applicable disorders that are encountered in the postoperative patient. Myocardial dysfunction after cardiopulmonary bypass and ischemic mediated disease are the most commonly encountered reasons for cardiogenic shock in this population.

Myocardial Dysfunction After Cardiopulmonary Bypass

A temporary impairment in contractility is seen after cardiopulmonary bypass. There are multiple theories to explain this, but the concept of myocardial stunning seems to be the prevailing thought at this time. The inflammatory state induced during heart surgery may also play a role in this impairment in contractility seen after the myocardium is reperfused. This is a transient phenomenon and resolves within 24 to 48 hours. Management of these patients includes inotropic support and management of the

volume overload that was related to the vasodilatation and capillary leak seen and addressed intraoperatively.

Ischemia

It is counterintuitive that individuals who have recently had cardiac surgery should become actively ischemic. Technical issues may develop intraoperatively and in the postoperative period that place these grafts at risk. Misplaced sutures, smaller receiving vessels, and inadequate revascularization may lead to postoperative ischemia. In addition, embolic phenomena from atherosclerotic plaque, thrombus, or air from the heart that may not have been completely deaerated can lead to ischemia. Postoperative ECGs should be obtained in all patients. If there are ischemic changes with clinical consequences, the patient may need investigation with cardiac catheterization or reoperation. It is rare that ischemia at this time leads to cardiogenic shock and it is more likely that the decrease in cardiac performance is related to the transient dysfunction described previously.

There is also a syndrome of refractory arrhythmia related to ischemia. Affected patients may develop recurrent ventricular tachycardia that is difficult to control with antiarrhythmics and cardioversion. These individuals also deserve further investigation and if possible, revascularization.

Devices

Multiple temporary devices are available to support a failing ventricle. The device longest in use is the intraaortic balloon pump (IABP).[37] This device can be placed in the aorta with the tip just below the left subclavian artery and may be inserted in the OR or at the bedside percutaneously. The IABP reduces afterload by deflating during systole and improves coronary blood flow by inflating in diastole. Both actions support the failing left ventricle until recovery and improve coronary perfusion.

The TandemHeart (Kardia srl, LivaNova, London, United Kingdom) and the Impella device are temporary devices that can support the systolic function of the failing ventricle.[38] Just introduced, but in limited centers, is an RP Impella that provides support for the failing right ventricle. This is a device that does not require arterial access but does require systemic anticoagulation because of the risk for thrombosis. Data are being gathered on safety and efficacy, but this device will provide another mode of support that has been missing.

ECMO is a modality that moves cardiopulmonary bypass out of the OR and into the ICU. This approach is reserved for the sickest patients and can support the failing heart or lungs and frequently both. It is a labor-intensive method of support. Patients who are candidates and who use ECMO should have a reasonable preoperative prognosis if they can survive this acute insult and sequela. ECMO may also be a bridge to transplantation or a permanent device if applicable. Centers that provide ECMO are limited, but it is becoming more accessible as more centers are developing these programs.

Permanent left ventricular assist devices as a bridge to transplantation or destination therapy are becoming more common. Immediate postoperative care should be provided in certified, specialized centers.[39] These devices are generally not placed in an emergent fashion as patients require rigorous evaluation before implantation.

Extracardiac Obstructive Shock

This form of shock can be the most difficult to recognize and diagnose. Treatment consists of relief of the obstruction and time is of great importance. Patients may appear to be in cardiogenic shock with dyspnea, jugular venous distention, and cyanosis. Attempts at preload reduction may precipitate a deterioration and should be avoided. Volume administration may be the only way to support these patients until the obstruction has been addressed. These are patients who are preload dependent. Vasopressors are usually ineffective because these individuals are maximally vasoconstricted. Pericardial pathology, pneumothorax, PE, and RV dysfunction are diagnoses that must be considered in patients with suspected extracardiac obstructive shock.

Pericardial Disease

Constrictive pericarditis is not often seen in the postoperative patient because the pericardium has just been opened and examined. If there is overt pathology, the surgeon would have addressed it at the time of surgery.

Closure of the pericardium at the end of the surgical procedure is at the discretion of the heart surgeon. The decision and consideration of the benefits of a closed pericardium are considered at the end of the procedure. Pericardial closure makes reoperation in the remote future technically easier and less hazardous. The closed pericardium prevents adherence of the heart to the back of the sternum and these patients will develop fewer pericardial adhesions. There is some evidence that a closed pericardium leads to less tamponade.

Tamponade can be early or late. In the first 24 hours, the anticoagulation has been reversed and freshly disrupted vessels have not had the opportunity to clot, but the drainage tubes may have been ineffective, allowing for accumulation of blood or fluid in the freshly invaded pericardial space. A later tamponade may be seen after pericardial or mediastinal tubes have been removed. Patients may not demonstrate the typical physical findings of hypotension, pulses paradoxus, or equalization of intracardiac pressures. Postoperative echocardiography is diagnostic and the increasing access of portable ultrasonography has been revolutionary. Percutaneous drainage may be dangerous and lead to cardiac laceration as the pericardial effusion may be loculated by adhesions. This should be undertaken only with visualization (if at all) and surgical reexploration/drainage is best.

Pulmonary Embolus

This is a rare disorder in postoperative cardiac surgical patients. Should shock develop after an embolus, thrombolytics are not an option and operative embolectomy may be necessary. Heparinization should be initiated until definitive therapy is available.

Tension Pneumothorax

Most patients emerge from cardiac surgery with multiple thoracostomy tubes. Tension physiology can occur with occlusion or kinking of these tubes. On occasion, loculated pneumothorax or tension bullae can be seen in individuals with bullous lung disease. Careful examination of the tubes, removing the dressing to examine the site, reinforcing connections, and stripping or suctioning may relieve the source of obstruction. A loculated pneumothorax may require separate chest tube or needle decompression. There is danger in patients with bullous lung disease whose conditions are misdiagnosed as loculated pneumothorax. Disruption of these bullae with a needle or chest tube may lead to a bronchopleural fistula that may require surgical correction.

Right Ventricular Dysfunction

RV dysfunction is not uncommon after cardiac surgery. The hemodynamic parameters are similar to extracardiac obstructive shock in that left ventricular filling is low to normal and there appears to be

elevated right-sided filling pressures. The etiology of this disorder is not related to obstruction but to cardiac dysfunction, specifically of the right ventricle. This is more common in those individuals with preexisting pulmonary hypertension as they may be at the limits of their RV compensation. Treatment involves correction of the RV afterload, judicious attention to preload, and some assistance, either mechanical or pharmalogic,[40] with contractility. Nitric oxide may be of benefit after acidosis and hypoxemia have been addressed. Inotropic support with dobutamine, milrinone, and epinephrine may be necessary to support the failing right ventricle. Levosimendan is an inotrope that works by increasing calcium sensitization of troponin C with beneficial effects in RV failure. This agent is not currently available in the United States. With adequate support, RV dysfunction may take 5 to 7 days to resolve.

Pulmonary

Respiratory care in the cardiac surgical ICU has benefited greatly from protocol-driven extubation from mechanical ventilation.[41] The benchmark standard for the STS is 6 hours from the time of arrival in the unit. Some institutions are extubating patients in the OR.[42] Despite these advances, meticulous care must be administered so that the strides can continue to prove beneficial to this population.

Atelectasis

There have been many improvements in surgical techniques, but entering the thoracic cavity and pleura irritation from chest tubes can be painful. Adequate analgesia and incentive spirometry are mainstays in the management in the first 24 to 48 hours. Volume overload can lead to hypoexpansion, especially in the lung bases. Earlier mobilization helps but it also leads to increased blood flow in the bases, which may increase hypoxemia by shunting. Patients can develop fever, impaired gas exchange, and if not addressed, postoperative pneumonia in the areas of atelectasis. Treatment is best begun proactively. Correction of volume overload, pain management, early mobilization, incentive spirometry, and aggressive pulmonary toilet with noninvasive positive pressure may also be beneficial. Continuous positive airway pressure, bilevel positive airway pressure, and EzPAP positive airway pressure system (Smiths Medical, Minneapolis, MN) are modalities that may be used by respiratory therapy that may help to avoid reintubation.

Pleural Effusion

Most patients entering the ICU from the OR will have chest tubes, either mediastinal or pleural, and frequently both. These tubes generally remain in place for 24 to 48 hours or until drainage is usually less than 200 mL for a 24-hour period. The normal amount of pleural fluid is about 10 to 15 mL, which lubricates and allows smooth sliding of the parietal and visceral pleura. The turnover of pleural fluid can be about 1 to 2 L/day, so chest tube drainage will usually be a measurable amount.

These tubes will not allow for an accumulation of significant amount of fluid in the thoracic cavity unless the fluid is loculated or the tube is occluded (by fluid, blood, or mechanical obstruction). Rarely the tube may be malpositioned in a fissure and not able to adequately drain the accumulating fluid. Effusions can become an issue after the tubes have been removed, because this fluid may not be susceptible to more aggressive diuresis. These residual or recurring effusions do not need to be drained unless they are accompanied by respiratory symptoms or impairment in gas exchange. A simple thoracentesis or small pigtail catheter with collection device may be the solution without replacing a larger chest tube.

Pneumothorax

Pneumothorax is not uncommon in the immediate postoperative period and can be corrected by increasing suction on the collection devices. If there is an air leak in the chest tube that is persistent throughout the respiratory cycle, then connections must be examined and reinforced. A more difficult problem is a disruption of a pleura that may take a few days to heal. Occasionally a video-assisted thoracotomy is necessary to correct this defect.

Acute Lung Injury

Cardiopulmonary bypass can lead to a profound inflammatory response, especially in prolonged procedures. Hemodilution and inflammation may lead to reperfusion injury in the lungs. Although this is not a recurring injury to the lung parenchyma, it can lead to a clinical picture similar to the acute respiratory distress syndrome. Reactive airways, diminished pulmonary compliance, decreased PaO_2/FIO_2 ratios, and increased alveolar-arterial gradients may be observed. These individuals will benefit from judicious fluid management and low tidal volume ventilation with increased positive end-expiratory pressure until recovery. The time course to recovery is more rapid than in traditional acute respiratory distress syndrome, unless there is a secondary insult or an inattention to ventilator-induced lung injury.

Transfusion-Related Lung Injury

Transfusion-related lung injury (TRALI) is the most common cause of morbidity or mortality related to the administration of blood products.[43] This results from the deposition of activated neutrophils in the parenchyma of the lung with increased extravascular lung water and an impairment in gas exchange.[44] The current hypothesis is that there is a "two-hit phenomenon." The first insult is that the patient is in a heightened inflammatory state. This sensitizes the individual for the second "hit," which is the transfusion with blood products that further activates or enhances the proinflammatory state.[45] Cardiopulmonary bypass provides the first hit with overall activation of the immune system. The intraoperative or postoperative need for transfusion is the second insult. It is not always possible to avoid transfusion, but there are clear risk factors that increase the incidence of TRALI in these individuals. In a case-controlled study, risk factors were divided into recipient and transfusion related factors[43] (Box 35.3).

Of note, the age of the red blood cells has little or no risk for TRALI. Despite the controversy that surrounds the age in storage of packed red blood cells,[46,47] treatment of TRALI is supportive. The principles that apply to acute lung injury are used in this disorder. Volume restriction and low tidal volume ventilation are mainstays of therapy. There are anecdotal reports that steroids may help but have not proven beneficial in a randomized, controlled fashion and cannot be recommended.

Diaphragmatic Dysfunction[48]

Unilateral diaphragmatic elevation may be an incidental finding on routine chest x-ray after cardiac surgical procedures. This is

• BOX 35.3 Factors Leading to Transfusion-Related Lung Injury

Recipient
Shock
Higher interleukin 8 levels
Liver surgery
Chronic alcohol use and abuse
Higher peak airway pressures on mechanical ventilation
Current smokers
Positive fluid balance
Transfusion
Plasma or whole blood from female donors
Volume of antineutrophil antigen-positive blood
Volume of human leukocyte antigen class II antibodies

From Toy P, Gajic O, Bacchetti P, et al. Transfusion-Related Acute Lung Injury: Incidence and Risk Factors. Blood. *2012;119:1757–1767.*

seldom clinically relevant and is much more infrequent in modern cardiac surgery. Hypothermic injury to the phrenic nerve was the most common etiology but the use of cardiac insulation pads has led to a decrease in incidence. This "stunned" diaphragm may be clinically relevant if the patient has a preexisting unilateral paralysis on the contralateral side resulting in inadvertent bilateral paralysis. The diagnosis of unilateral diaphragmatic paralysis can be made using a fluoroscopic sniff test. Transdiaphragmatic pressures can be measured using lower esophageal and gastric manometry, which are invasive. Bedside ultrasound has been used as a diagnostic tool for both unilateral and bilateral dysfunction and can also be used to monitor recovery of the paralyzed diaphragm.

Deep Vein Thrombosis and Pulmonary Embolism

The rate of deep vein thrombosis (DVT) after cardiac surgery had a reported incidence of 48.3% in the early 1990s. But a larger randomized prospective study from the same institution with the same investigators published several years later reported an incidence of 20%.[49] The major differences between the two studies were the randomization of the second trial and earlier mobilization of patients in this latter trial. These studies also found that the occurrence of DVT in the lower extremity was independent of the side of vein harvesting. The development of DVT could not be explained by the trauma or disruption of the venous system in coronary bypass patients. Current estimates are that DVT occurs in 23% of all ambulating cardiac surgical patients treated with graded compression stockings and aspirin. As with most patients, DVT in cardiac surgical patients is mostly silent and difficult to recognize.

The risk of DVT and PE is increased in individuals with immobility, delayed recovery, or congestive heart failure. The risk may be accentuated in this group by prior history of DVT/PE, recent myocardial infarction, obesity, hyperlipidemia, and heparin-induced thrombocytopenia (HIT).

Given the high risk of DVT in patients undergoing cardiac surgery, the actual incidence of PE is low and fatal PE is negligible. Even though these rates are lower than other major surgical specialties, this should not be an argument against DVT prophylaxis. Strong consideration should be given to prophylaxis in the first 48 hours postoperatively. Sequential decompression devices have been used in patients who remain intubated in the ICU but are not recommended as routine primary prophylaxis after cardiac surgery. There has been no evidence that prophylactic dosing of anticoagulants leads to increased bleeding in routine postoperative cardiac surgical patients if initiated after 48 hours.

Pneumonia

Postoperative pneumonia is common after cardiac surgery with a reported prevalence of between 2% and 10%.[50] As a result, this is the most common infectious complication after cardiac surgery. The first postoperative week finds patients at greatest risk. Not all pneumonias are ventilator associated, although these are considered to be more preventable and have garnered much attention. Independent of the reason for pneumonia, there is an association with increased mortality in the cardiac surgical patients.

The Institution for Healthcare Improvement developed a "bundle" for prevention of ventilator-associated pneumonia that includes five elements:

1. Elevation of the head of the bed
2. Sedation interruption for readiness to wean
3. Peptic ulcer prophylaxis
4. Deep venous thrombosis prophylaxis
5. Daily oral care with chlorhexidine

In addition, Fitch and Whitman[51] identified two risk factors that are independently associated with ventilator-associated pneumonia. Individuals who receive perioperative transfusion of blood products and require reintubation are at much higher risk for postoperative pneumonia.

A series of factors have been recognized that identify patients with a higher risk of developing postoperative pneumonia not associated with mechanical ventilation.[50] Age older than 70 years, chronic obstructive pulmonary disease, preoperative left ventricular ejection fraction less than 60%, the interaction between the transfusion of packed red blood cells, and an increased duration of cardiopulmonary bypass were all independent risk factors that increase the incidence of postoperative pneumonia. These factors were used to create a risk score to predict postoperative pneumonia and cardiac surgical patients. This may be a useful tool in initiating antibiotic therapy earlier because it is becoming increasingly evident that delaying antibiotics in infectious disease is associated with a higher mortality.[52]

Tracheostomy

The optimal timing of tracheostomy is fraught with controversy. There is a trend toward early tracheostomy in respiratory failure. Tracheostomy in cardiac surgery had typically been delayed because of concern over contamination of the sternal wound and an association with mediastinitis. This concern was unfounded. There was also no benefit in patient outcomes in cardiac surgery that would advocate for delaying tracheostomy.[53] There is no evidence for optimal timing of tracheostomy in the cardiac surgical population.

Neurology

A spectrum of neurologic complications may be seen in the postoperative cardiac surgical patient.[54] This is not unexpected because the same risk factors that predispose individuals to heart disease also lead to cerebrovascular disease. Diabetes, hypertension, smoking history, and hyperlipidemia can lead to systemic pathology

TABLE 35.2 Incidence of Stoke Associated With Cardiac Surgery

Type of Surgery	Incidence of Stroke
Isolated CABG	1.4%–3.8%
CABG and valve	7.4%
Isolated valve	4.8%–8.8%
Multiple valves	9.7%
Aortic surgery	8.7%

CABG, Coronary artery bypass grafting.
From Selim M. Perioperative Stroke. *N Engl J Med.* 2007;356(7):706–713.

that is not limited just to heart disease. Neurologic findings in this population can be related to the operative procedure. Different procedures have different risks. A prime example is that of stroke. The risk of stroke is variable depending on the procedure performed (Table 35.2).

Although stroke is a devastating complication of the cardiac surgical population, it is not the only neurologic issue that these patients face. Consideration of postoperative neurologic care can be divided into a more generalized (global) or more localized (focal) process.

Focal Neurologic Dysfunction

Focal or localized neurologic complications in cardiac surgery can be limited, as in transient ischemic attacks (TIAs), or long-lasting with increased morbidity and mortality, as with certain vascular distributions in stroke. Focal neurologic defects related to stroke can be associated with a mortality of up to 20% in the first postoperative month. This can also prolong both ICU and hospital length of stay. Stroke/TIA are the main focal complications but brachial plexus injury and phrenic nerve paresis/paralysis can also be seen.

Stroke[55]

The risk of stroke in cardiac surgery can be minimized but the goal of never having a postoperative stroke is thus far unobtainable. Systemic anticoagulation with high-dose heparin and preoperative identification and intervention in patients with carotid disease have gone a long way minimizing the risk. There are aspects of open-heart surgery that are modifiable, but at times, unavoidable. Cross-clamping and cannulating an atherosclerotic aorta that results in microemboli traveling to the brain remains problematic. Opening the cardiac chambers with entrapment of air and possible air embolus remains another possible source for embolic stroke.

The majority of strokes are embolic and very few are initially hemorrhagic, despite the use of supertherapeutic dosing of heparin in cardiopulmonary bypass. Hemorrhagic conversion can occur in up to 20% of ischemic strokes, whereas embolic strokes present with more focality owing to involvement of a typical vascular territory. Hemorrhagic strokes can have a delayed awakening and coma. Strokes related to hypoperfusion lead to defects in watershed areas where there is a transition between major vascular distributions.

Once a stroke is suspected a computed tomography (CT) scan must be obtained. The timing for an intervention in stroke management is critical but because cardiac surgical procedures last between 3 and 6 hours the time of onset of the stroke is only able to be estimated. The CT scan can show a more discreet stroke, which suggests a more prolonged delay in the identification of the event. These individuals are placed in a more conservative support treatment strategy. Tolerance of a higher perfusion pressure, judicious fluid administration, and limiting anticoagulation and antiplatelet therapy to avoid hemorrhagic conversion are the mainstays of the conservative support strategy. More often in acute stroke (within 3–8 hours) only subtle findings are evident on CT scan. The loss of a gray-white interface, focal effacement, suggestion of a hyperdense area that conforms to neurologic deficit, and the loss of insular ribbon may be seen early in stroke. These individuals would be candidates for possible intervention. Because thrombolytic therapy is contraindicated in the immediate postoperative period, they would be considered for mechanical embolectomy if available. Although magnetic resonance imaging is much more sensitive in the acute stroke, devices, epicardial pacing wires, and the hemodynamic stability of the patient often preclude travel to remote areas that usually house the magnetic resonance scanner.

Anticoagulation is not usually administered in these patients because of the risk of bleeding in the fresh postoperative patient. There is also concern for hemorrhagic conversion in this tenuous vascular distribution. There are certain clinical circumstances that warrant consideration of anticoagulation. Internal carotid dissection, basilar stenosis, and AF with embolic stroke deserve a more in-depth risk-benefit consideration.

The longer the time since surgery that the stroke occurs, the more therapeutic options are available. Thrombolytics may become an option. Intraarterial thrombolytics were shown to be safe and effective in postoperative cardiac surgical patients. Administration of intraarterial thrombolytics was performed within the first 12 days postoperatively (average 4.3 days).[56] Although this is a small series, it opens the discussion and consideration of a previously closed therapeutic avenue.

Transient Ischemic Attacks

TIAs are reversible neurologic defects that spontaneously resolve within the first 24 hours of occurrence. To some extent a TIA is a threatened stroke that abates without neurologic residual. It should be viewed as a warning sign and an in-depth investigation to discover the cause for this near miss should be undertaken. Because there is no obvious ischemia or infarction, anticoagulation after resolution should be a serious consideration.

Brachial Plexus Injury

Injury to the brachial plexus during cardiac surgery is not infrequent but is underdiagnosed and underreported because it is often transient.[57] The mechanisms proposed for this injury are multiple. Hyperabduction of the arms, traction, and compression during sternal retraction and direct trauma owing to insertion of internal jugular lines have been postulated as possible mechanisms of injury. Harvesting of the internal mammary artery with asymmetric sternal retraction has been reported to have a higher rate of plexopathy. It is important to distinguish between brachial plexus injury and ulnar neuropathy. This injury to the ulnar nerve is less frequent after the recognition that this disorder was due to intraoperative positioning and compression of the ulnar nerve in the posterior condylar groove, although transient ulnar neuropathy tends to persist longer than brachial plexopathy.

Phrenic Nerve Injury

This isolated neuropathy, with resultant hemidiaphragm dysfunction,[48] was recognized as being related to cold cardioplegia and

is much less common with the use of cardiac insulation pads. Further discussion of this disorder was reviewed in the pulmonary section.

Global Neurologic Dysfunction

Global neurologic dysfunction is more anxiety-provoking to families than to individual patients. Although seizures can be more focal motor in origin, the progression to status epilepticus and resultant postictal state would argue that this is a global disorder. In addition to seizures, coma, delirium, and cognitive decline are considered in this category of generalized neurologic dysfunction.

Coma

Coma is defined as a state of deep unconsciousness that lasts for a prolonged period. In cardiac surgical patients, the use of anesthetics, opiates, and other central nervous system (CNS) depressants must have time to metabolize before coma is considered. Delayed awakening may be a more appropriate label for this group of patients. When patients are slow to emerge from anesthesia, a CT scan of the brain should be performed. Up to 20% of patients with stroke may have delayed awakening and some may have a hemorrhagic ischemic component.[58] Serial evaluations and documentation are crucial. The Glascow Coma Scale score may be a good starting point and is reproducible across examiners. Individuals with preoperative renal or hepatic dysfunction are at risk for delayed awakening. The proposed mechanism is impaired metabolism of CNS depressant drugs. Individuals with severe heart failure and an idiopathic delayed awakening have a worse prognosis.

Delirium[59]

Delirium is a prevalent issue across all ICUs. There are multiple factors that contribute to this disorder. The aging population, disruption of sleep patterns, CNS active medications, and loss of visual cues in unfamiliar surroundings are a few considerations that should be taken into account. Frequent reorientation, allowing for a more normal sleep-wake environment, and engaging familiar people or family may be useful nonpharmacologic maneuvers. Patients may need sedation if they are a threat to themselves or others, but these agents should be avoided because they may be of transient benefit in the short term and worsen or prolonged the delirium. The hyperadrenergic state that accompanies this delirium may be detrimental in the postoperative patient and should be treated with β-blockers and other antihypertensives. Short-acting agents are preferred because as the delirium lifts, the adrenergic activation may resolve with resultant hypotension. Drug and alcohol withdrawal are an important consideration and a frequently missed diagnosis in the ICU population with delirium.

Cognitive Impairment

Patients who undergo cardiac surgery may exhibit some decrease in cognitive function. Patients were told that they had "pump head," which was attributed to use of cardiopulmonary bypass. A similar decline was seen in "off pump" bypass patients, which would contradict this theory. In addition, a mild postoperative cognitive decline was also seen in noncardiac surgical patients.

This cognitive impairment can be seen in terms of short-term and long-term decline.[60] The short-term decline can be observed for up to several weeks postoperatively. The risk factors include older age and the risks that predispose for cerebrovascular disease. The mechanism of this deterioration is not well understood but there is some resolution within 3 months postoperatively. This area of research has been affected by poorly controlled studies that led to erroneous conclusions.[60] Long-term cognitive impairment in cardiac surgical patients seems to be a function of both aging and concomitant cerebrovascular disease. Just as in short-term decline, these variables may be confounding and limited by the lack of an appropriate control population. Cognitive decline accelerated by cardiac surgery has been postulated, but to this point the evidence is less compelling.

Seizures[61]

Seizures are rare in the immediate postoperative period. Most anesthetic agents are anticonvulsants, and in individuals with status epilepticus general anesthesia is the final step in the treatment algorithm. Seizures in the postoperative population either herald an underlying, unrecognized neurologic defect or are related to drug withdrawal (therapeutic drugs, illicit drugs, or alcohol). On rare occasions, a global tonic-clonic seizure may develop in patients who are hypoglycemic or hypoperfused. These patients need to have correction of their serum glucose and hypoperfused state as a primary treatment. After seizures are controlled, a CT scan of the brain should be performed to rule out CNS pathology. The next step would be an electroencephalogram as some anticonvulsants may be proconvulsants at elevated levels. Some cardiac medications, like lidocaine at toxic levels, may lower the seizure threshold. This can be seen in individuals with renal failure at normal dosing of lidocaine.

Tranexamic acid has proconvulsant activity. This antifibrinolytic agent should be avoided in any individuals with a seizure disorder or in those who have exhibited seizures in the perioperative or postoperative period.[62]

Endocrine

The endocrinologic system is in overdrive after cardiac surgery. The combination of adrenergic stimulation from major surgery and the inflammatory state induced at that time lead to an activation of the stress response.

Pituitary Adrenal Axis

Cardiac surgery leads to a massive outpouring of adrenocorticotropic hormone (ACTH) from the pituitary with subsequent cortisol secretion from the adrenal glands. Despite a return to normal ACTH, cortisol remains elevated. This suggests a hypersensitivity of the adrenal glands to ACTH.[71] Impaired cortisol clearance is also described in critically ill patients. This reduced cortisol breakdown may be related to the effect of stress on the activity and an expression of cortisol-metabolizing enzymes.[72] This effect should be considered when treating individuals who may need exogenous steroids. Stress dosing may need to be adjusted in such patients.

Diabetes

It has been long recognized that diabetics have more complications postoperatively and that poorly controlled diabetics are at even higher risk.[73] Intensive care of the diabetic patient in the ICU was revolutionized by a study in Leuven, Belgium, in 2001.[74] This study investigated the goals of glucose control in the management of hyperglycemic critically ill patients. The randomized controlled trial showed that individuals who had intensive insulin management

had increased morbidity and mortality compared with individuals who underwent a more liberal (routine) management strategy. The intensive insulin group maintained a blood glucose level between 80 and 110 mg/dL, whereas the conventional group had a goal glucose of between 180 and 200 mg/dL. This study was heavily populated by patients who had undergone cardiac surgery. A full 62% to 63% of the enrollees had been cardiac surgical patients and may have affected the conclusions that were generalized to all critically ill patients. What was clear from subsequent studies was that all patients who had cardiac surgery would benefit from tighter glucose control.

The STS published a practice guideline series addressing blood glucose management during adult cardiac surgery in 2009.[75] They recommended that patients should have their glucose controlled during the intraoperative and immediate postoperative period (<180 mg/dL) even if they were not recognized as diabetic.[76] An insulin drip should be used for glycemic. Their conclusions were that this glucose management strategy would:

1. Reduce mortality and morbidity
2. Lower incidence of wound infections
3. Reduce hospital length of stay
4. Enhance long-term survival

It was further recommended that the immediate goal of insulin therapy should be a glucose level less than 180 mg/dL. However, those who require a more prolonged ICU stay (>3 days), the glucose control should be a bit tighter (<150 mg/dL). The transition to subcutaneous insulin should be initiated before discontinuation of an insulin drip.

Care must be taken to avoid hypoglycemia because of an association with increased mortality in individuals who develop pathologically low sugar levels. These patients who have recently had cardiac surgery may be exquisitely sensitive to this hyperactive adrenergic state.

Thyroid

The syndrome of hyperthyroidism has clear indications for treatment, and the effects of thyroid hormone on cardiac function have been well described.[77] Increased CO and AF are possible complications of this syndrome. Hyperthyroidism should be recognized before surgery and treatment should not be altered or changed in the immediate postoperative period. If hyperthyroidism was not recognized before surgery, β-blockers should be aggressively used to control symptoms related to this disorder.

The effects of open-heart surgery on thyroid function have been linked to sick euthyroid syndrome,[78] and this response has been seen in both cardiopulmonary bypass and off-pump surgery.[79] Patients exhibit a normal thyroid-stimulating hormone and thyroxine (T_4) but have a depressed triiodothyronine (T_3) and free T_3 with elevated reverse T_3 (which is the inactive form of T_3). The mechanism is thought to be a decrease in the di-iodination of T_4 to T_3 in the peripheral tissues. Because T_3 is a more active compound, this is considered an adaptive mechanism that reduces catabolism in patients recovering from surgery when they need to be more anabolic.

Low levels of T_3 have been shown to lead to a decreased CO and increased systemic vascular resistance.[80] There have been multiple studies of replacement of T_3 in postoperative cardiac surgical patients and although the hemodynamics improved, there was no change in clinical outcomes. At this point, there is insufficient evidence to recommend routine replacement of T_3 in postoperative cardiac surgical patients.

Renal

Acute kidney injury after cardiac surgery is associated with a significant increase in mortality.[63,64] There are multiple definitions and models for predicting acute kidney injury; as a result the incidence can be anywhere from 3% to 30% of patients.[65] The risk of mortality can exceed 60% and in this population in which mortality is in the range of 2% to 8%, this is a substantial increase in risk. It is this group with the risk of increased mortality that will most probably progress to need renal replacement therapy.

Understanding risk factors that predispose individuals to acute kidney injury is the initial step to minimizing this progression that leads to increased mortality in this population.[66] The incidence of acute kidney injury is low in the range of 1% to 5%, in more conservative estimates, but the consequences are catastrophic. Female gender and left ventricular ejection fraction less than 35% are characteristics that may not be modified. The factors that may be addressed are exposure to angiographic contrast dye, duration of cardiopulmonary bypass, and hypotension during cardiopulmonary bypass. Preoperative consideration as it affects the intraoperative management of this at-risk population is crucial.

Traditionally acute kidney injury has been divided into three broad categories. The prerenal, renal, and postrenal injury categories are based on the breakdown that is a description of the location of the inciting insult. There is some overlap with this generalization, but the categorization is helpful in understanding, evaluating and treating patients with acute kidney injury, and being able to avoid renal replacement therapy.

Prerenal causes relate to impaired perfusion of the kidney. Most commonly prerenal azotemia is related to dehydration. In the immediate postoperative period this is less of an issue given the intensive intraoperative monitoring (TEE, PAC, mean arterial pressure, urine output, and so on). There is an enhanced emphasis on volume resuscitation in the OR. Hypotension, cardiac performance, anemia, and hypoxemia should be investigated and corrected in the immediate postoperative period. Upon admission to the ICU attention should be paid to output (urine, chest tube, gastric, and so on) because this may be the first clue to hypovolemia. In addition, individuals with a prior history of poorly controlled hypertension may require a mean arterial pressure that is higher than may be desirable in routine postoperative cardiac surgical patients. The kidneys may need a higher perfusion pressure to maintain routine function.

Renal causes of acute kidney injury are generally the result of ischemia or nephrotoxicity from diagnostic or therapeutic interventions. Impairment of blood flow or delivery of deoxygenated blood to the kidneys may lead to acute tubular necrosis. This sloughing of the renal tubular cells into the tubules may be a defense mechanism to protect the kidney from further, potentially irreversible damage. Renal tubular endothelium has the capacity to regenerate but these cells are exquisitely sensitive to hypoxia and nephrotoxins.[67] The recovery process has limitations and can be impaired by recurrent insults or prolonged hypoperfusion. Nephrotoxins can have direct tubular toxicity and can be related to the contact time that the tubules are exposed to these toxins. Repeated or concentrated exposure can be equally harmful. An interstitial nephritis can be due to exposure to a causative agent.[68] Penicillins, nonsteroidal antiinflammatory drugs, proton pump inhibitors, or diuretics are the most frequent agents seen in postoperative cardiac surgery. Patients may exhibit an eosinophilia with

eosinophiluria. The treatment is discontinuation of the offending agent, and although eosinophils have a role in this disorder, there is no evidence that corticosteroids have a beneficial effect in treatment.

Postrenal causes of acute kidney injury involve mechanical disruption of the urinary tract, from the kidney to the urethra. The abrupt cessation of urine production is an emergency that should be investigated and corrected before this leads to irreversible kidney damage. Ultrasonography of the kidneys or bladder may pinpoint the site of obstruction or disruption. Insertion or irrigation of a Foley catheter may be diagnostic of the etiology if the blockage is between the urethra and bladder.

The workup of acute kidney injury in postoperative patients should focus on the preoperative risk factors and stage of chronic kidney disease, with special attention to prior exposure to nephrotoxins. A review of intraoperative events with correction of intravascular volume depletion and perfusion defects is essential. Laboratory tests should include serologic evaluation of electrolytes, blood urea nitrogen, and creatinine. Urine should be obtained for electrolytes (to calculate the functional excretion of sodium), urine sediment, eosinophils, and specific gravity, although it must be noted that the fractional excretion of sodium can be affected by diuretics and should be interpreted in this context. Finally, radiologic examination of the urinary tract with ultrasound or CT scanning may be diagnostic. The goal is to halt the progression to renal replacement therapy with the associated increase in mortality postoperatively.

If renal replacement therapy becomes necessary, then hemodialysis is the gold standard for treatment.[69] There are defined serologic and metabolic indicators for initiation of dialysis. Occasionally patients may need to undergo ultrafiltration for volume management. In patients that are hemodynamically unstable, continuous renal replacement therapy is a viable option. This mode of renal replacement therapy is well tolerated hemodynamically but may not be available in all centers where cardiac surgery is performed. Sustained low-efficiency dialysis may be an alternative and can be performed with routine hemodialysis equipment. Initial trials have shown equivalence in clinical outcomes when sustained low-efficiency dialysis is compared to continuous renal replacement therapy.[70]

Hematology

Thrombocytopenia

Platelets have an integral function in the expression of coronary artery disease and are equally important in the postoperative cardiac surgical patient. The cornerstone in the management of ischemic heart disease is the use of antiplatelet agents. These same agents can lead to excessive bleeding in the perioperative and postoperative phase. This is more a function of the action of platelets and not the quantity of platelets.

Thrombocytopenia is defined as a platelet count of 150,000 or less platelets per milliliter and severe thrombocytopenia as 50,000 or less platelets per milliliter. Thrombocytopenia in patients can be due to one of six major mechanisms[81]:

1. Pseudothrombocytopenia
2. Hemodilution
3. Increased platelet consumption
4. Increased platelet destruction
5. Decreased platelet production
6. Increased platelet sequestration

When there is a slow and gradual falling platelet count over 5 to 7 days, this is more consistent with bone marrow failure (production) or consumption. A decrease in platelets within 1 to 2 days after the initial postoperative increase is more suggestive of immunologic etiology. Of these immunologic mechanisms HIT deserves a more in-depth consideration because of the association of HIT with cardiopulmonary bypass[82] and the use of heparin in this postoperative population.

Heparin-Induced Thrombocytopenia

HIT is the descriptive name of the syndrome heralded by the occurrence of a decreasing platelet count. The devastating and potentially life-threatening aspect of this disorder relates to the thrombotic complications owing to the induction of antiplatelet antibodies caused by exposure to heparin. It is estimated that HIT with possible thrombosis occurs in 1% to 3% of cardiac surgical patients.

Two distinct forms of HIT have been described. Type I HIT is a nonimmunologic response to heparin that leads to an early (48–72 hours) thrombocytopenia that is mediated by a direct interaction between heparin with circulating platelets. This reaction can occur in up to 10% of patients and causes platelet clumping or sequestration. This thrombocytopenia is mild and transient with returned to normal platelet count within 4 days after stopping heparin. This form of HIT is not associated with thrombotic complications.

Type II HIT is an immunologic disorder and associated with venous or arterial thrombosis. Heparin combines with platelet factor 4 and this interaction leads to an immunoglobulin G antibody that activates platelets. The subsequent release of prothrombotic particles from the platelets results in an excessive thrombin formation, platelet aggregation, and thrombus formation. Prior exposure to heparin can stimulate earlier manifestations of HIT, but this typically occurs 5 to 10 days after exposure to heparin. Major surgery resets the clock and type II HIT almost never occurs within the first 5 days after surgery.[83]

The incidence of type II HIT is low but the morbid consequences make consideration of this disorder an important decision point. The scoring system called the 4T's can be useful[84] (Table 35.3). This system uses four criteria to give weight to the probability of HIT and has a good negative predictive value when combined with the overly sensitive HIT antibody. A low score has a 1% likelihood of antibody positivity. Because the antibody is so sensitive there are false-positive results and a serotonin release assay may need to be obtained for confirmation.

Two agents have been approved for treatment of HIT: the direct thrombin inhibitor argatroban, which is available in the United States, and the anti–thrombin-dependent factor Xa inhibitor danaparoid (Canada, European Union, and Australia).[85] Argatroban can be used in patients with impaired renal function and has a short half-life. However, argatroban can prolong the prothrombin time and international normalized ratio, which makes institution and monitoring of warfarin effect difficult. The short half-life of argatroban allows it to be discontinued for a couple of hours to determine the prothrombin time/international normalized ratio when a patient is taking warfarin in order to separate the individual drug effects. Warfarin should not be initiated until the platelet count has returned to normal when anticoagulation is necessary in patients with HIT. Finally, platelet transfusion should be avoided unless the patient is actively bleeding as additional platelets may further fuel the thrombotic effect.[86]

TABLE 35.3 The 4T's Assessment for Patients With Suspected Heparin-Induced Thrombocytopenia

T	2 Points	1 Point	0 Points
Thrombocytopenia	<20,000 or >50% from baseline	<10,000–19,000 or 30%–50% from baseline	<10,000 or <30% from baseline
Timing of fall	Day 5–10 from exposure or <1 day if heparin exposure in <30 days	>10 days from exposure <1 day and exposure in past 30–100 days	<1 day with no recent heparin exposure
Thrombosis	Proven thrombosis, systemic reaction after heparin skin necrosis	Erythema "silent" recurrent or progressive thrombosis	None
Other cause for thrombocytopenia	None	Possible	Definite
	6–8 points = high likelihood	4–5 points = intermediate likelihood	0–3 points = low risk of heparin-induced thrombocytopenia

HIT, Heparin-induced thrombocytopenia.
From Jang IK, Hursting MJ. When Heparins Promote Thrombosis: Review of Heparin-Induced Thrombocytopenia. *Circulation.* 2005;111:2671–2683.

Anemia

Blood loss anemia is by far the most common reason for transfusion in this population. The issue comes about because multiple studies have shown that transfusion in cardiac surgery is associated with increased morbidity and mortality.[87,88] Iron replacement therapy and tolerance of lower thresholds for transfusion should be initiated to avoid this complication. The use of recombinant erythropoietin has a theoretic complication of a prothrombotic effect and is used when there is an advantageous risk-benefit ratio.[89]

Hemolysis can occur in this postoperative population and can be related to cardiopulmonary bypass, shearing across mechanical valves, and transfusion reactions. Less commonly it can be seen in thrombotic thrombocytopenic purpura, which also results in thrombocytopenia, but there is nothing associated with cardiac surgery that increases the risk of thrombotic thrombocytopenic purpura.

Treatment of patients who are Jehovah's Witnesses needs to be considered, and their religious-based refusal of blood products makes anemia a particularly important issue. The management of this population is best begun preoperatively when possible. Optimization should occur before surgery with iron administration and when acceptable, erythropoietin. Emergent surgery does not always make this possible. Postoperatively these patients may need continued erythropoietin with iron administration, and judicious phlebotomy is advisable.

Gastrointestinal[90]

GI complications can develop in about 1% to 3% of cardiac surgical patients. The GI tract is sensitive to hypoxia and hypoperfusion, and as a result these complications are common in all critically ill patients. The common thread in the pathophysiologic mechanism is sympathetic vasoconstriction, with resultant hypoperfusion and hypoxia of the splanchnic bed. The three strongest predictive factors for GI complications are (1) prolonged mechanical ventilation, (2) sepsis, and (3) acute kidney injury, all of which may contribute to splanchnic hypoperfusion.

Intestinal Ischemia

Intestinal ischemia is a rare but highly lethal complication of cardiac surgery. In a study from Massachusetts General Hospital, 8700 patients were reviewed and although GI complications were rare (<1%), mesenteric ischemia was the most common with mortality of 67%.[91] This increased mortality was seen whether patients had surgery or were treated conservatively.

The diagnosis was entertained by the findings of pain disproportionate to physical findings, lactic acidosis, and leukocytosis. A CT angiogram may reveal pneumatosis intestinalis, bowel wall thickening, and possible thrombosis. Endoscopy may reveal a dusky, ischemic colon. It is at that time that operative intervention may be successful, before bowel rupture and peritoneal contamination. When peritoneal signs are present on physical examination, surgery is much less successful.

Pancreatitis

Hyperamylasemia is very common in the early postoperative phase but clinical pancreatitis is rare and seen in only about 1% to 3% of cardiac surgical patients. True symptomatic pancreatitis is rare in this population but carries a high mortality because of its association with multiple organ system failure. Amylase levels are not always helpful, and isolated hyperamylasemia will be associated with a normal lipase and abdominal complaints are not usually present. CT scan or ultrasonography of the abdomen should be obtained when the diagnosis is in question. Treatment of pancreatitis begins and ends with bowel rest and nasogastric drainage. Antibiotics remain a source of controversy as indiscriminate dosing can lead to selection of more resistant organisms, whereas this exuberant inflammatory state can be difficult to distinguish from sepsis. The decision remains at the clinical discretion of the treating physician.

Gastrointestinal Bleeding

The GI tract and especially the large and small intestine are sensitive to hypoperfusion and hypoxemia. The mucosal sloughing and disruption can be seen after cardiopulmonary bypass. The low incidence of obvious GI bleeding suggests that postoperative care has been successful. The use of GI prophylaxis with histamine H_2 blockers and proton pump inhibitors has improved the rate of upper GI bleeding. These agents should be discontinued when the patient leaves the ICU and is taking a full diet because of evidence of gastric bacterial overgrowth with increased incidence of gram-negative infections in those with decreased gastric acidity.

Hypoperfusion is not the only cause for upper GI bleeding. The intraoperative monitoring with transesophageal echocardiogram may lead to trauma to the esophagus. Although Mallory-Weiss tears are infrequent, esophageal erosions especially in combination with anticoagulants and antiplatelet agents can be a source of GI blood loss. Aspirin, in addition to antiplatelet actions, may have a localized, topical effect on the gastric mucosa. This is much less of a concern with enteric-coated formulations of aspirin.

Lower GI bleeding can be catastrophic when it is due to an ischemic-mediated process; however, a lower GI bleed usually is self-limited. Arterial venous malformations are unpredictable and can be corrected with interventional colonoscopy if they appear to be the source of recurrent blood loss. Diverticular disease and hemorrhoids may be an issue because of straining with bowel movements. Constipation is not uncommon for multiple reasons in the postoperative arena. Anesthesia, narcotic administration, psychological inhibition, and immobility contribute to the lack of regular bowel habits. Stool softeners and fiber are used immediately postoperatively but over the next few days laxatives may be necessary to avoid straining.

Elevated Liver Function Test Results

Evidence of hepatic dysfunction is not uncommon after open-heart surgery. It is estimated that approximately 25% of patients will develop a transient hyperbilirubinemia but few progress to frank liver failure. There are also low-grade elevations in transaminases and alkaline phosphatase. These are generally short-lived and multifactorial. Anesthetic agents, cardiopulmonary bypass, and hypoperfusion may give rise to elevations that resolve once these insults have been removed. Individuals with preexisting liver disease or congestive hepatopathy as the result of right-sided heart failure may require a longer time to correction.

Drugs are also a source of elevated liver function test results. Amiodarone, clopidogrel, and statins may contribute to this increase. Once the cause is identified, dosing of acetaminophen should be limited because of an increased susceptibility to toxicity in patients with liver impairment. In addition, several other factors should be considered. Cholecystitis is a rare occurrence in postoperative cardiac surgical patients but should be considered in individuals with fever, right upper quadrant tenderness, and leukocytosis. These symptoms should warrant an investigation with an ultrasound or CT scan of the abdomen. Hemolysis, especially in valve replacement surgery and patients who require recurrent transfusion, should be considered. A peripheral smear, haptoglobin, and lactate dehydrogenase are the initial screening laboratory tests necessary in this workup.

These elevations usually are limited and the liver can recover. The emphasis is avoidance of agents that may perpetuate or prolonged insult and injury, which can result in a delayed recovery.

Miscellaneous

Many GI issues that occur postoperatively do not rise to the level of complication, but providers need to be aware of these.

Pharyngeal dysfunction is not uncommon after intubation. This is usually time related, in that it is more common with longer intubation and usually resolves quickly after extubation. There may be pain on swallowing or inability to swallow. If there is a question, then speech evaluation with fiberoptic endoscopic evaluation of swallowing or modified barium swallow may be necessary. A nasogastric feeding tube may be a temporary means for medication administration and nutritional support.

Anorexia or nausea is frequently seen in those emerging from anesthesia and usually resolves after 24 to 36 hours. Narcotic analgesia may prolong the symptoms and patients respond to antiemetics or promotility agents. Patients require a more thorough workup after that initial time period if symptoms persist.

Diarrhea is usually a late finding postoperatively (3–5 days). This may be related to watery feces passing around an impaction because constipation is more common immediately after surgery. Medications should be reviewed. Stool softeners, laxatives, and promotility agents may be overlooked as they may be a part of the postoperative order set. Magnesium oxide is a common cause for increasingly frequent loose bowel movements because low magnesium is aggressively corrected owing to the concern for arrhythmias. Patients receiving tube feeds may benefit from a less hyperosmolar concentrated formula or by administration of water with the feeds to dilute the osmolarity of these feeds. *Clostridium difficile* colitis should be ruled out in those individuals with an elevated white blood cell count who have received antibiotics because without treatment these patients may progress to frank sepsis or develop a toxic megacolon.

Conclusion

As with critical care more generally, postoperative care of cardiothoracic patients is becoming increasingly complex and specialized. A wider range of bedside diagnostic tools is now available, which can allow clinicians to be more nuanced in their responses to the rapidly changing clinical status of a patient. Best practices are anticipatory instead of reactive, with an understanding of the common complications to be expected. As the practice continues to evolve, cardiothoracic intensivists from a surgical, medical, or anesthesia background will play a larger role in the postoperative care provided to patients.

Key Points

- Handoff from the OR team to ICU staff is an important component to the transfer of information necessary for care of this patient population.
- Meticulous attention to lines, tubes, and medication can help to avoid iatrogenic misadventures.
- Weaning from mechanical ventilation should be prioritized and some centers are extubating patients in the OR.
- Postoperative cardiac arrest may necessitate emergent reexploration.
- AF is very common and the most costly complication in postoperative cardiac surgical population owing to its frequency. The strategies of rhythm control versus rate control are of equal benefit.
- Increased blood utilization is associated with increased morbidity and mortality.
- Neurologic complications are frequent and can be categorized as focal or global dysfunction.
- Postoperative glucose management is mandatory in both diabetic patients and those without diabetes.
- Acute renal failure in the postoperative period is associated with a greater than 10-fold risk in mortality.
- Heparin-induced thrombocytopenia occurs in 1% to 3% of cardiac surgical patients postoperatively.

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Review Questions

1. Each of these factors lead to prolonged intubation times *except*:
a. Long pump runs
b. Coagulopathy
c. Increased age
d. Prior stroke
Answer: d. Prolonged pump runs intraoperatively, coagulopathy, and increased age have all been shown to delay extubation times, but previous stroke has not been shown to affect the ability to wean and extubate patients in a timely manner.

2. Which of the following is true about postoperative atrial fibrillation?
a. It is uncommon and resolves frequently without intervention.
b. It is associated with increased mortality and length of stay.
c. It can be prophylactically treated with digoxin.
d. It requires rhythm control and not rate control.
Answer: b. Postoperative atrial fibrillation is the most common complication in cardiac surgical patients and is associated with increased mortality and morbidity. Rhythm control confers no long-term benefit over rate control. Digitalis has not been shown effective in keeping postoperative patients in sinus rhythm.

3. Each of the following is true of postoperative stroke in cardiac surgery *except:*
a. These strokes are usually hemorrhagic because of the high dose of heparin use in cardiopulmonary bypass.
b. Cross-clamping and cannulating the aorta can lead to atheroemboli.
c. The recognition of carotid disease preoperatively has decreased the risk of stroke.
d. Timing of the stroke occurrence can be difficult after surgery.
Answer: a. The incidence of postoperative stroke has been reduced by investigation, recognition, and treatment of carotid disease but cardiopulmonary bypass with cross-clamping and cannulation of atherosclerotic aorta can lead to embolic stroke. The timing of stroke can be difficult to gauge because anesthesia renders physical/neurologic examination ineffective during the 4- to 6-hour procedure/recovery. Most strokes are embolic in nature, and there is a decrease incidence of hemorrhagic stroke despite the anticoagulation intraoperatively.

36

Acute Respiratory Failure

DAVID P. GURKA AND ROBERT A. BALK

CHAPTER OUTLINE

Acute Respiratory Failure—Types 1 and 2

Hypoxemic Respiratory Failure
- Basic Mechanisms
- Assessment of Oxygenation

Hypercapnic Respiratory Failure
- Assessment of Ventilation
- Clinical Manifestations

Acute Respiratory Distress Syndrome
- Risk Factors

Incidence and Prevalence
- Clinical Manifestations
- Pathologic Manifestations
- Pathophysiology
- Management Strategies
- Drug Therapy for Prevention of ARDS
- Fibroproliferative Phase and Steroid Treatment
- Multiple-Organ Dysfunction/Failure
- Lung-Protection Strategy for Prevention of ARDS
- Prognosis

Future Considerations

Summary

Acute Respiratory Failure—Types 1 and 2

Acute respiratory failure is defined as the inability of the respiratory system to meet the oxygenation, ventilation, or metabolic requirements of the patient.[1] Although the main function of the lungs appears to be related to gas exchange (i.e., oxygenation and ventilation), it should be remembered that the lung is also a metabolically active organ.[1,2] Respiratory failure has been divided into two main types. Type 1 is hypoxemic respiratory failure (oxygenation failure), and type 2 is hypercapnic failure (ventilatory failure) with or without hypoxemic respiratory failure.[2] Operationally, type 1 respiratory failure is defined by a partial pressure of oxygen in arterial blood (Pao_2) less than 60 mm Hg, and type 2 respiratory failure is defined by a partial pressure of carbon dioxide (CO_2) in arterial blood ($PaCO_2$) greater than 50 mm Hg. The respiratory failure can be acute or chronic in nature, related to the onset and duration of the failure.[2,3] Some patients may present with an acute deterioration or worsening of their chronic respiratory dysfunction termed *acute-on-chronic respiratory failure.*[4]

Acute respiratory failure is commonly encountered in the intensive care unit (ICU) setting and may be the primary reason for the admission or a complication of the patient's medical condition(s) or treatment. Respiratory failure may be the result of a variety of causes, some of which may not directly involve the lungs or the respiratory muscles.[2] Like a chain composed of individual links representing the brain, peripheral nervous system, upper airway, lower airway, respiratory muscles, cardiovascular system, and lungs (Fig. 36.1),[2] respiratory failure may result when any of the links become sufficiently dysfunctional or weak. Like a chain, the body is only as strong as its weakest link, and respiratory failure may result when there is significant compromise. Common causes of hypoxemic and hypercapnic respiratory failure are listed in Box 36.1. This chapter reviews the basic mechanisms and clinical manifestations of type 1 and 2 respiratory failure and concludes with a more in-depth discussion of acute respiratory distress syndrome (ARDS); ventilator management is addressed in more depth in other chapters.

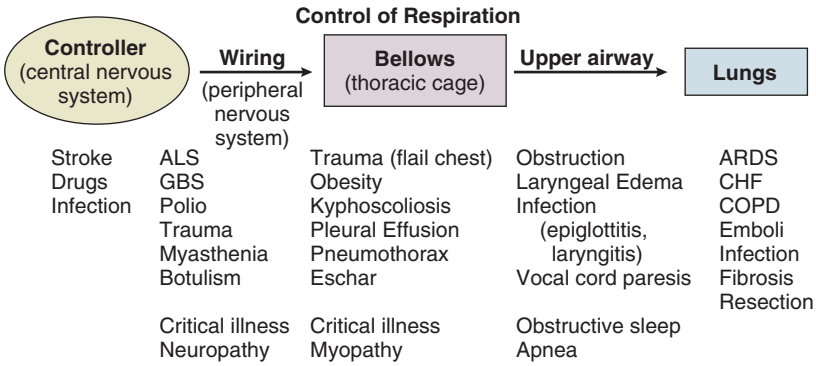
Hypoxemic Respiratory Failure

Basic Mechanisms

The five basic mechanisms of hypoxemia are listed in Box 36.2. Ventilation-perfusion abnormality is the most common.[2,3] Multiple mechanisms may be instrumental in the development of respiratory failure. Most of the abnormalities improve with the administration of supplemental oxygen, except for a shunt abnormality in which the Pao_2 continues to be low despite the administration of high levels of supplemental oxygen. The shunt may be either intracardiac (such as a right-to-left shunt through a patent foramen ovale) or intrapulmonary (as seen with pulmonary arteriovenous malformations, pneumonia, or ARDS).[5,6] A diffusion abnormality is infrequently the cause of hypoxemia in clinical practice and typically is clinically significant only in the setting of tachycardia, high cardiac outputs, and when the diffusion capacity is below 25% of predicted.[3]

Assessment of Oxygenation

The hallmark of type 1 respiratory failure is hypoxemia, which is primarily assessed by the Pao_2 with an arterial blood gas (ABG) analysis. Estimates of the patient's oxygenation status can be obtained by measuring the oxygen saturation using a pulse oximeter. An appreciation of the sigmoid shape of the oxyhemoglobin dissociation curve allows for a rough estimation of the Pao_2 (Fig. 36.2). The curve shifts rightward or leftward in relation to changes in the



• **Fig. 36.1** Control of respiration. *ALS,* Amyotrophic lateral sclerosis; *ARDS,* acute respiratory distress syndrome; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *GBS,* Guillain-Barré syndrome; *Myasthenia,* myasthenia gravis or the Eaton-Lambert myasthenic syndrome.

• BOX 36.1 Common Causes of Hypoxemic and Hypercapnic Respiratory Failure

Brain
Bulbar poliomyelitis
Central alveolar hypoventilation
Cerebrovascular accident
Cerebral malignancy
Drug overdose (e.g., narcotic, sedative/hypnotic)
Elevated intracranial pressure
Encephalitis and meningitis
Pontine herniation
Postoperative anesthetic depression

Spinal Cord
Amyotrophic lateral sclerosis
Cervical cordotomy
Guillain-Barré syndrome
Poliomyelitis
Spinal cord trauma

Neuromuscular System
Acute intermittent porphyria
Botulism
Cholinergic crisis
Curariform drugs
Electrolyte disorders (e.g., hypophosphatemia, hypomagnesemia)
Hypokalemic periodic paralysis
Multiple sclerosis
Myasthenia gravis
Myxedema
Neuromuscular blocking antibiotics (e.g., polymyxin, streptomycin)
Organophosphate insecticides
Peripheral neuritis
Polymyositis
Respiratory muscle fatigue—critical illness polyneuropathy/polymyopathy
Tetanus

Upper Airway
Epiglottitis and laryngotracheitis
Large tonsils and adenoids
Obstructive sleep apnea
Postintubation laryngeal edema
Tracheal obstruction
Vocal cord paralysis

Thorax and Pleura
Chest wall burn with eschar formation
Chest wall trauma—flail chest
Kyphoscoliosis
Massive abdominal distention
Massive obesity
Muscular dystrophy
Large pleural effusion/pleural fibrosis
Pneumothorax
Rheumatoid spondylitis
Thoracoplasty

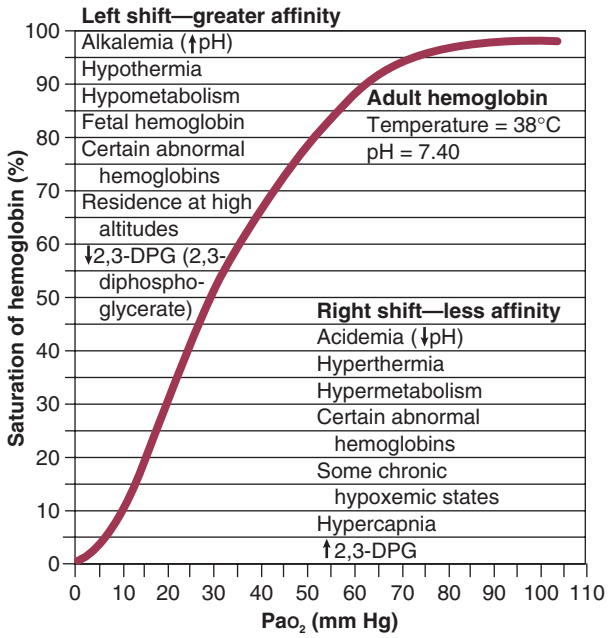
Cardiovascular System
Cardiogenic pulmonary edema
Left ventricular failure
Mitral stenosis
Biventricular failure
Fat embolism
Snake bite
Uremia
Volume overload
Pulmonary venoocclusive disease

Lower Airway and Alveoli
Acute respiratory distress syndrome
Aspiration
Asthma
Atelectasis
Bronchiectasis
Bronchiolitis
Chronic obstructive pulmonary disease
Cystic fibrosis
Interstitial lung disease
Massive bilateral pneumonia
Near-drowning
Pancreatitis
Pulmonary contusion
Radiation lung injury
Sepsis
Smoke inhalation
Surgical resection of lung parenchyma

• BOX 36.2 Mechanisms of Hypoxemia

- Inadequate P_{AO_2}
  Alveolar hypoventilation
  Decreased F_{IO_2}
- $\dot{V}/\dot{Q}$ mismatch
- Shunt
  Intrapulmonary
  Intracardiac
- Diffusion abnormality
- Low $M\bar{v}O_2$

F_{IO_2}, *Fraction of inspired oxygen;* $M\bar{v}O_2$, *pulmonary arterial oxygenation;* P_{AO_2}, *Partial pressure of oxygen in the alveolus;* $\dot{V}/\dot{Q}$, *ventilation-perfusion mismatch.*



• **Fig. 36.2** Oxyhemoglobin dissociation curve. *P_{aO_2},* Partial pressure of oxygen in arterial blood.

pH, P_{aCO_2}, temperature, and phosphate ion (PO_4^{-3}) concentration.[7] Determination of the ABG and knowledge of the exact fraction of inspired (F_{IO_2}) allows for the calculation of the alveolar-arterial oxygen gradient[3] (A-a gradient) using the formula $P_{AO_2} - P_{aO_2} =$ A-a gradient, according to the following:

$$P_{AO_2} = F_{IO_2}(P_B - P_{H_2O}) - P_{aCO_2}/R$$

where

P_{AO_2}	Partial pressure of oxygen in the alveolus
P_{aO_2}	Partial pressure of oxygen in the arterial blood
F_{IO_2}	Fraction of inspired oxygen
P_B	Barometric pressure
P_{H_2O}	Water vapor pressure at standard temperature and pressure
P_{aCO_2}	Partial pressure of carbon dioxide in the arterial blood
R	Respiratory quotient (R = 0.8)

The A-a gradient is F_{IO_2} dependent and increases as the F_{IO_2} increases. Because of the F_{IO_2} dependency, some have preferred to evaluate oxygenation abnormalities by calculating the P_{aO_2}/P_{AO_2} ratio, which is independent of the F_{IO_2}.[3] For simplicity's sake, many individuals use the P_{aO_2}/F_{IO_2} ratio as a measure of oxygenation abnormality. This value is used in the definition of ARDS and has gained wide-scale acceptance as a measure of abnormal oxygenation.[8] The shunt fraction or venous admixture can also be calculated while a patient breathes 100% oxygen and has reached steady state.

Hypercapnic Respiratory Failure

Hypercapnic respiratory failure can result from a variety of disorders as listed in Box 36.1.[9] Acute hypercapnic respiratory failure, also termed *acute ventilatory failure*, occurs when a patient has acute respiratory acidemia (pH <7.35) with a P_{aCO_2} greater than 50 mm Hg. This definition is not generally applicable to patients with severe chronic obstructive lung disease or neuromuscular disorders who have developed a compensatory metabolic alkalemia in response to their chronic hypercapnia. However, these patients may have acute exacerbations or comorbid conditions that cause them to decompensate into *acute-on-chronic respiratory failure*.

In steady-state conditions the rate of carbon dioxide (CO_2) production ($\dot{V}CO_2$) equals the rate of CO_2 elimination. CO_2 elimination ($\dot{V}CO_2$) is equal to the alveolar ventilation (VA) multiplied by the partial pressure of CO_2 in the alveolar gas (P_{ACO_2}). Thus the equation for CO_2 production is $\dot{V}CO_2 = VA \times P_{ACO_2}$. In the pulmonary capillary, CO_2 is readily diffusible through the endothelial and epithelial cell membranes down a substantial concentration gradient of approximately 45 to 50 mm Hg (normal pulmonary arterial CO_2 [P_{aCO_2}] versus essentially zero for the partial pressure of inspired CO_2 in room air [P_{ICO_2}]) so that the alveolar and capillary blood partial pressures of CO_2 are equal ($P_{ACO_2} = P_{aCO_2}$).

Not all respired air is effective alveolar ventilation because some of the total tidal ventilation (V_t) ventilates nonperfused areas or dead space (VD) (both anatomic and pathologic). This relationship between V_t, VD volume, and alveolar volume can be expressed as[3]:

$$V_t = VA + VD \text{ or } VA = V_t - VD$$

The minute ventilation (VE) is equal to the sum of the dead-space ventilation (VD) and the alveolar ventilation (VA): VE = VD + VA. Combining and rearranging terms from these various equations yields the following relationship of CO_2 production and alveolar ventilation with the P_{aCO_2}:[3]

$$P_{aCO_2} = \frac{\dot{V}CO_2}{V_t - V_D}$$

Therefore elevated P_{aCO_2} can result from a combination of any of three clinical alterations: increased CO_2 production, decreased V_t, or increased VD ventilation.[9] Increased CO_2 production arises from hypermetabolic states such as exercise, fever, sepsis, burns, trauma, excessive carbohydrate intake, and hyperthyroidism.[9] In isolation, these relatively common conditions rarely induce hypercapnic respiratory failure because the normal physiologic response to an elevated P_{aCO_2} is to increase minute (and therefore alveolar) ventilation to maintain eucapnia and a normal pH. Only those patients who are unable to increase their effective alveolar ventilation as a result of neuromuscular disorders affecting the muscles of respiration, the presence of excessive ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching, or increased VD ventilation develop

• BOX 36.3 Causes of Decreased Respiratory Muscle Strength or Endurance

Disorders of the phrenic nerve
- Guillain-Barré syndrome
- Poliomyelitis

Respiratory muscle atrophy

Disorders of neuromuscular transmission
- Myasthenia gravis
- Ventilator dependence
- Malnutrition
- Myopathy
- Critical illness polyneuropathy/myopathy

Altered diaphragmatic force-length relationship
- Dynamic hyperinflation and diaphragmatic flattening

hypercapnic respiratory failure as a consequence of elevated CO_2 production.

Ventilatory deficiencies, decreased V_t ventilation, and increased VD ventilation that result in hypercapnic respiratory failure can be differentiated by using the A-a gradient equation. The $PAO_2 - PaO_2$ difference breathing room air is normally less than 10 to 15 mm Hg when simple alveolar hypoventilation is responsible for the hypoxemia. An increased $PAO_2 - PaO_2$ difference suggests a parenchymal lung process, usually associated with $\dot{V}/\dot{Q}$ abnormalities, to account for the additional hypoxemia in these patients with hypercapnic respiratory failure.

Decreased V_t hypoventilation can be caused by disorders affecting any component of the "neuromuscular sequence," starting in the central nervous system and ending at the muscles of respiration (see Fig. 36.1). Among the more common causes are CNS depressants such as narcotics and sedatives, which diminish respiratory drive; cerebral vascular disorders, especially those that involve the brainstem, which impair the efferent signals to breathe; and disorders of neuromuscular transmission such as myasthenia gravis and the paraneoplastic Eaton-Lambert myasthenic syndrome (Box 36.3).[10,11] Abnormal respiratory mechanics can result from airflow obstruction, chest wall deformities, and loss of lung volume. Disorders that increase the respiratory load (such as a circumferential chest burn eschar or flail chest) or impair function of the respiratory muscles (such as kyphoscoliosis) also lead to hypoventilation.

Assessment of Ventilation

The hallmark feature of inadequate ventilation is the presence of an elevated $PaCO_2$ with or without hypoxemia.[3,9] In the adult population the best method to detect an elevated $PaCO_2$ is with an ABG measurement. Noninvasive evaluation of ventilation in the critically ill adult, using capnometry or end-tidal CO_2 ($PETCO_2$) measurements is gaining in use.[7] Transcutaneous CO_2 ($PtCO_2$) determinations in adults are not as reliable as in the neonate.[7]

Clinical Manifestations

The risk factors for developing acute respiratory failure include the postoperative state, preexisting chronic illness, malnutrition, advanced age, morbid obesity, chronic bronchitis, and cigarette smoking. The clinical manifestations of respiratory distress may be subtle and nonspecific or may be obvious to even the untrained observer. The patient with respiratory distress may have an abnormal respiratory rate (too high or low) or display an irregular pattern of breathing. The patient with respiratory distress may manifest gasping ventilation, nasal flaring, or use of the accessory muscles of respiration. Intercostal retractions may be seen, and the patient may exhibit paradoxical respiratory movement. Typically patients with acute respiratory failure, whether type 1 or type 2, have altered heart rate and blood pressure. The majority demonstrate a sympathetic response with tachycardia and hypertension, but patients may be hypotensive and bradycardic. Cardiac arrhythmias may be seen in both type 1 and type 2 respiratory failure. Patients with acute respiratory failure are usually in distress and often appear apprehensive.[2,9] Many are diaphoretic and have altered mental status or level of consciousness. Hypercapnic patients may demonstrate signs of a respiratory encephalopathy, including somnolence, coma, asterixis, seizures, tremors, or myoclonic jerks. Papilledema and congested conjunctivae may be present. Patients with type 1 respiratory failure may appear cyanotic. Although the management of acute respiratory failure is complex and reviewed elsewhere in this textbook, a great deal of effort has targeted the use of noninvasive ventilation or high-flow nasal cannula to avoid the use of intubation and invasive ventilatory support.[12–14]

Acute Respiratory Distress Syndrome

Since the initial 1967 description of acute catastrophic respiratory failure in 12 patients who were subsequently declared to have the acute respiratory distress syndrome, there has been a great deal of research and clinical study attempting to understand the mechanism of injury and improve the outcome of these critically ill patients.[8,15–19] The hallmark of this disorder was the rapid onset of acute hypoxemic respiratory failure that was characterized by refractory hypoxemia despite the administration of high concentrations of supplemental oxygen; decreased pulmonary compliance; bilateral pulmonary infiltrates; the absence of left-sided heart failure; and histologic evidence of alveolar damage with early hyaline membrane formation, which was followed by fibrosis of the lung.[8,15] The subsequent 10 to 20 years of ARDS management were associated with extremely high mortality rates, at times approaching 90%, despite the provision of extremely aggressive supportive care.[15–20] Some of the initial clinical and basic investigations that attempted to improve the outcome of patients with ARDS were hampered by the lack of a uniformly accepted definition.[21–25] In 1994 an American-European Consensus Conference (AECC) defined acute lung injury (ALI) and ARDS in an attempt to eliminate confusion related to terminology for these conditions.[21,22] The definitions were clinically based and regard ALI as a continuum with the more severe oxygenation abnormalities reflective of ARDS. Among the main benefits of the uniform definition would be improved communication and enhanced clinical trial design.

The AECC definition of ALI and ARDS was challenged related to discrepancies between the clinical and pathologic findings in individuals who died with ARDS.[25] Esteban and colleagues[25] found that one-third of the people who died with a clinical diagnosis of ARDS did not have histologic evidence of diffuse alveolar damage on postmortem examination. In addition, diffuse alveolar damage, the hallmark pathologic finding of ARDS, was evident in 10% of patients who died without a clinical diagnosis of ARDS. Since its introduction, the AECC definition has been used by the vast majority of clinical trials evaluating new treatment strategies for patients with ARDS, particularly those conducted by the ARDS Network investigators, supported by the U.S. National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.[26,27] In 2011 experts from the European Society of Intensive

Care Medicine, the American Thoracic Society, and the Society of Critical Care Medicine met in Berlin and proposed a new definition for ARDS that also provides a staging as mild, moderate, or severe, based on the oxygenation impairment measured on a minimum of 5 cm H_2O positive end-expiratory pressure (PEEP) (10 cm H_2O for severe).[28] The Berlin definition of ARDS does not drastically differ from the AECC definition but clarifies several important concepts:

1. Timing—patients with ARDS should be identified within 72 hours of a recognized risk factor and nearly all patients should be identified within 7 days.
2. Chest imaging—bilateral opacities consistent with pulmonary edema are seen on chest radiograph or chest computed tomography (CT) scan.
3. Origin of pulmonary edema—ARDS may be present in the setting of coexisting cardiogenic edema or volume overload if in the opinion of the treating physicians the respiratory failure is not fully explained by these conditions and there is a recognized risk factor for ARDS. In the absence of a recognized risk factor for ARDS, there should be some objective assessment of cardiac function such as echocardiography or pulmonary capillary wedge pressure measurement.
4. Oxygenation—because PEEP can affect the Pao_2/FIO_2 ratio there should be a minimum of 5 cm H_2O PEEP and 10 cm H_2O in those patients with severe ARDS ($Pao_2/FIO_2 < 100$).[28]

The Berlin definition for ARDS eliminates the use of the term "acute lung injury" and classifies the severity as mild ARDS ($Pao_2/FIO_2 \leq 300$ but >200), moderate ARDS ($Pao_2/FIO_2 \leq 200$, but >100), and severe ARDS ($Pao_2/FIO_2 \leq 100$), with associated morality rates of 27%, 32%, and 45%, respectively.[28]

To date there is no specific diagnostic laboratory test for the diagnosis of ARDS.[8,21,26] All of the current definitions for ARDS require the presence of bilateral pulmonary infiltrates on chest imaging, but interpretation is not always straightforward, with experts disagreeing up to 50% of the time in some studies.[21,27,29]

Risk Factors

It has been recognized that ARDS may arise in association with a number of clinical conditions or risk factors, with sepsis the most common (Box 36.4).[8,20,21,28,30–34] Various studies report that ARDS develops in approximately 5% to 40% of patients with sepsis.[8,31,33,34] Shock (prolonged hypotension) and the systemic inflammatory response syndrome (SIRS) are also common risk factors. Other frequently encountered clinical risk factors include multiple emergency transfusions; aspiration injury; near-drowning; pancreatitis; trauma (e.g., DIC lung contusion, fat emboli from long bone fractures); burns; cardiopulmonary bypass; and disseminated intravascular coagulation. These clinical risk factors are synergistic, and when more than one of the clinical risk factors is present, the likelihood of ARDS is greater than just the sum of the collective risk factors.[8,20] The clinical risk factors associated with the development of ARDS appear to greatly influence the expected outcome. Whether ARDS arises from a direct pulmonary insult or from an extrapulmonary cause affects the subsequent response to PEEP and ventilatory support (Box 36.5).[20] Age also has an impact on the likelihood for ARDS development.[34] Older individuals have a greater likelihood of developing ARDS from most of the risk factors noted earlier. In the setting of trauma the risk for ARDS seems to peak in the sixth and seventh decades and then declines.[34]

Negative-pressure (postobstructive) pulmonary edema (NPPE or POPE) is a type of noncardiogenic pulmonary edema that can manifest as ARDS.[35] It is rare (five cases reported from a large tertiary medical ICU in 4 years),[36] can range in severity from mild hypoxemia treated with low-flow supplemental oxygen to profound hypoxemia requiring mechanical ventilation, and may even present as alveolar hemorrhage.[37–41] It is believed to be caused by increased vascular permeability resulting in alveolar and capillary damage from large levels of negative intrathoracic pressure generated by attempting to inspire against an occluded airway or airway obstruction.[42,43] This leads to a protein-rich alveolar exudate impairing gas exchange in mild to moderate cases and leaking of capillary blood into the alveoli in more severe circumstances. Most of the reported cases are related to surgical procedures: thyroidectomy,[44] septorhinoplasty,[45] tonsillectomy/adenoidectomy,[46] mandibular open reduction and internal fixation,[47] or cryosurgery for a tracheal obstruction.[48] Nonoperative conditions leading to NPPE have included laryngospasm,[49,50] occlusion of an endotracheal tube,[51,52] excessive tube thoracostomy suction pressure,[53] nonlethal hanging,[54] and even hiccups.[55,56] The common element is the rapid relief of a large airway occlusion. Patients often have no underlying cardiopulmonary disorders. NPPE may account for a small percentage of immediate postoperative extubation failures, particularly if an unrecognized mainstem intubation is present in an awake and spontaneously breathing patient. Clinical manifestations of hypoxemia and respiratory distress may be delayed up to 6 hours.[43]

• BOX 36.4 Common Clinical Risk Factors for ARDS

Sepsis and the systemic inflammatory response syndrome (SIRS)
Prolonged hypotension/shock
Trauma (long bone fractures, lung contusion, fat embolism)
Acid aspiration
Near-drowning
Multiple emergency blood product transfusions
Pancreatitis
Disseminated intravascular coagulation
After cardiopulmonary bypass
Burn injury

• BOX 36.5 Common Pulmonary and Extrapulmonary Causes of ARDS

Direct Pulmonary Causes

Pneumonia
Acid aspiration
Inhalational lung injury
Lung contusion
Chest trauma
Near-drowning

Extrapulmonary Causes

Sepsis—systemic inflammatory response syndrome
Shock—hypotension
Pancreatitis
Trauma (fat embolism)
After cardiopulmonary bypass
Massive transfusion therapy
Burns
Elevated intracranial pressure (traumatic brain injury, intracerebral hemorrhage)

Therapy is supportive with supplemental oxygen and, if needed, positive-pressure ventilation (invasive or noninvasive).

Elevated intracranial pressures, either from traumatic brain injury, intracerebral hemorrhage, or status epilepticus can induce an ARDS-like clinical syndrome termed neurogenic pulmonary edema.[57,58] Although the exact mechanisms are not clear, an abrupt and massive release of catecholamines from injured neuronal tissues is thought to act directly on the pulmonary vasculature to promote a "capillary leak" of a protein-rich exudate and an increase in pulmonary vascular resistance.[59] In addition, there may be a neurohumoral (takotsubo) cardiomyopathy, which has the distinctive echocardiographic feature of ventricular apical ballooning that can persist for months.[60–63]

Incidence and Prevalence

The exact incidence and prevalence of ARDS has been variable and influenced by the definition used (Box 36.6).[8,34] Early reports suggested that there were 150,000 patients with ARDS each year in the United States.[8,30,64] This statistic led to an estimated incidence of 75 cases per 100,000 population. Proposed estimates have suggested that the incidence of ARDS ranges from 1.5 to 64 cases per 100,000 population.[34,64,65] The authors noted that increasing age was associated with an increased incidence and mortality rate in ARDS. A recent Spanish prospective observational study (the ALIEN) using the AECC definition and treatment with lung protective ventilatory support strategies reported an ARDS incidence of 7.2 per 100,000 population per year with an ICU and hospital mortality rate of 42.7% and 47.8%, respectively.[66]

Clinical Manifestations

When ARDS becomes clinically apparent, the patient is usually noted to be in significant respiratory distress manifesting dyspnea, tachypnea, accessory muscle use, and increased work of breathing.[8,23,30] ARDS typically presents as an acute catastrophic complication in a patient who has one or more of the clinical risk factors. The precipitating injury need not directly involve the pulmonary system.[8,20] Past definitions have emphasized the need to exclude patients with previous or known chronic pulmonary or cardiovascular diseases.[20,21,26] The AECC definition excluded patients with elevated left-sided heart filling pressures and chronic infiltrative lung disease as the cause of the radiographic or physiologic alterations, but the Berlin definition allows for the concomitant presence of ARDS and cardiac edema/volume overload as long as the predominant process is thought to be ARDS.[21,28]

The physiologic hallmark of ARDS is the presence of hypoxemia despite high concentrations of inspired oxygen, evidence of an increased shunt fraction, decreased pulmonary compliance, and increased V_D ventilation.[8,24,28] The chest radiographic manifestation of ARDS is the presence of bilateral pulmonary infiltrates with a normal cardiac silhouette. Recent reports have cautioned that even among trained experts there is often disagreement concerning the interpretation of the chest radiograph.[27,29,64,67] Chest CT has also demonstrated that the radiographic injury is not homogeneous and has a predominance in the dependent portions of the lung.[8,67] It is important to remember that ARDS is a clinical syndrome and the diagnosis is made clinically, not on the basis of a single radiograph, ABG analysis, or laboratory test.

• BOX 36.6 Incidence of ARDS

1985 Canary Island Conference: 1.5/100,000 person-years
1990 Utah: 4.8–8.3/100,000 person-years
1991 Berlin: 3/100,000 person-years
1995 Maryland: 10.5–14.2/100,000 person-years
1997 Sweden/Denmark: 13.5/100,000 person-years
2002 Australia: 28/100,000 person-years
2005 Seattle: 58.7–64/100,000 person-years

Modified from Bersten AD, Edibam C, Hunt T, et al. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. Am J Respir Crit Care Med. *2002;165:443–448; Rubenfeld GD, Neff MJ. Epidemiology of acute lung injury: a public health perspective. In: Matthay MA, ed.* Acute Respiratory Distress Syndrome. *Boca Raton, FL: CRC Press; 2003:30–44; and Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury.* N Engl J Med. *2005;353:1685–1693.*

Pathologic Manifestations

Type 1 alveolar epithelial cells compose the major gas exchange surface of the alveolus and are integral to the maintenance of the permeability barrier function of the alveolar membrane.[8] Type 2 pneumocytes are the progenitors of type 1 cells and are responsible for surfactant production and maintaining homeostasis.[8] During ARDS there is damage to both capillary endothelial and alveolar epithelial cells.[8] Cellular injury and alteration of the normal barrier function results in a permeability defect that gives way to flooding of the alveoli with protein-rich fluid and inflammatory cells.[8,30,68] This results in the alteration of pulmonary mechanics, physiology, and gas exchange.[8,69] There is alteration of surfactant that results from damage to the type 2 pneumocyte and from the inactivation and dilution of alveolar surfactant from the protein and fluid that have entered into the alveolar space, respectively.[70,71] Surfactant dysfunction can lead to atelectasis and a further reduction in pulmonary compliance.[8,70–73] In addition, dysfunction of the alveolar epithelial cells can impair the resorption of fluid from the alveolar space, which augments the parenchymal injury process and gas exchange abnormalities.[8,74]

The observed pathologic findings in ARDS depend on the timing of the tissue sampling. During the initial stages of clinically evident lung injury there is histologic evidence of diffuse alveolar damage.[8] Histologic features of the injury include microthrombi composed of platelets and white blood cells within the capillary lumen, denudation of the alveolar epithelial lining cells, swelling of the capillary endothelial cells, interstitial and alveolar infiltration by polymorphonuclear leukocytes (PMNLs), and hyaline membrane formation within the alveoli.[8] Grossly, the lungs appear heavy and wet. Later, areas of type 3 collagen deposition with fibrosis will be present.[74] An intense inflammatory reaction involving PMNLs, activated monocytes, macrophages, and endothelial cells is present in the fibroproliferative phase of lung injury.[68,71,75] Proinflammatory and antiinflammatory molecules produced by these activated cells may be found in the circulating blood and bronchoalveolar lavage fluid.[75–77] This phase may be followed by fibrosis, but this fibrosis does not appear to have the same permanence as typical fibrosis would have and may actually resolve over time in some survivors of the injury.[78]

Pathophysiology

ARDS may develop as a result of epithelial or endothelial cell injury.[8,79,80] Both sites of injury and cells are important for maintenance of normal barrier function and are capable of initiating an inflammatory response. In the majority of clinical settings the

initial site of the ARDS involves the capillary endothelial cell, which may be the initial manifestation of a "panendothelial cell injury" resulting from SIRS.[77] Endothelial cell injury compromises the integrity of the vascular barrier and results in transudation of fluid and inflammatory mediators into the interstitial tissues and ultimately into the alveoli.[8] The frequent occurrence and early involvement of lung dysfunction as a component of multiple organ dysfunction/failure lends support to the hypothesis of a panendothelial cell injury as one of the target injuries in the setting of sepsis or SIRS.[81]

The complex pathophysiologic processes that culminate in the production of ARDS involve a delicate balance between the body's proinflammatory and antiinflammatory responses to the inciting clinical event.[77,81] The balance that exists between the various inflammatory molecules or mediators and the endogenous compensatory responses evoked by the inflammatory response dictates whether or not lung injury and other forms of organ dysfunction will develop.[75] The ensuing interaction between SIRS and the compensatory antiinflammatory response syndrome (CARS), coupled with activation of the clotting cascade and with inactivation of the normal fibrinolytic pathway, thus determines whether a patient successfully deals with an injury or is predisposed to develop organ dysfunction (excessive SIRS response) or immunosuppression and infectious complications (excessive CARS response).[77,81] This mixed antagonistic response syndrome has tremendous impact on the fate of the critically ill patient.[81]

Management Strategies

Basic management strategies for patients with ARDS are listed in Box 36.7.[8,21,23,30,82] Initial attention must be directed to providing lung-protective ventilator support along with identification and treatment of the predisposing underlying clinical risk factor(s) or condition(s).[8,21–23] The recognition of sepsis and infection as frequent causes of ARDS should prompt an aggressive search for undiagnosed foci of infection and the administration of appropriate antimicrobial treatment and source control as indicated.[20,83]

• BOX 36.7 Basic Management Strategies for Patients With ARDS

Identify and treat underlying/predisposing cause of ARDS
Ventilatory support
- Lung-protective ventilatory support strategy
- Application of PEEP (per ARDS Network protocol)

Restore and maintain hemodynamic function
- Conservative fluid replacement strategy using goal-oriented approach
- Vasopressor and inotropic support as needed to meet goals

Prevent complications of critical illness
- Stress ulcer (stress-related mucosal disease) prophylaxis
- Preventive strategies for pulmonary embolism and deep venous thrombosis
- Prevent infections such as ventilator-associated pneumonia
- Control glucose and metabolic function

Prevent development of multiple-organ dysfunction/failure
Ensure adequate nutrition
Avoid oversedation and medication errors
Use of weaning protocol with spontaneous breathing trials when ready to wean
Cautious use of steroids for fibroproliferative phase (avoid if patient has received neuromuscular blocking drugs)

ARDS, *Acute respiratory distress syndrome;* PEEP, *positive end-expiratory pressure.*

Both experimental and clinical data report significant survival benefit from the use of lung-protective ventilatory support strategies in the management of ARDS.[84,85] The primary goal of this support is to maintain adequate oxygenation and ensure that the lung is allowed to heal and avoid further injury. Use of nonprotective ventilatory support strategies may have a role in the persistent proinflammatory response and the development of multiple-organ dysfunction syndrome (MODS) and multiple-organ failure (MOF).[84–87]

Mechanical Ventilation

See Chapter 11 for a more detailed discussion of mechanical ventilatory support in the management of patients with ARDS. Over the past 20 years there has been increasing recognition that the ventilatory support strategy used in the management of patients with ARDS may produce or augment lung injury or impair the healing process (Box 36.8).[86–91] Results of experimental animal studies demonstrated clinical, physiologic, and histologic abnormalities similar to those observed in patients with ARDS when animals with normal lungs were ventilated with large V_ts or were given high inflation pressures.[90,91] The alveolar overdistention produced by these ventilatory modes was considered the critical element in production of the lung injury.[90,91] Lung injury could result from the administration of large V_ts or the administration of positive-pressure or negative-pressure breaths that were sufficient to produce alveolar overdistention (termed *volutrauma*).[91–94]

Other mechanisms that could potentially result in lung injury were the repetitive recruitment-derecruitment of distal airways (termed *atelectotrauma*) and alveoli or the disruption of alveoli resulting in translocation of organisms or air emboli.[90,91] Alveolar overdistention can also give rise to bioactive molecules that may contribute to the SIRS response and drive the development of MODS/MOF.[86,91] This has been termed *biotrauma*.[91] Interestingly, the lung injury produced by high inflation pressures or large V_ts in these experimental models could be ameliorated by the addition of therapeutic amounts of PEEP.[91] Subsequent human studies have used chest CT scanning to evaluate the distribution of the radiographic injury in ARDS and have noted the dependent nature of the injury.[67,95] The injury to the lungs was not diffuse and homogeneous as once believed. These dependent areas of injury consist of regions of alveolar flooding from the gravitational accumulation of lung water, areas of lung injury, and normal lung regions. The relatively normal ventral (nondependent) lung has been referred to as the "baby lung," and the injured (dependent) lung has been called the "sponge lung."[95] With the use of higher V_ts, PEEP, or high distending pressures, there was evidence of alveolar overdistention, particularly in the areas of normal lung. A multicenter trial of low versus traditional V_t ventilation in patients with ARDS demonstrated increased proinflammatory cytokines in the serum and bronchoalveolar lavage fluid of patients ventilated with the larger traditional V_ts, supporting the concept of biotrauma from alveolar overdistention.[86] Pulmonary barotrauma (pneumomediastinum, pneumopericardium, pneumoperitoneum, pneumothorax, subcutaneous

• BOX 36.8 Causes of Ventilator-Associated Lung Injury

Volutrauma
Atelectotrauma
Biotrauma
Barotrauma
Air embolism/translocation

emphysema, pulmonary interstitial emphysema, and air embolism) is a well-recognized complication of ventilatory support that has been reported in 7% to 15% of patients with ARDS.[96]

The landmark study by NHLBI ARDS Network compared low V_ts (6 mL/kg of ideal body weight) against conventional V_ts (12 mL/kg of ideal body weight).[88] A protocol governed the use of PEEP according to the FIO_2 required to meet the oxygenation goals. A weaning protocol was used once the patient was receiving a reduced amount of ventilatory support. The trial was terminated after 861 patients were enrolled after the determination of a significant (22% relative reduction) decrease in mortality rate associated with the use of low V_ts (39.8% vs. 31%; $P = 0.007$). A significant difference occurred between the low- and high-V_t groups in length of stay, ventilator days, and development of MODS.[88] No difference occurred in the development of barotrauma between the two ventilator support strategies. On further analysis, this survival benefit was present irrespective of the patient's body mass index.[97] The ARDS Network (ARDSnet) lung-protective protocol strove to keep the end-inspiratory plateau pressure (P_{plt}) ≤30 cm H_2O to avoid alveolar overdistention and the potential production of ventilator-induced lung injury (VILI).[91] The transalveolar pressure [(P alveolar pressure (P_{ao}) − P pleural (P_{pl})] likely governs the production of VILI, but some have evaluated the driving pressure (P_{plt} − PEEP) as a more readily identifiable variable associated with poor outcome.[98,99] Using an administrative dataset from past studies of lung protective ventilatory support an increase in driving pressure was associated with increased mortality, whereas a decrease was associated with decreased mortality in patients with ARDS.[98]

The use of lower V_ts typically results in controlled hypoventilation or permissive hypercapnia and can lead to hypercapnic acidosis.[100] Some experimental animal models of lung injury suggest that hypercapnic acidosis may be beneficial to the lung and produce less lung injury as measured by extravascular lung water (Box 36.9).[101] Other reports have detailed potentially harmful effects of hypercapnia on epithelial and endothelial barrier function, lung edema, edema clearance, innate immunity, and host defenses and have reported increased mortality as the hypercapnia worsens.[101,102]

PEEP is a major component of the ventilatory support strategy and may actually have a direct therapeutic role in the prevention of VILI, as noted in some experimental models.[8,90,103–105] PEEP is beneficial in the recruitment of atelectatic lung units and prevention of recruitment-derecruitment, and it increases the functional residual capacity, decreases the shunt fraction, and allows for a reduction to a less toxic FIO_2 while still maintaining adequate oxygen saturation and tissue oxygen delivery.[105–109] The application of the "right amount" of PEEP has been the topic of investigation and controversy over the past few decades (Fig. 36.3).[110–115]

PEEP has the potential to have profound hemodynamic consequences in selected patients and clinical circumstances, and it is important to closely monitor patients with hemodynamic, echocardiographic, or other sophisticated monitors if there is a question of the adequacy of cardiac function when PEEP is applied.[6,104,109] Right-to-left shunting through a patent foramen ovale can occur in up to a third of patients with severe ARDS, and increasing PEEP may not produce the expected oxygenation benefits in these individuals.[116] The effect of PEEP may not be the same in the supine and prone positions. There is an enhanced ability to recruit alveoli when the patient is in the prone position compared with the supine position related to stabilization of the anterior chest wall.[117] There may be a different responsiveness to the use of PEEP depending on whether the ARDS results from a direct pulmonary injury or a nonpulmonary process.[20]

A multicenter French study has reported that the use of neuromuscular blockade with cisatracurium during the initial 48 hours of severe ARDS was associated with improved 90-day survival and longer time off ventilatory support in contrast to conventional ventilator management.[118] A prior study by these investigators noted decreased inflammatory response associated with the use of neuromuscular blockade in patients with ARDS.[119] Although there is always a risk for prolonged neuromuscular weakness associated with the use of neuromuscular blocking drugs, as well as in critical illness, there are many potential benefits in support of using neuromuscular blocking agents early in severe ARDS.[120] Some of these potential benefits include better patient-ventilator synchrony and interaction, less VILI as a result of better control of driving pressure and transpulmonary pressure, better recruitment effect from administered PEEP, and decreased oxygen consumption.[118,120,121]

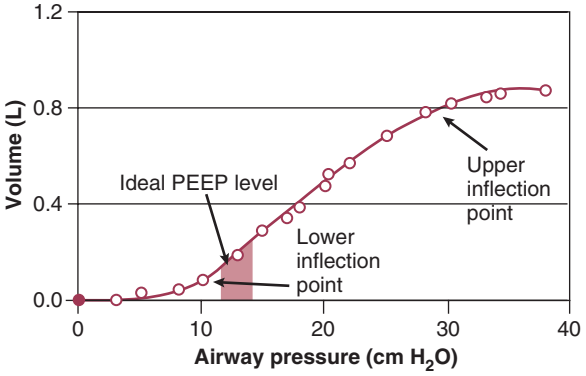
Noninvasive ventilation (NIV) is increasingly used in patients with ARDS, although the evidence supporting its use remains sparse. A substudy of the observational LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study examined the current practice of NIV use in ARDS, the utility of the PaO_2/FIO_2 ratio in classifying patients receiving NIV, and the impact of NIV on outcome.[122] Data suggested an association between mortality and the use of NIV in the setting of moderate to severe ARDS (PaO_2/FIO_2 < 150 mm Hg). It is possible that if this association is cause and effect that it could be related to delayed implementation of lung-protective ventilatory support.

• BOX 36.9 Potential Benefits of Hypercapnia in Patients With ARDS

↓ TNF-α release by alveolar macrophages
↓ PMNL-endothelial cell adhesion
↓ Xanthine oxidase activity
↓ NF-κB
↓ NOS activity
↓ Production of IL-8 and TOR from PMNLs

IL-8, *Interleukin 8;* NF-κB, *nuclear factor κ–light-chain enhancer of activated B cells;* NOS, *not otherwise specified;* PMNL, *polymorphonuclear leukocyte;* TNF-α, *tumor necrosis factor α;* TOR, *toxic oxygen radicals.*

From Kregenow DA, Rubenfeld GD, Hudson LD, et al. Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med. *2006;34:1–7.*



• **Fig. 36.3** Pulmonary volume-pressure curve. *PEEP,* Positive end-expiratory pressure. (Modified from *Hospital Physician Pulmonary Disease Board Review Manual.* Wayne, PA: Turner White Communications; 2000:7.)

Fluid Management and Vasoactive Support

Patients with ARDS, like other critically ill patients, need adequate oxygen delivery to tissues, which implies an adequate oxygen saturation and hemodynamic function. The past controversy concerning optimal fluid management in patients with ARDS[123–125] has been addressed by the ARDSnet Fluid and Catheter Treatment Trial (FACTT) study.[126] This study compared a liberal versus conservative fluid replacement strategy and also evaluated the utility and safety of using a pulmonary artery (PA) catheter to guide volume replacement as opposed to a central venous catheter.[126,127] The safety and potential benefits of using PA catheters in the critically ill has been an area of controversy since the 1990s.[128–130] The trial evaluated liberal versus conservative fluid management on the basis of the central venous catheter data (central venous pressure [CVP] versus PA catheter [PA occlusion pressure]) data in 1000 patients with established ARDS.[127,128] There was no difference between the groups in lung or renal function, use of vasopressors, renal replacement therapy, or hypotension. The PA catheter group did have twice as many catheter-related complications, predominantly in the form of arrhythmias, compared with the central venous catheter group. The liberal fluid management arm of the FACTT study had an average net gain of almost 7 L over the first 7 days, whereas the conservative fluid management group averaged a loss of 136 mL over 7 days.[126] The use of the conservative fluid management strategy was associated with a significant improvement in oxygenation index and lung injury score and increased the number of ventilator-free days compared with the more liberal strategy. There was no difference in the development of shock or the need for renal replacement therapy between the two fluid management strategies.[126] As a result of this trial the use of conservative fluid management without the use of a PA catheter is the recommended strategy for patients with ARDS.

Prevention of Complications of Critical Illness

Patients with ARDS are at risk for the expected complications of critical illness, which are largely preventable. Prophylactic strategies should be used whenever possible. Common complications include deep venous thrombosis and pulmonary embolism, stress-related gastrointestinal hemorrhage, ventilator-associated pneumonia (VAP) and hospital-acquired infections, metabolic abnormalities, critical illness polymyoneuropathy, pressure ulcers, delirium, and malnutrition.[131–139] Anticipation and prevention of these complications are vitally important. Prophylactic strategies to prevent stress-related mucosal disease and gastrointestinal bleeding using H_2-blockers, proton pump inhibitors, or possibly early enteral nutrition should occur in all patients unless otherwise contraindicated.[135,136] Deep vein thrombosis and pulmonary embolism prophylaxis should also be administered unless there are contraindications.[136] The use of enteral nutrition may be valuable in an attempt to prevent stress-related gastrointestinal bleeding and prevent translocation when normal barrier function of the gastrointestinal mucosa is compromised.[135–140] Nutritional support may also be important to maintain the proper level of immune function and potentially to prevent the development of malnutrition in the catabolic critically ill patient. The use of special enteral formulas designed to enhance the immune response remains controversial, but recent trials have failed to demonstrate a survival benefit with their use.[141–143] The ARDS Network found that the use of twice-daily enteral supplementation with ω-3 fatty acids, γ-linolenic acid, and antioxidants did not improve clinical outcome and was associated with a greater amount of diarrhea.[142] A subsequent (EDEN) randomized trial by the same investigators found that ARDS patients who received trophic (minimal enteral) feeding did just as well and had less gastric residual volume, vomiting, and constipation and a lower blood sugar and insulin requirement than the patients who received full enteral feeding over the first 6 days.[143] For patients who did not tolerate enteral nutrition, waiting to provide parenteral nutritional support for up to 8 days was found to be well tolerated, had fewer complications, and was associated with a faster recovery in critically ill adult patients.[144]

A major goal of management should be the prevention of hospital-acquired infections/sepsis and multiple-organ dysfunction/failure because these two conditions are currently responsible for the high mortality rate seen in patients with ARDS.[135,140] VAP is a frequent complication in critically ill ventilated patients. As previously mentioned, prevention of VAP should be a primary management goal for patients with ARDS. Detection of a complicating VAP can be difficult in the setting of the pulmonary infiltrates seen in patients with ARDS. Diagnosis of VAP and identification of the offending pathogen often requires the use of bronchoscopy with bronchoalveolar lavage or protected specimen brushes coupled with semiquantitative culture techniques.[131,133] Some advocate the use of biomarkers for bacterial infection (e.g., soluble triggering receptor expressed on myeloid cells, procalcitonin, and so on) may be beneficial in the detection of VAP but does not identify the specific etiologic organism.[145] Ventilator management bundles that include keeping the head of the bed elevated above 30 degrees, not routinely changing ventilator tubing, and daily oral mouth care have been shown to be effective at preventing VAP.[146] Additional measures designed to decrease the development of VAP include continuous subglottic suction, coated endotracheal tubes, closed suction systems, and kinetic therapy.[136] Most centers use a ventilator management bundle to decrease ventilator-associated complications and now attention is directed toward early reduction in sedation and analgesia, timely extubation, and increased mobility.[147] It is important to wean patients who no longer require ventilatory support in a timely fashion using guideline-based protocols that speed the separation process and decrease the risk for reintubation.[148,149] Recent consensus guidelines have been published to facilitate the weaning process.[148,149] Use of strategies to decrease the risk of complications in the critically ill has been associated with decreased morbidity, length of stay, cost of care, and possibly mortality rate compared with those patients in whom complications do develop.[135,136]

Strategies to Improve Oxygenation and Rescue Strategies

In patients with severe ARDS and persistent hypoxemia various rescue strategies have been used in an attempt to improve oxygenation, lessen F_{IO_2} requirements, and improve outcome. Included in these strategies are neuromuscular blockade, recruitment maneuvers, prone positioning, inhaled vasodilators, sophisticated modes of ventilatory support (airway pressure release ventilation, high-frequency oscillation, and so on) and extracorporeal membrane oxygenation (ECMO) support.[117,118,150–162] The proposed benefits of early neuromuscular blockade in severe ARDS have been described earlier in this chapter. The efficacy of some of these techniques remains controversial at this time and should be subjected to rigorous evaluation to adequately determine their ability to improve outcome for patients with ARDS. It should be remembered that the use of higher V_ts (12 mL/kg ideal body weight) in the ARDS Network trial was associated with an improvement in oxygenation, but significantly decreased survival in patients with ARDS.[88]

Recruitment maneuvers represent an attempt to open the atelectatic distal airways and alveoli on the border of the collapsed flooded alveoli that compose the dependent area of radiographic lung injury.[91] Some experts believe that this maneuver should precede the application of directed PEEP and ventilator support in the early phases of ARDS.[163] The maneuver is accomplished by increasing the PEEP to 35 to 50 cm H_2O and holding that level of pressure for 30 to 40 seconds. The ARDS Network attempted to define the value of a recruitment maneuver in 43 patients with ARDS by randomly assigning them to a recruitment maneuver with 35 to 40 cm H_2O for 30 seconds versus a sham recruitment maneuver.[151] The efficacy of the recruitment maneuver was assessed based on a sustained improvement in oxygenation as judged by the ability to titrate PEEP/FIO_2 on the basis of the network algorithm and changes in lung compliance. There was no significant difference in the magnitude or duration of the oxygenation effect, compliance, or change in PEEP/FIO_2 titration. The group that received a recruitment maneuver did have a greater decrease in blood pressure during the maneuver. It should be noted that the recruitment maneuver was not followed by PEEP setting to compliance or by increase in PEEP, which some believe is necessary to maintain any improvement in oxygenation that occurs with a recruitment maneuver. The Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) attempted to address this factor.[164]

More than a thousand patients with moderate to severe ARDS (PaO_2/FIO_2 ratio <200) were randomly assigned to receive either PEEP as indicated on the ARDSnet low PEEP table (control) versus a lung recruitment maneuver followed by PEEP titration according to best respiratory system compliance (experimental group). Mortality was greater in the experimental group. The worse outcome in the experimental group was potentially due to an unfavorable balance between the potentially positive effect of decreasing driving pressure and negative effects of increasing overdistention and hemodynamic impairment. Other studies have reported that recruitment maneuvers are well tolerated from a hemodynamic standpoint and are not associated with increased cytokine release as may be expected with alveolar overdistention.[165]

Patients with ARDS may improve their oxygenation abnormalities when they are placed in the prone position.[145,166–173] This position may be more physiologic for most mammals and results in improved secretion removal, better ventilation-perfusion matching, and enhanced aeration of the dorsal lung units.[145] The prone position may also prevent the heart from collapsing the left lower lobe and augment the recruitment effects of PEEP by stabilizing the more flexible ventral chest wall.[145] Prone positioning may also unload the right ventricle in the setting of severe ARDS.[145] A number of trials have demonstrated an improvement in oxygenation during and after being placed in a prone position, but have failed to demonstrate a survival advantage.[145,167–170] After a meta-analysis detected a possible survival benefit for patients with severe ARDS managed with prone positioning,[174] a subsequent multicenter clinical trial demonstrated improved survival with prone positioning for patients with a PaO_2/FIO_2 ratio <150.[175] However, there are potential complications that can result from the process of changing the patient from a supine to a prone position.[171,172] The potential complications include tube/catheter malposition/problems, pressure sores, blindness, and difficulty with patient assessment and resuscitation.[171,172] Most experts now agree that prone positioning should be considered in patients with severe ARDS who require high FIO_2 and PEEP despite optimization with a lung-protective ventilatory support strategy.

Inhaled Vasodilator Therapy

Inhaled vasodilators, like nitric oxide or prostacyclin, are bronchial and vascular smooth muscle dilators that also decrease platelet adherence and aggregation.[153,176] Inhaled vasodilator therapy has been shown to improve oxygenation by improving ventilation-perfusion relationships in the lung.[153,176,177] A reduction in PA pressure and pulmonary vascular resistance also occurs. These beneficial pulmonary effects of nitric oxide are associated with minimal systemic effect because it is rapidly inactivated when the nitric oxide enters the circulation and is taken up by red blood cells. However, multiple prospective, randomized, placebo-controlled clinical trials failed to demonstrate an improvement in survival despite the early improvement in oxygenation associated with the administration of inhaled nitric oxide.[154,155,178,179] This therapy is not approved by the U.S. Food and Drug Administration, is costly, may affect platelet function, and may be associated with an increase incidence of acute kidney injury.[154,178,179] Some centers are using inhaled epoprostenol as an alternative inhaled vasodilator for rescue therapy (i.e., other more accepted therapies have failed to achieve the PaO_2/FIO_2 target), but there are no data to support an improved outcome from this treatment.[180]

Surfactant Replacement Therapy

Surfactant abnormalities are present in patients with ARDS related to decreased production, inactivation by alveolar proteins and proteolytic enzymes, and dilution by the alveolar fluid.[181] Theoretically, surfactant replacement should produce a survival benefit, just as it does in the infant respiratory distress syndrome.[181–183] However, multiple trials have failed to demonstrate significant survival benefit using surfactant replacement therapy in adults with ARDS.[181–183]

Extracorporeal Life Support

Since the 2009 H1N1 influenza A pandemics we have seen a dramatic rise in the use of extracorporeal life support, particularly ECMO, in patients with severe ARDS.[184,185] The use of ECMO support was in part driven by the CESAR (Conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure) trial, which demonstrated a 31% decrease in death or severe disability in U.K. patients who were transferred to the ECMO center for care as opposed to standard care provided at the other referring hospitals.[186] Although there were several criticisms of the trial, particularly related to the use of lung-protective ventilatory support strategy in only 63% of the non-ECMO centers, the improvement in composite endpoint associated with ECMO center management likely fueled the resurrection of ECMO use for adults with ARDS. Extracorporeal life support can be provided to remove CO_2 (extracorporeal CO_2 removal [ECCOR]), to provide oxygenation support (venovenous [VV] ECMO), or to provide additional cardiac support using venoarterial (VA) ECMO or venoveno-arterial (VVA) ECMO.[159]

The most common form of ECMO support for patients with ARDS and adequate cardiac function involves the use of VV ECMO. Blood is drawn from a large-bore venous catheter (typically placed in the femoral vein or a bicaval catheter placed in the internal jugular vein) and then passed through an oxygenator where oxygen is added and CO_2 is removed from the blood. The oxygenated blood is then returned to the patient via a catheter in the right side of the heart or the PA. For patients with high cardiac output needs, adequate flow can be ensured by using large-bore catheters or central cannulation techniques. Indeed, ECMO may be the

paramount means of lung-protective ventilatory support during ARDS because it can provide all of the needed gas exchange and oxygenation support without the need for invasive mechanical ventilatory support.[159,186] Without the use of positive-pressure ventilation there should not be further lung injury and the lungs will be allowed to rest and heal.[187–189] In addition, the patient managed by ECMO and off ventilatory support may require less sedation and analgesia and thus be more able to participate in early rehabilitation and mobilization, which could translate into improved postrecovery status from the ARDS injury state and may have less potential for delirium, which is associated with worse postrecovery outcome from critical illness.[189,190] Our center uses lung-protective ventilatory support with ECMO runs and typically starts with a pressure control mode of 20 cm H_2O, PEEP of 10 cm H_2O, FIO_2 of 1.0, and respiratory rate of 10 breaths/min and then titrates as necessary. Our goal is to work toward early extubation, if possible, so that we can reduce sedation and allow the patient to participate in rehabilitation and mobilization.

Experimental and Antiinflammatory Therapies

In an attempt to reduce the high mortality rate associated with ARDS, a number of experimental and innovative therapeutic approaches have been evaluated. A majority of these approaches target abnormalities that either produce or result from the systemic inflammatory response that is considered central to the pathogenesis of the injury. To date, none of these approaches has been demonstrated to offer significant benefit in well-conducted, prospective, randomized controlled, multicenter clinical trials. These approaches have included the early administration of high-dose corticosteroids, prostaglandin E_1, nonsteroidal antiinflammatory drugs, antiendotoxin, and anticytokine therapy.[191–208]

Many investigations in experimental animal models of ARDS have demonstrated benefit from pretreatment and early treatment with high-dose corticosteroids.[209] To further complicate this clinical situation, it has been demonstrated that a significant proportion of patients with septic shock and other critical illnesses have relative adrenal insufficiency as defined by the inability to elevate the plasma cortisol level more than 9 μg/dL after adrenocorticotropic hormone stimulation.[210] This relative adrenocortical deficiency has been implicated as a potential cause of the persistent shock state and impaired perfusion. However, these patients have not always been responsive to the administration of steroids, and the adrenergic hyporesponsiveness may be related to sepsis-induced nitric oxide production, desensitization, or downregulation of α- and β-adrenergic receptors.[210] Lower-dose, more physiologic steroid replacement may restore the α- and β-adrenergic responsiveness and potentially turn off the inflammatory reaction to allow for better healing and less injury.[211] Attempts to prevent the development of ARDS in high-risk patients with severe sepsis and septic shock with high-dose corticosteroids have not been shown to prevent the development of ARDS, improve the reversal of ARDS, or improve the outcome from ARDS.[193] There are a number of potential beneficial effects of steroids for patients with ARDS, such as suppression of systemic inflammatory response.[212,213] In addition, a recent meta-analysis of steroids in the treatment of severe community-acquired pneumonia has demonstrated a decrease in ARDS development in those patients treated with corticosteroids.[214]

Steroid therapy has been shown to be beneficial in patients with severe *Pneumocystis jiroveci* (*carinii*) pneumonia and ARDS and possibly in patients with fat embolism.[215,216] In the patient with adrenal insufficiency, stress dose steroids should be administered. There was an increase in mortality seen in those patients with viral-induced ARDS (H1N1 influenza A) treated with steroids compared with controls.[217,218] The use of corticosteroids to treat patients with established ARDS is controversial and is discussed later. Ibuprofen, a nonsteroidal antiinflammatory drug, failed to significantly improve the outcome of patients with severe sepsis or septic shock and failed to prevent the development of ARDS in a prospective, randomized, placebo-controlled, multicenter clinical trial.[219]

Additionally, several investigative clinical trials have evaluated "antimediator therapy" in sepsis and ARDS and failed to demonstrate a significant survival benefit.[8,193,198,199,201] Attempts to change the inflammatory response by changing the ratio of ω-3/ω-6 fatty acids have evaluated the potential benefit of an enteral nutritional formula rich in eicosapentaenoic acid and γ-linoleic acid.[220]

Pentoxifylline and lisofylline are xanthine derivatives that were believed to have utility in the management of sepsis and ARDS.[221] Pentoxifylline is a rheologic agent with the ability to inhibit toxic oxygen radical release, decrease platelet aggregation, decrease phagocytosis, diminish the response to platelet-activating factor stimulation, and inhibit the release of tumor necrosis factor into the systemic circulation. Clinical evaluation of this treatment strategy by the National Institutes of Health (NIH) ARDS Network found no significant benefit.[221]

ARDS may be produced or worsened by the elaboration of toxic oxygen radicals from the activated inflammatory cells.[8] The abundant production of toxic oxygen radicals may overwhelm the ability of the endogenous oxygen radical scavengers, superoxide dismutase, catalase, and the glutathione redux cycle. The administration of antioxidants, such as N-acetylcysteine, procysteine, vitamin E, β-carotene, and vitamin C, has been evaluated in the prevention and management of patients with ARDS.[207,222,223] No survival benefit was seen associated with the administration of N-acetylcysteine or procysteine versus control in patients with ARDS.[207]

Drug Therapy for Prevention of ARDS

The ability to prevent the development of ARDS would be a welcome achievement that to date has been elusive. Two older trials demonstrated a significant reduction in the development of ARDS in surgical patients when ketoconazole, an imidazole thromboxane A_2 synthetase inhibitor, was administered to an at-risk population of patients.[224,225] However, when ketoconazole was evaluated by the ARDS Network in the treatment of patients with ARDS there was no benefit on survival.[226] The use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) as a prevention for ARDS was evaluated in an observational study of a large cohort of patients at risk for developing ARDS and was not found to decrease the development of ARDS or improve mortality rates, organ failure–free days, or ventilator-free days.[227] It has been suggested that aspirin may help prevent the development of ARDS in at-risk patients.[228] Research is under way evaluating the use of mesenchymal stem cells to improve outcome and lung repair in ARDS patients. Preliminary studies have suggested that microparticles released from mesenchymal stem cells may be instrumental in lung protection and repair that may be responsible for this beneficial effect.[229] The current emphasis of the NHLBI in ARDS management has focused on *p*revention and *e*arly *t*reatment of *a*cute *l*ung injury (PETAL) projects. The first two projects are ROSE (Reevaluation of Systemic Early neuromuscular blockade) and VIOLET (Vitamin D to Improve Outcomes by Leveraging Early Treatment).[230,231]

Fibroproliferative Phase and Steroid Treatment

An improved understanding of the injury and repair phase of ARDS has resulted in the recognition of the late fibroproliferative phase.[8,75–78,232,233] This stage of the injury/repair process is characterized by replacement of damaged epithelial cells and accumulation of mesenchymal cells and connective tissue products in the airspaces and the intraacinar microvessels.[68,74,75] Clinical manifestations include fever, leukocytosis, diffuse alveolar infiltrates on the chest radiograph, and persistent inflammatory mediators in the serum.[68,74,75] Physiologic manifestations include the worsening of static pulmonary compliance, abnormal gas exchange, increased V_D ventilation, pulmonary hypertension, and lack of PEEP response.[232,233] This picture of persistent inflammation requires a dedicated approach to ensure that there is not an ongoing uncontrolled infectious process that has not been adequately addressed.[232] Once it is determined that this state is not the result of inadequately treated infection, therapy with corticosteroids is used by some experts.[232] Several anecdotal reports have suggested that this therapy may have potential efficacy in patients with a persistent inflammatory response.[215,232] A small, single-center, prospective, randomized, placebo-controlled, double-blind clinical trial in 24 patients with the fibroproliferative phase of ARDS demonstrated an improvement in survival, lung function, and organ system dysfunction.[233] This study has been criticized because it included the crossover of patients at day 10 and had a smaller study population than a previously reported uncontrolled trial from the same center.[233]

The use of steroid rescue for the patient with persistent ARDS or the fibroproliferative phase of ARDS was evaluated by the NIH-sponsored ARDS Network.[234] The study prospectively randomly assigned 180 patients with ARDS for 7 days or longer to a placebo-controlled trial of methylprednisolone versus placebo. The primary efficacy outcome was being alive at home at 60 days. Patients with septic shock, a defined need for corticosteroid therapy, disseminated fungal infection, or undrained abscess were excluded. The trial was conducted over 6 years and included a modification of the study protocol that included a reduction in the number of subjects from 400 to 180 and an increase in the inclusion P_{AO_2}/F_{IO_2} ratio. The use of methylprednisolone was associated with an early improvement in mortality rate, P_{AO_2}/F_{IO_2} ratio, blood pressure, ventilator, and ICU-free days. An increase in the white blood cell count and glucose level related to steroid administration occurred, along with a decrease in body temperature. No difference was measured in the primary efficacy endpoint 60-day mortality rate, and no significant difference in 180-day outcome occurred between the two groups. The steroid treatment was not associated with an increase in serious infections. In fact, there was more pneumonia and septic shock in the placebo group than in the steroid-treated group. Unfortunately, the use of steroids was associated with more neuropathy and myopathy, but it is important to note that 30% of the steroid-treated patients were receiving neuromuscular blocking drugs.[234]

Meduri and colleagues evaluated a low-dose prolonged methylprednisolone infusion in patients with early severe ARDS and noted a significant decrease in lung injury score and C-reactive protein level along with a decrease in ICU mortality rates, duration of mechanical ventilation, and multiple-organ dysfunction scores.[235] The steroid infusion decreased levels of inflammatory biomarkers and coagulation.[236] The prolonged infusion strategy appeared to be safe and well tolerated, but this was a small study of 91 patients and the topic of steroid treatment in ARDS remains controversial; we eagerly await more definitive studies. With the recent benefit of steroid treatment in severe community-acquired infection, some argue that steroids are likely beneficial in ARDS that results from sepsis, as long as the infection is not viral in etiology.[214] A recent multispecialty task force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine has critically reviewed the evidence related to steroid use in patients with ARDS and has suggested the use of methylprednisolone treatment (1 mg/kg per day for early ARDS up to day 6; 2 mg/kg per day after day 6) of patients with early moderate to severe ARDS (P_{aO_2}/F_{iO_2} < 200) and then slow tapering over 13 days.[237]

Macrolide antibiotics have been reported to have important immunomodulatory properties that could prove beneficial in patients with ARDS. The ARDS Network has reviewed initial antibiotic data on 235 patients enrolled in the LARMA (Lisofylline and Respiratory Management of Acute Lung Injury) trial and found that 20% received a macrolide antibiotic within the first 24 hours of the trial.[238] These patients were more likely to have a pulmonary infection as a cause of ARDS. Of interest was the observation that the macrolide-treated patients had a 23% mortality rate compared with a 36% mortality rate for nonmacrolide antibiotic regimens.[238] This interesting observation may warrant additional study.

Multiple-Organ Dysfunction/Failure

A frequent complication of an exaggerated proinflammatory state in the setting of sepsis, SIRS, and ARDS is the development of organ system dysfunction.[83,140,239,240] This dysfunction may involve single or multiple organs.[140,239] A recent consensus conference has suggested that the dysfunction of two or more organs such that normal homeostasis cannot be maintained in the setting of a systemic inflammatory response to a variety of insults is considered MODS.[241] This dysfunction may be partial or complete, reversible, or irreversible.[140] A continuum of abnormalities ranging from dysfunction to failure for each organ is probable.[140] Unfortunately, to date there has been no consensus on the threshold that separates these two phenomena or the threshold between reversible and irreversible organ system dysfunction.[140]

MODS and MOF are the most common causes of death in the noncoronary ICU.[239,242] Many authorities consider ARDS the earliest manifestation of an uncompensated systemic inflammatory process with excessive proinflammatory component.[81,145] One hypothesis for this injury suggests that in the absence of a direct injury to a specific organ, there must be multiple inflammatory insults to produce the clinically apparent MODS/MOF.[140] This hypothesis, called the "two-hit hypothesis,"[140] suggests that an initial sensitizing insult is followed within a specific period of time by a second insult that is capable of initiating a more profound proinflammatory response because the target cells have been upregulated or primed by the initial insult.[140] Multiple combinations of direct injury, ischemic injury, circulating humoral or inflammatory mediators, translocation of endotoxin or colonic bacteria, altered rheologic properties of the blood cells, or iatrogenic effects of the therapy administered may interact in the eventual production of MODS/MOF.[140]

Lung-Protection Strategy for Prevention of ARDS

There are now several well-conducted studies and systematic meta-analyses that support the benefit of lung-protective ventilatory support in the emergency department operating room, and for non-ARDS patients in the ICU, as a way to improve outcome and even prevent the development of ARDS.[243–246] Neto and colleagues conducted a meta-analysis of lung-protective ventilation with lower

V_ts in patients who did not have ARDS and found that this technique was associated with decreased lung injury, decreased mortality, and reduced pulmonary infections compared with conventional V_t ventilatory support.[243] Using lung-protective ventilatory support strategies in the operating room was noted to decrease postoperative pulmonary complications.[244] Fuller and colleagues conducted the LOV-ED (Lung-Protective Ventilation Initiated in the Emergency Department) trial comparing lung-protective ventilatory support initiated in the emergency department and noted a decrease in the composite primary endpoint of mortality and ventilatory days compared with ventilatory support with conventional V_ts.[245] These studies suggest that prevention of ARDS by using lung-protective ventilatory support from the beginning of invasive mechanical ventilation may be the most effective way to deal with ARDS.

Prognosis

Recent studies report a significant reduction in the mortality rate from ARDS using lung protective ventilatory support and proper levels of PEEP.[8,77,88,247,248] Current trials report mortality rates in the range of 30% to 60% compared with 60% to 90% of the past.[8,88,161,249] The 30-day mortality rate seen in patients enrolled in the NIH-sponsored ECMO trial of the 1970s was 91% with both conventional and ECMO treatment.[161] Older reports from large tertiary referral centers documented mortality rates of 90% for patients with gram-negative septic shock and ARDS.[249] A large multicenter trial of inhaled surfactant in 725 patients with sepsis-induced ARDS demonstrated survival rates of 60% at 28 days in both the treatment and the control groups.[182] Today the mortality rate from ARDS appears to depend on the cause of the injury, the patient's underlying disease status, patient age, and institutional factors.[8,34,240] This improvement in the mortality rate mandates the use of a concomitant control group as opposed to using historical control subjects in the assessment of new innovative therapeutic strategies.

The most common causes of death in patients with ARDS continues to be from MOF and recurrent sepsis.[8,185,250] Fewer than 20% of patients die because of the inability to adequately oxygenate or ventilate them.[250] When infection is present, the lung is a frequent site for the process and may be extremely difficult to diagnose.[32,83,131,132] Patients with pulmonary infections were found to typically have a septic clinical picture without definitive positive culture results.[32] On the other hand, in patients who were found to have positive blood cultures without antemortem identification of a specific site, the site of occult infection was commonly found to be in the abdomen at postmortem examination.[32] Predictors of high mortality rates from ARDS include the development of multiple-organ dysfunction/failure, development of secondary sepsis, concomitant cancer, and the presence of cirrhosis or hepatic dysfunction.[8,251] A clinical study in ARDS patients receiving lung protective ventilatory support reported that the oxygenation index (mean airway pressure $\times$ F_{IO_2} $\times$ 100 $\div$ P_{aO_2}) was an independent predictor of mortality rate.[251]

Survivors of ARDS may be subject to persistent pulmonary function abnormalities, quality-of-life disruption, and neurocognitive dysfunction. A long-term follow-up study found that 80% of ARDS survivors who were discharged from the ICU were still alive 5 years later.[252,253] Although most ARDS survivors have initial abnormalities in pulmonary function, the majority return to near their baseline pulmonary function status within 3 to 6 months.[254,255] The major residual abnormality in pulmonary function is a restrictive pulmonary defect and a reduction in the carbon monoxide diffusion capacity.[254–256] These alterations may result in exercise desaturation in some patients or, more commonly, a decrease in timed walked distance.[254–256] When observed over the next 5 years, their pulmonary function did not improve a great deal after this initial improvement.[252,256] However, most patients continue to experience exercise limitation at 5 years, despite the fact that 65% have returned to work.[252,256]

Survivors of ARDS have been found to have a decreased health-related quality of life, increased respiratory symptoms, insomnia, depression, anxiety, and posttraumatic stress disorder.[257–262] They also have been found to have a clinically significant reduction in their physical function and increased pulmonary symptoms compared with matched survivors of critical illness.[257–265] Survivors of ARDS have also been found to have long-term cognitive impairment, problems coping with their disability, and relationship strains.[260,261,263] Elderly patients (>70 years of age) seem to have worse outcomes with an increase in mortality rate compared with ARDS patients who are younger than 70 years of age.[259]

Future Considerations

The growing knowledge of molecular biology and the elaborate mechanisms that govern a person's response to injury, repair, and cell death will likely have a major role in the management of patients with ARDS. Individuals with increased risk for ARDS development will no doubt be identified on the basis of their genetic profiles. This knowledge will likely affect and direct future management as we move further along the path of precision management of clinical conditions. In years to come, scientists may potentially modify the genetic makeup or the biologic response of a susceptible individual by inserting selected genes or modifying the transcription or function of various regulatory proteins. Studies with mesenchymal stem cells have been conducted in rodents with lung injury and demonstrate potential promise for future therapy.[266]

Summary

Acute respiratory failure is the inability of the respiratory system to meet the oxygenation (type 1 or hypoxemic failure) or ventilation (type 2 or hypercapnic failure) requirements of the patient. Hypoxemic respiratory failure is defined as a P_{AO_2} of less than 60 mm Hg and is the result of one of six potential mechanisms: low inspired F_{IO_2}, hypoventilation, ventilation-perfusion mismatching, shunt, low pulmonary arterial oxygenation, or diffusion impairment. The exact cause may be elucidated by analysis of the alveolar-arterial oxygen gradient, response to the administration of supplemental oxygen, and the clinical context. Hypercapnic or ventilatory failure is defined as a P_{ACO_2} of greater than 50 mm Hg, generally with acidemia; it can be acute, chronic, or acute-on-chronic and is the result of one of three potential mechanisms: hypoventilation, increased V_D ventilation, or increased CO_2 production. Clinical manifestations can range from adrenergic sympathetic hyperactivity (tachycardia and hypertension) to tachypnea and respiratory distress to encephalopathy with somnolence. Therapy is with supplemental oxygen, assisted ventilation with or without high levels of PEEP, or both.

ARDS continues to have a significant morbidity and mortality rate despite the advances in understanding and management that have occurred over the past 5 decades. Major advances have

occurred in our understanding of the pathogenesis and in our ability to adequately provide the required ventilatory support while the injury is allowed to heal. Attention has been directed toward lung-protective ventilatory support, the use of local and systemic therapies, and prevention of injury in high-risk patient populations. Despite recent improvements in management and knowledge of the pathophysiologic alterations likely involved, the mortality rate continues to be unacceptably high. Recent improvements in prognosis have occurred, primarily in those patients younger than age 60 years. Remembering the systemic nature of the injury and developing effective preventive and reparative strategies are important as we look to the future of ARDS management. Repair of the acutely injured lung, whether from the initial event, the ventilator, or complicating infection, is an important target and may be more achievable than attempting to prevent the initial injury or intervening early enough to prevent the development of ARDS.

Key Points

- Both type 1 and type 2 acute respiratory failure are common problems in the ICU and may represent the primary reason for ICU admission or be a complication arising in the critically ill patient.
- The ABG value is the cornerstone for the diagnosis and management of the patient with acute respiratory failure.
- The American-European Consensus Conference definition of ARDS has now been replaced by the Berlin Definition, which does not include ALI, just ARDS. The Berlin definition suggests that the degree of oxygenation abnormality when assessed on appropriate F_{IO_2} and PEEP has prognostic importance and defines mild, moderate, and severe ARDS.
- The most common clinical risk factors for the development of ARDS include sepsis, SIRS, hypotension, shock, trauma, near-drowning, and aspiration injury.
- The pathophysiology of ARDS represents a complex interrelationship of antiinflammatory and proinflammatory responses, activation of the coagulation system, abnormal function of the microcirculation, and altered surfactant function. Alterations affect both the capillary endothelium and the epithelial lining cells.
- At this time the management of patients with ARDS is primarily supportive, but it is important to (1) provide specific treatment directed at the underlying predisposing cause, (2) use lung-protective ventilation, and (3) prevent complications of critical illness.
- The concept of VILI has now been supported by the results of recent clinical trials demonstrating a survival benefit associated with the use of lower V_ts to avoid alveolar overdistention.
- The proper amount of PEEP therapy is important in the management of patients with ARDS to avoid alveolar overdistention and the repetitive collapse and recruitment-derecruitment of alveoli and small airspaces.
- The use of steroids to treat the fibroproliferative phase of ARDS remains a controversial area. If there is no active untreated infectious process and there is a persistent inflammatory process in the lung, there may be a benefit associated with corticosteroid therapy; however, a trial conducted by the ARDS Network did not find a survival benefit at 60 days. Current recommendations favoring steroid treatment of severe community-acquired ARDS may sway the clinician to use steroids in the management of septic patients with ARDS.
- Although the overall prognosis in ARDS has been improving, the mortality rate still ranges from 30% to 60% and decreased overall health status and function persist for as long as 5 years after recovery.

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Review Questions

1. Which one of the following causes of hypoxemia would be expected to have a normal alveolar-arterial oxygen (A-a) gradient?
   a. 25-year-old man with heroin overdose
   b. 32-year-old woman with near-drowning
   c. 40-year-old man with an acute asthma attack
   d. 60-year-old with a pulmonary embolus
   Answer: a. Hypoventilation alone (as occurs with respiratory drive suppression with heroin overdose) can be a cause of hypoxemia but there is a normal A-a gradient because there is no abnormality at the oxygen exchange interface. All of the other conditions are associated with some degree of ventilation-perfusion mismatch, which will be associated with an increase in A-a gradient as a contributing mechanism for the hypoxemia (alveolar flooding with water, bronchospasm, and release of mediators owing to clot in pulmonary arterial vessels respectively).
2. Which one of the following disorders is least likely to result in a good outcome when noninvasive ventilatory support is used for management?
   a. Acute respiratory distress syndrome (ARDS) secondary to pneumonia
   b. Chronic obstructive pulmonary disorder (COPD) with hypercapnia
   c. Obesity with hypoventilation
   d. Congestive heart failure (CHF) with hypoxemia
   Answer: a. There has been a growing interest in the use of noninvasive ventilatory support in treating COPD exacerbation, CHF, and hypoventilation associated with neuromuscular disease, but noninvasive ventilation has not proved as universally beneficial in the setting of pneumonia and in moderate to severe ARDS. In fact, recent data suggest higher mortality with the use of noninvasive ventilation in the setting of moderate to severe ARDS, likely related to delayed implementation of lung-protective ventilatory support.
3. The Berlin definition of ARDS includes which one of the following components?
   a. Bilateral pulmonary infiltrates
   b. Progression from acute lung injury
   c. Evidence of elevated pulmonary artery occlusion pressure (PCWP)
   d. Elevated serum brain natriuretic peptide (BNP)
   Answer: a. The Berlin definition of ARDS includes (1) an onset with 1 week of a known clinical insult or new or worsening respiratory symptoms, (2) bilateral pulmonary opacities (not pleural effusions), (3) respiratory failure not fully explained by cardiac failure and/or fluid overload, and (d) abnormal oxygenation with a Pao_2/FIO_2 ratio of 300 or lower. The oxygenation abnormality on PEEP therapy defines the severity of the ARDS as mild (Pao_2/FIO_2 ratio ≤300, but >200), moderate (Pao_2/FIO_2 ratio ≤200, but >100), or severe (Pao_2/FIO_2 ratio ≤100).
4. Lung-protective ventilatory support is a ventilator management strategy that incorporates which one of the following:
   a. Tidal volumes of 4 to 6 mL/kg ideal body weight
   b. Keeping positive end-expiratory (PEEP) levels continuously above 10 cm H_2O
   c. Maintaining a peak inspiratory pressure below 40 cm H_2O
   d. Maintaining the fraction of inspired oxygen (FIO_2) less than or equal to 0.6 to avoid oxygen toxicity
   Answer: a. Lung-protective ventilatory support is designed to limit the development of ventilator-induced lung injury and in ARDS patients to allow the injured lung to heal. The constituents of lung-protective ventilatory support include using a tidal volume of 4 to 6 mL/Kg based on predicted body weight (at least 6 mL/kg and lower if end-expiratory plateau pressure is not ≤30 cm H_2O), using adequate PEEP to maintain open airways and prevent atelectrauma, which occurs when PEEP is set too low such that the lung collapses at end expiration and then reopens with the next breath, producing shear force injury with reopening. PEEP is often dosed based on a high or low PEEP strategy nomogram with higher PEEP use in more severe ARDS. The least toxic FIO_2 should be used to maintain a Pao_2 of 55 to 80 mm Hg.
5. Neuromuscular blocking drugs may be beneficial in the management of a patient with ARDS because of which one of the following?
   a. Decreased transalveolar pressure
   b. Increased ventilator dyssynchrony
   c. Increased sedation requirements
   d. Decreased venous return
   Answer: a. Neuromuscular blocking drugs in early ARDS may be beneficial and lead to improved outcome by decreasing the transalveolar pressure and improving patient-ventilator synchrony. Reducing the intrathoracic pressure by lessening the positive pressure required for delivering the tidal breath and possibly reducing PEEP requirements improves venous return and cardiac output. Improved patient-ventilator synchrony leads to more consistent application of PEEP, lessens the transalveolar pressure gradient, and lessens end-inspiratory plateau pressure. There are also data to demonstrate less biotrauma (ventilator-induced lung injury [VILI] associated with systemic release of proinflammatory mediators) and the potential for less systemic organ dysfunction. The Reevaluation Of Systemic Early neuromuscular blockade (ROSE) trial of the National Heart, Lung, and Blood Institute PETAL (*p*revention and *e*arly *t*reatment of *a*cute *l*ung injury) Network is currently conducting a large multicenter trial to evaluate the effect of early neuromuscular blockade in the management of moderate to severe ARDS.
6. Which one of the following strategies may improve the outcome of ARDS patients?
   a. Liberal fluid management
   b. Early high-dose steroids
   d. Prone positioning for severe hypoxemia
   d. Immune-enhancing nutritional support
   Answer: c. Prone positioning has been shown to improve survival in patients with moderate to severe ARDS and persistent hypoxemia. Prior trials in all patients with ARDS did not produce a survival benefit. Conservative fluid management was shown to decrease organ dysfunction and increase ventilator-free days compared with liberal fluid administration. High-dose steroids have not been beneficial in ARDS or sepsis, but recent studies and meta-analyses now favor the use of early and/or rescue lower-dose methylprednisolone in the management of patients with moderate to severe ARDS. Recent studies have not demonstrated a benefit associated with the use of immune-enhancing diets for patients with ARDS.

7. The risk of ventilator-induced lung disease is reduced by which one of the following strategies?
a. Increasing the tidal volume to 10 mL/kg PBW
b. Providing PEEP
d. Adding sighs every 10 minutes
d. Performing recruitment maneuvers every shift
Answer: b. Provision of adequate PEEP has been shown to minimize the production of VILI and even prevent VILI in experimental models. Using high tidal volumes (i.e., ≥10 mL/kg PBW), sighs, and recruitment maneuvers may all induce alveolar overdistention, which can result in volutrauma and the production of VILI.

8. Corticosteroid treatment should be considered for use in patients with ARDS secondary to which one of the following?
a. Viral infections
b. Severe pneumonia
c. Acid aspiration injury
d. Multiple blood transfusions
Answer: b. A meta-analysis and systematic review of studies treating patients with severe pneumonia with corticosteroids added to the antibiotic regimen have demonstrated improved survival and decreased development of ARDS. This meta-analysis in large part is responsible for the recent recommendation of the Society of Critical Care Medicine–European Society of Intensive Care Medicine consensus recommendation for the use of corticosteroids either early (onset to day 6) or late (after 6 days) for the treatment of patients with moderate to severe ARDS.

9. Prone positioning is best used in ARDS patients with which one of the following?
a. A history of abdominal surgery
b. Partial pressure of oxygen in arterial blood (Pa_{O_2})/F_{IO_2} ratio <150
c. Obesity hypoventilation syndrome
d. Predominantly upper lobe disease
Answer: b The benefit of prone positioning for ARDS management has been demonstrated in those patients with moderate to severe ARDS or a Pa_{O_2}/F_{IO_2} ratio of 150 or less. Although patients as classified by answers a., c., and d. may benefit from prone positioning based on the degree of oxygenation defect, these specific diagnoses do not in their own right indicate benefit from prone positioning.

10. Which one of the following statements concerning inhaled vasodilator therapy in ARDS is true?
a. Inhaled nitric oxide (NO) has been found to improve survival.
b. Inhaled NO causes systemic hypotension.
c. Inhaled NO will increase the Pa_{O_2}.
d. Inhaled NO is approved by the U.S. Food and Drug Administration (FDA) for use.
Answer: c. Inhaled NO has been shown in multiple trials to produce an early increase in oxygenation in patients with severe ARDS. Unfortunately, the improvement in oxygenation did not translate into an improvement in survival or assist in earlier weaning of the patient from ventilatory support. The NO is rapidly scavenged by the hemoglobin of circulating red blood cells and there is not a systemic effect from the inhaled vasodilator therapy. Inhaled NO is not approved by the FDA for use in ARDS. Inhaled epoprostenol (a less expensive selective inhaled vasodilator), also not FDA-approved, and inhaled NO have been used for "salvage" therapy in patients in whom ARDS net mechanical ventilation protocol, neuromuscular blockade, and prone positioning have failed to achieve an acceptable Pa_{O_2}.

37

Life-Threatening Asthma

JENNIFER LAROSA

CHAPTER OUTLINE

Epidemiology

Genetics and Pathophysiology

Signs and Symptoms

Inhaled Therapies
- Oxygen
- Inhaled Short-Acting β_2-Selective Agonists: Albuterol, Levalbuterol, and Salmeterol
- Inhaled Anticholinergics: Ipratropium
- Heliox

Systemic Therapies
- Corticosteroids
- Methyxanthines: Theophylline and Aminophylline
- Magnesium Sulfate
- Anti-IgE Antibodies: Omalizumab
- Leukotriene Antagonists: Montelukast
- Alternative and Investigational Agents

Mechanical Ventilation in Patients With Asthma
- Indications for Mechanical Ventilation
- Neuromuscular Blocking Agents
- Noninvasive Positive-Pressure Ventilation

The Future for Those With Life-Threatening Asthma

Summary

Epidemiology

Asthma has been recognized for literally thousands of years. Around 2600 BC, Chinese records reveal a disease of "noisy breathing." Around 400 BC, Hippocrates defined the term asthma as a derivation of the Greek word for wind (ἄνεμος). Similar accounts follow through the ages and early Romans, Jews, and Egyptians used various natural remedies, some of which were valid and effective (smoking stramonium, a herb with anticholinergic properties) and some of which were not (drinking the blood of wild horses).[1]

Since the early 1980s, the prevalence of asthma has continued its relentless climb, affecting more than 25 million individuals (roughly 1 in 12 people) and 8.4% of the population as of 2010. Higher rates of adult disease exist in those of mixed racial background, African American, and Puerto Rican ancestry, females, those living at lower income levels, and those with a genetic predisposition for the disease.[2–5]

Although the overall mortality of asthma has steadily decreased since the turn of the millennium (0.15 per 1000 persons per 2007–2009 data), specific subgroups are continuing to die at alarming rates. Female African American patients older than 65 years of age have a considerably increased likelihood of death at a rate of 0.58 per 1000 persons. Although persons of Puerto Rican ethnicity have the highest rates of asthma exacerbations, African Americans have an almost 200% greater chance of having asthma and of dying from it (Figs. 37.1 and 37.2).

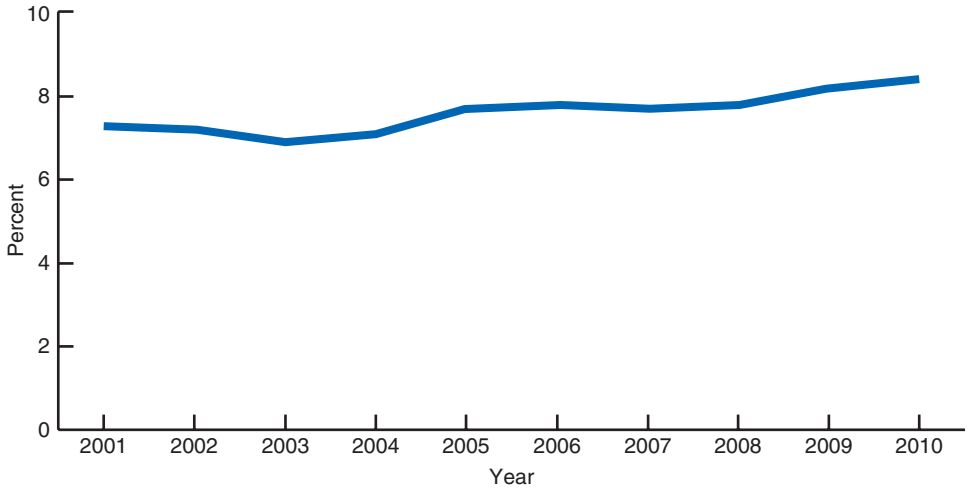
In addition to the costly effects of asthma on morbidity and mortality, it is estimated that the United States spends as much as $56 billion annually on medical care, lost productivity, and mortality for asthmatics. This equates to more than $3000 per person in the United States every year.[6,7]

We are failing to adequately control and manage this disease. As many as 65% of adults with asthma have chronic and persistent symptoms, and up to 50% of adults with asthma meet criteria for uncontrolled asthma at any given time. It is not surprising, then, with increasing rates of disease and increasing disease severity that so many of these patients require critical care services.[8,9]

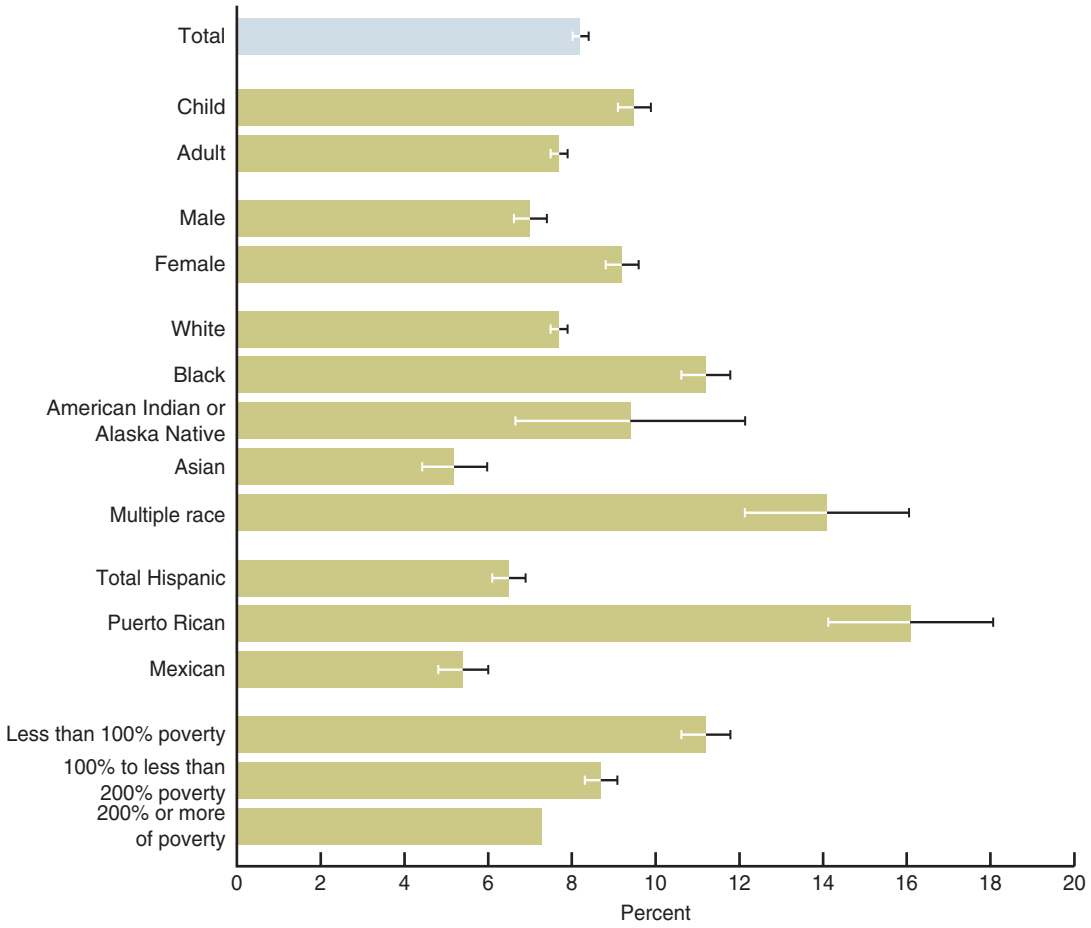
Genetics and Pathophysiology

Asthma is a disease of the distal airways characterized by bronchoconstriction, mucus hypersecretion, and intense cellular infiltration. Although asthma is, by definition, a reversible illness, the disease is poorly controlled in many patients and this chronic disease eventually leads to airway remodeling, which includes increased basement membrane thickness, increase smooth muscle, and metaplasia of goblet cells. Over time, inadequately controlled disease and airway remodeling can lead to a chronic and no longer reversible condition.

The American Thoracic Society defines severe asthma as "asthma which requires treatment with high dose inhaled corticosteroids (ICS)…plus a second controller (and/or systemic CS) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy."[10] Louie et al. further subdefine asthma that requires critical intervention as status asthmaticus and near-fatal asthma.[11] Status asthmaticus is a severe asthma attack that does not respond to immediate and consecutive bronchodilator therapy. Near-fatal asthma refers to persistent status asthmaticus that ultimately requires ventilatory support. Pendergraft and colleagues reported that among 29,430 admissions in the United States with a primary diagnosis of asthma, 10.1% were admitted to intensive care units (ICUs) and 2.1% were intubated.[3] The risk of in-hospital death was significantly higher in patients who were intubated and



• **Fig. 37.1** Asthma prevalence in the United States, 2001–2010. Asthma prevalence refers to the percentage of people who have ever been diagnosed with asthma and still have asthma. Data are age-adjusted to the 2000 U.S. standard population. (Data table available at http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#1. From Centers for Disease Control and Prevention/National Center for Health Statistics, National Health Interview Survey.)



• **Fig. 37.2** Asthma prevalence by selected demographic characteristics: United States, average annual 2008–2010. Asthma prevalence refers to the percentage of people who have ever been diagnosed with asthma and still have asthma. 95% confidence interval. (Data table available at http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#2. From Centers for Disease Control and Prevention/National Center for Health Statistics, Health Data Interactive and National Health Interview Survey.)

who had comorbid conditions. Near-fatal events occur in 2% to 20% of patients admitted to ICUs with acute severe asthma and in 2% to 4% of those intubated for respiratory failure.[3,11] Box 37.1 provides a comprehensive list of factors noted to increase both the likelihood of and the mortality from a severe asthma attack.

Genetic predispositions to asthma are well known. According to the Centers for Disease Control and Prevention, a child with at least one parent with asthma is three to six times more likely to develop asthma than their counterparts with nonasthmatic parents.[2,6] The genes listed in Box 37.2 (and up to 75 others) have been associated with clinical asthma. Discrete genes have been correlated with phenotypic variations in asthma as noted in Box 37.2, but considerable work remains to conclusively associate these factors.[13] Needless to say, the phenotypic manifestations of such genetic predispositions remains highly variable based on exposures to respiratory illnesses, pollution, and various other known and unknown triggers.[13]

Histologically, severe asthma is characterized by smooth muscle hypertrophy, influx of inflammatory cells, excessive mucus production, and, over time, airway remodeling. Cellular host responses are the platform for asthmatic inflammation and, when allowed to persist, for airway remodeling. In response to noxious stimuli (usually allergic or infectious triggers), epithelial and dendritic cells trigger T- and B-cell subsets and lymphoid cells to modulate airway inflammation via various cytokines and chemokines, such as interleukins (ILs) and granulocyte-stimulating factors. Excessive immunoglobulin E (IgE) production is triggered by these cytokines and chemokines, and neutrophils, eosinophils, and mast cells infiltrate the airways and continue the cascade of inflammatory damage. Over time, especially with poorly controlled disease and recurrent or persistent injury, the airways remodel with thickening of the basement membrane, mucus hypersecretion and plugging, goblet cell metaplasia, and smooth muscle hypertrophy. Many, if not all, of the cytokines implicated in asthmatic histopathology have been identified in various concentrations in bronchoalveolar lavage samples of patients with asthma. Although by no means exhaustive, some of the more common offenders include specifically IL-4, -5, -8, -13, and -17; neutrophil chemoattractant; and matrix metalloproteinase. Studies vary as to whether a predominance of neutrophils or eosinophils confers more serious disease, although most investigations favor the former.[11,13–18]

Phenotypically, the most severe form of asthma occurs in roughly 5% of all patients with asthma and presents symptomatically in one of two ways as described by Rodriguez-Trigo and colleagues.[5] The fundamental distinction between the two is based on time and rapidity of inset. In type 1, or "slow onset–late arrival" asthma, the asthmatic patient has chronic moderate to severe airflow obstruction that progresses over a course of days to weeks. Disease is characterized by copious mucus, capillary leak with boggy airways, intense eosinophilic infiltration, and recalcitrant disease when routine treatment is applied. Type 1 asthma is estimated to be responsible for as many as 80% to 85% of deaths in asthmatic patients.[5]

Conversely, type 2, or "sudden asphyxic" asthma is characterized by intense cellular infiltrate and rapidly progressive airflow obstruction with almost immediate responsiveness to conventional therapy when it is applied in a timely fashion. This subtype accounts for 15% to 20% of asthma deaths.[19–21]

• BOX 37.1 Risk Factors for Severe and Fatal Asthma in Adults[11–14]

- History of prior nonfatal asthma attack
- Prior intubation
- Female gender
- Age >65 years
- African American ethnicity
- Obesity
- Tobacco use
- Inhalational drug abuse
- Poorly controlled disease
- Poor recognition of dyspnea and other symptoms
- Steroid dependence
- H1N1 viral infection
- Misuse or lack of proper use of maintenance medications
- Psychiatric illness
- Lack of access to medical care
- Lack of ability to limit triggers (i.e., persistent exposure to pollutants, dust)
- Comorbid heart disease, obesity, and/or diabetes
- Bronchoalveolar lavage predominance of neutrophils, interleukin 8, and matrix metalloproteinase

• BOX 37.2 Genetic and Phenotypic Associations in Asthma

- *ADAM33*: gene bronchoconstriction
- *ORMDL3/GSDMB* locus, chromosome 17q21: childhood onset
- CpG portion of *ACSL3*: associated with maternal exposure to automobile pollution
- *IL33* on chromosome 9
- *IL2RB* on chromosome 22

Signs and Symptoms

Asthma was recognized by the ancient Chinese as "noisy breathing" and is, in fact, often associated with wheezing. However, wheezing lacks sensitivity and may be a manifestation of many other cardiac, pulmonary, and oropharyngeal conditions, such as cardiogenic pulmonary edema, pulmonary embolism, and vocal cord dysfunction syndrome. Furthermore, severe and life-threatening asthma, the topic of primary discussion in this chapter, often represents disease that has progressed beyond the traditional wheeze. A silent chest is a particularly ominous sign as it represents some degree of cessation of any air movement. Other signs of advanced and life-threatening asthma may be seen in Box 37.3.[21–24]

Physiologically, these findings are accompanied by severe ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch with perfusion of poorly ventilated areas leading to derangements in both ventilation, and as disease progresses, oxygenation. Both decreased expiratory time and the physiologic need for additional expiratory time contribute to concomitant air trapping. Trapped air leads to increased intrathoracic pressure with decreased venous return, a reduced effective tidal volume, and increased likelihood of barotrauma, all of which further compound impaired ventilation and oxygenation.[4,22] A patient's inability to markedly improve peak expiratory flow rates with aggressive bronchodilator therapy is the best predictor of asthma-associated morbidity, and a prior near-fatal asthma exacerbation is the best predictor of mortality.[4,11]

1. Ancillary studies have variable utility in predicting morbidity, mortality, and the need for mechanical ventilation in patients

• BOX 37.3 Signs and Symptoms of Severe Asthma

- "Tripoding"—sitting upright and leaning forward
- Diaphoresis
- Use of accessory muscles
- Asynchronous accessory muscle use
- Air trapping and hyperinflation manifesting as decreased inspiratory stroke volume and pulsus paradoxus
- Peak flow <200 L/min and/or <30% predicted[a]
- FEV_1 <1 L/min and/or <20% predicted[a]
- Evidence of barotrauma
  - Unilateral diminution in breath sounds
  - Tracheal deviation
  - Thoracic crepitus
- Signs of impending respiratory arrest
  - Altered mentation
  - Cyanosis
  - Hypoxia
  - Hypercarbia
  - Hemodynamic instability
  - Silent chest

[a]*Note that these values are estimations because both peak expiratory flow rate and forced expiratory volume in 1 second (FEV_1) vary with age, gender, and height.*

with severe asthma. A routine chest x-ray is likely to demonstrate flattened diaphragms as the result of air trapping and, in cases associated with barotrauma, pleural or mediastinal emphysema and tracheal shift.

2. The arterial blood gas (ABG) analysis can be as dangerous as it can be useful. A novice practitioner's finding of "normal" ABG findings in this setting is tantamount to an increased mortality rate in his or her practice. In other words, a normal or near-normal partial pressure of arterial carbon dioxide ($PaCO_2$) level in any patient with tachypnea is an ominous sign and one that requires immediate attention. That said, most patients with this degree of airflow obstruction will also, as noted above, exhibit tripoding (see Box 37.3), tachypnea, tachycardia, anxiety, diaphoresis, and demand attention. As with the ABG analysis, the quiet patient or asthmatic is one who has been left unattended for too long.
3. The electrocardiogram (ECG) and other serum laboratory studies are largely nonspecific in this setting and thus of greatly limited utility. The ECG may demonstrate right heart strain, which resolves with control of airflow obstruction. Muscle enzyme and inflammatory markers, such as creatinine kinase MB fraction, erythrocyte sedimentation rate, and C-reactive protein, may be elevated and bicarbonate levels may be acutely skewed as the body attempts to compensate for acid-base abnormalities. Elevated exhaled nitric oxide levels can be found in severe allergic asthma and may predict future exacerbations and steroid treatment response; however, use of this biomarker is not recommended at this time and needs further evaluation.[25–30]

Inhaled Therapies

Oxygen

As with all respiratory illnesses, clinical effects can be roughly divided into abnormalities of ventilation and derangements in oxygenation or, of course, both. Although ventilator disturbances are typically the earlier and more predominant abnormality seen in severe asthma, hypoxia often follows. Derangements in ventilation are covered in the sections on noninvasive and invasive support.

If ABG analysis or peripheral oximetry confirms the presence of hypoxemia, oxygen should be given to maintain oxygen saturation at greater than 92%. Hypoxemia may initially be further exacerbated by the use of serial bronchodilation secondary to β-adrenergic vasodilation and subsequent increased perfusion of persistently poorly ventilated lung segments. This effect is usually transient and has been observed primarily in children with severe asthma exacerbations using aerosolized salbutamol administration; these effects have been poorly replicated in adults. However, because the benefits of inhaled β-agonists far outweigh the risks in this scenario, they should continue to be used with supplemental oxygen provided as needed. Humidification of oxygen using a heated cascade humidifier is an important adjunct to avoid addition of bronchoconstriction induced by dried air. Although hypoxia is unusual with judicious use of oxygen therapy, it can occur and may, in turn, worsen hypercarbia owing to regional release of hypoxic pulmonary vasoconstriction.[31–36]

Inhaled Short-Acting β_2-Selective Agonists: Albuterol, Levalbuterol, Salmeterol

Inhaled β_2-selective agonists remain the cornerstone of rescue treatment in asthmatic patients with acute severe exacerbations. Initial therapy, as recommended by the National Asthma Education and Prevention Program Update, is 2.5 to 5 mg of albuterol (0.5–1 mL of 0.5% solution in 5 mL of normal saline solution) nebulized every 20 minutes for 3 doses (for optimal delivery, dilute aerosols to a minimum of 3 mL at gas flow of 6–8 L/min), followed by 2.5 to 10 mg every 1 to 4 hours as needed, or 10 to 15 mg/hr continuously, with the titration based on response and ongoing severity of symptoms. Those with the most severe bronchoconstriction usually require consecutive treatments, which may lead to tachycardia and hypokalemia. β_2-Selective agents delivered parenterally or orally lose much of the β_2 selectivity, which provides the rationale for inhalation treatment as the cornerstone of therapy.[37–41]

β-Agonists delivered by metered-dose inhaler (MDI) have been consistently shown to be equally efficacious and cheaper in cost and resource utilization than the nebulized equivalent. Adequate delivery requires patient cooperation and spacer technique as well as increased dose requirements compared with nebulized therapy. Four puffs of albuterol by MDI with a spacer (0.36 mg) is equipotent to 2.5 mg of nebulized albuterol. In mechanically ventilated patients, drug deposition in the endotracheal tube and ventilator circuit may effectively reduce the delivered dose so that dose doubling is recommended in this scenario.[42–45]

Although long-acting inhaled β-agonists are now recognized as an important adjunctive therapy in the management of obstructive lung disease, they have little role in the treatment of a patient with acute life-threatening asthma.

β-Agonist therapy, in the form of subcutaneous epinephrine or terbutaline, may also be delivered to adult patients at the following doses: epinephrine: 0.3–0.5 mL of a 1:1000 dilution (1 mg/mL) and terbutaline: 0.25 mg. Both may be repeated as needed up to 3 times at 20-minute intervals. However, both medications have undesirable therapeutic-to-toxicity ratios, especially in patients with cardiac disease, and neither drug has demonstrated a superior outcome benefit compared to inhalational therapy.[46,47]

Inhaled Anticholinergics: Ipratropium

Inhaled anticholinergics, most commonly in the form of ipratropium, are effective mainly as an adjunct to inhaled β-agonists as they attenuate bronchodilation. This combination has been demonstrated to accelerate improvements in lung function and to reduce the need for hospitalization in patients with acute asthma. Those patients with severe asthma who require hospitalization do not typically continue to enjoy the benefits of combination therapy after the first 24 hours or so.

Although ipratropium achieves less bronchodilation at peak effect than β-agonists and a less predictable clinical response, the effects of both are additive. Most published evidence supports the addition of ipratropium to inhaled β-agonist therapy for patients with acute asthma. It produces a clinically modest improvement in lung function compared with albuterol alone, especially in those with very severe disease.[35,37,48,49]

Ipratropium is administered at a dose of 0.5 mg by nebulizer every 20 minutes for 3 doses and then every 2 to 4 hours as needed. Nebulization occurs by a handheld nebulizer either simultaneously or after inhalation of β-agonists to maximize the attenuated effect. Nebulization of ipratropium by face mask may be dangerous because contamination of the ocular area with precipitation of narrow-angle glaucoma may occur in susceptible individuals. Ipratropium may be combined with the nebulized albuterol dose as long as a handheld device is used. The onset of action of ipratropium is slow and may occur over 20 to 90 minutes with more rapid results in patients with severe asthma and a slower effect in those with chronic obstructive pulmonary disease.[37,41]

Heliox

Heliox is a mixture of helium and oxygen in varying ratios from 60:40 to 80:20 with helium representing the predominant gas. By transitioning airflow from turbulent to laminar, this low-density mixture reduces airway pressure. Although its utility has historically been in modifying airflow through large stridorous airways, it appears to have some promise in facilitating improved flow through distal bronchioles. The need for intubation and mechanical ventilation as well as mortality were reduced with the use of heliox in patients with chronic obstructive pulmonary disease in an observational study by Gerbeaux and colleagues.[50] The more recent ECHO ICU trial was unable to duplicate these findings.[51]

In patients with severe asthma, heliox has been studied as an adjunct to better distribute bronchodilators in the lower airways, and in one study this combination demonstrated greater peak expiratory flow rate improvements than bronchodilation accompanied by oxygen. The effect was most pronounced in those with the most severe disease.[52] A similar study demonstrated nearly identical improvements in airflow, measured as forced expiratory volume (FEV), with the combination of inhaled heliox and bronchodilators. Again, the effects were most notable in those with the most severe airflow obstruction.[53]

Systemic Therapies

Corticosteroids

Corticosteroids, like bronchodilators, are critical in the management of asthmatic patients with a life-threatening exacerbation. Although long-term outcome differences have failed to be shown between the use of intravenous (IV) versus oral steroids, IV forms have a faster onset of action. Steroids are administered in considerably more temperate doses than in the past; the National Institutes of Health Expert Panel currently recommends IV methylprednisolone, 40 to 80 mg/day in one or two divided doses, until peak expiratory flow reaches 70% of predicted or personal best. Higher doses offer no benefit, IV is not superior to oral therapy (expect for afore-stated more rapid onset of action), and treatment durations of 3 to 10 days without need for taper are considered sufficient. The delay in effect may reflect the time necessary for steroids to induce upregulation of new β_2-receptors and reversal of β_2-receptor desensitization and downregulation. Given this relatively lengthy onset of action, steroids play a role in the hospital course of life-threatening asthma but are not considered immediate rescue therapy as bronchodilators are.

Inhaled corticosteroids play a role in the management of chronic disease but have no role in acute rescue maneuvers. However, it may be beneficial to start inhaled corticosteroids while asthmatic patients are inpatients to teach and reinforce appropriate use techniques.[31,37,54]

Methyxanthines: Theophylline and Aminophylline

Although methylxanthines are effective bronchodilators compared with placebo in patients with acute bronchospasm, inhaled β-agonists are superior agents for acute rescue. Although a few studies have demonstrated some physiologic benefits with methyxanthines between 24 and 48 hours, the availability of safer and more efficacious drugs and the high toxicity side effect profile of methylxanthines makes them a last choice for those who do not otherwise respond.[41,55–58]

Magnesium Sulfate

Magnesium sulfate works by inhibiting calcium channels, thereby reducing smooth muscle bronchoconstriction and reducing airway parasympathetic tone. It can be administered via IV infusion or in inhalational form and is relatively contraindicated in those with renal insufficiency. Onset of action is slower than bronchodilators but faster than corticosteroids. Most studies support its use as adjunctive therapy. A Cochrane meta-analysis concluded that use of IV magnesium sulfate improves pulmonary function and decreases hospital admissions in acute severe asthma, particularly in patients with severe exacerbations. Inhaled magnesium sulfate improves pulmonary function during acute exacerbations of asthma, although it fails to modify clinically important outcomes, such as hospital admissions.[59,60]

Anti-IgE Antibodies: Omalizumab

The use of monoclonal antibodies and other immunologic modulators has exploded over the past several years. Such therapies are now commonly used for immune-mediated arthritis, inflammatory bowel disease, and a host of other diseases in which the immune cascade can be interrupted. For asthma, the most commonly studied agent in this category is the recombinant anti-IgE antibody omalizumab, which is indicated as step-up therapy for severely allergic asthmatic patients with markedly elevated IgE levels. Several studies have demonstrated a reduced number of severe exacerbations,

fewer episodes requiring systemic corticosteroids, and fewer health care visits associated with its use. Each of these benefits has been demonstrated in patients with severe allergic asthma but not at the time of life-threatening exacerbation. Drawbacks include high cost, subcutaneous administration, and unknown optimal duration of treatment. Studies examining the use of such agents in severe acute exacerbations are limited and potential clinical utility is unknown at this time.[61–64]

Leukotriene Antagonists: Montelukast

Leukotriene receptor antagonists (LTRAs), such as montelukast, are another asthma management strategy based on immune modulation. Significant and rapid (about 10 minutes) improvement in lung function (measured as forced expiratory volume in 1 second [FEV_1]) has been noted in patients with severe asthma given IV LTRAs; these drugs appear to have the greatest impact on patients with allergic and exercise-induced asthma. Similar studies in patients with life-threatening asthma have not been undertaken. A 2012 Cochrane review by Watts and Chavasse confirmed improvements in lung function, but this benefit did not translate to reduced hospital admissions and investigators advised against the routine use of LTRAs in acute exacerbations.[65] A 2016 study by Altawalbeh and colleagues actually revealed that the addition of LTRAs in older adults with asthma increased emergency department visits and hospital admissions compared with the addition of long-acting β-agonists.[66] As with omalizumab, any clinical utility of this agent in acute severe asthma is unknown.

Alternative and Investigational Agents

New medications and old medications with historically nonasthma indications are postulated to have potential utility in the treatment of asthma every day. Such agents that have demonstrated early or intermittent promise include methotrexate, antifungal agents, macrolide antibiotics, ketamine, inhaled heparin, furosemide, and anesthetics. None have been studied as acute rescue agents in life-threatening asthma and we are, at best, years away from endorsing any such recommendation.[10]

Immunomodulatory therapy holds promise as future asthma control agents that may reduce steroid use and concomitant side effects, manage disease more seamlessly with fewer overall agents, and reduce the frequency, severity, and mortality associated with life-threatening asthma. Such investigations are directed against various interleukins (specifically IL-4, -5, -8, -13, and -17), chemokine antagonists, Toll receptor agonists, and tyrosine kinase inhibitors.[13]

Also gaining notoriety is bronchial thermoplasty, an endoscopic procedure in which the bronchial smooth muscle is ablated using radiofrequency waves. Although this intervention has historically been performed only in patients who are not having an acute exacerbation, a recent small study by Langton and colleagues in Australia demonstrated that patients with severe chronic asthma had improved lung function and fewer exacerbations even when their disease was poorly controlled before the intervention.[67]

Finally, extracorporeal membrane oxygenation is gaining support as a potential means to rescue patients with very severe asthma exacerbations, especially those with refractory acidosis and/or hypercarbia. However, this therapy remains invasive and controversial and consideration for its use should be reserved for those with appropriate expertise and experience.[68]

Mechanical Ventilation in Patients With Asthma

Indications for Mechanical Ventilation

Medication management in life-threatening asthma is often not enough. Roughly 10% of admitted patients with asthma require critical care services and about 2% require mechanical ventilator support. Although this certainly does not represent the majority of patients with this disease, the attributable mortality remains too high in this ostensibly reversible disease.[3,11]

Signs of impending respiratory failure should trigger endotracheal intubation and mechanical ventilation. Such signs may include central cyanosis, altered mentation, paradoxical breathing, refractory hypercarbia and/or hypoxemia, and a silent chest. An elevated $PaCO_2$ indicates an FEV_1 less than 25% predicted and is an ominous predictor for the need for ventilator support. Not surprisingly, asthmatic patients in whom ventilator support is initiated before formal respiratory arrest have better outcomes.[69] The estimated attributable mortality rate for those with severe asthma who required mechanical ventilation varies between 6.5% and 10.3%.[3,70–73]

Physiologically, life-threatening asthma is characterized by severe airway resistance, which leads to incompletely exhaled tidal volume and subsequent increased dead-space ventilation and trapped air. Plateau pressure is a reliable surrogate for measuring auto–positive end-expiratory pressure (PEEP) and levels of 30 cm H_2O and greater are associated with more barotrauma and more hemodynamic instability related to poor venous return. Mechanical ventilation, in and of itself, is not a curative therapy for the patient with acute asthma. Ventilator support settings should be chosen to maximize expiratory time, reduce air trapping, and avoid barotrauma. Excessive tidal volumes and respiratory rates with insufficient expiratory time may worsen an already tenuous ventilator status.[73,74]

By definition, patients with life-threatening asthma require improved ventilation, manifested, of course, as minute ventilation. Herein lies the dichotomy of too much or too little of a good thing. Too much minute ventilation may lead, as stated earlier, to reduced expiratory time and worsening air trapping. Too little ventilation can be viewed as inadequate management of the very disease being treated. Two investigations by Tuxen and colleagues demonstrated that ventilator strategies aimed at normalizing $PaCO_2$ required such high minute ventilation that risk for barotrauma was unnecessarily invoked.[75,76] Conversely, permissive hypercarbia and associated acidemia can increase intracranial pressure and cerebral blood flow and may further adversely affect those with anoxic brain damage. Current data suggest that the best strategy is to allow mild hypercarbia for brief periods to facilitate reduced air trapping and improved venous return. In extreme cases, alkalinizing agents may be considered as an additional temporizing measure.[77,78]

Recommended initial ventilator settings are a tidal volume of 6 to 8 mL/kg ideal body weight and a frequency of 10 to 14 breaths/min. Minute ventilation of less than 8 to 12 L/min is ideal with increased expiratory time to facilitate avoidance of auto-PEEP and oxygen saturation greater than 90%. Peak inspiratory flow rates should be set at 60 to 80 L/min with a square inspiratory waveform to assist in maximizing expiratory time. In healthy adults, inspiratory:expiratory time ratios are usually 1:2, whereas patients with acute asthma may require ratios of 1:3 to 1:5 or greater. The use of noncompressible tubing also facilitates shorter inspiratory and longer expiratory times.[79]

Controlled mechanical ventilation in patients with acute asthma almost invariably requires heavy sedation and analgesia, or at times, sedation, analgesia, and muscle paralysis. Assisted controlled ventilation without heavy sedation or sedation/paralysis predisposes the patient to hyperinflation if the patient's intrinsic drive to breathe exceeds that of the ventilator. Heavy sedation with or without paralysis reduces carbon dioxide production, facilitates accurate measurement of airway pressures, and reduces dyssynchrony and discomfort. Pressure-control ventilation is discouraged because of fluctuating high airway resistance and intrinsic PEEP. There is no role for synchronized intermittent mechanical ventilation.[78,80,81]

Delivery of inhaled therapies while a patient is supported by mechanical ventilation can be challenging. The length and acute angles of the ventilator circuitry predispose toward deposition of medication in the endotracheal tube and extension tubing and not in the patient's airways. Strategies to facilitate proper delivery include doubling doses and placing the nebulization device as close to the patient as possible.[82]

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBAs) are increasingly being studied for their utility as adjunctive agents in severe asthma, acute respiratory distress syndrome, and septic shock with ventilator failure. By achieving complete muscle paralysis, NMBAs are theorized to reduce patient-ventilator dyssynchrony and to reduce the untoward but expected consequences of severe air hunger—air trapping and barotrauma. Most studies focus on the collective muscle weakness and polyneuropathies that occur as a result of their use, particularly in conjunction with corticosteroids, heavy sedation, and the critical care environment. Such neuromuscular derangements are more prevalent in females with renal failure and hypophosphatemia. Concomitant use of corticosteroids and NMBAs typically produces proximal and distal muscle weakness. Creatine kinase may be elevated and myoglobinuria may be present. Steroid myopathy, by contrast, primarily involves proximal muscles and the creatine kinase levels are typically normal.

Ideally, NMBAs should be avoided or used for as brief a time as possible and delivered by intermittent dosing. In the rare patient who needs to be continuously paralyzed, infusions must be stopped every 4 to 6 hours to minimize dosing and accumulation and to facilitate neurologic evaluation. A peripheral nerve stimulator should be used to limit paralysis to no less than a recording of one or two twitches in response to a train-of-four stimulus. In patients with asthma, cisatracurium is the first-choice NMBA because it is eliminated by esterase degradation and spontaneous breakdown in the serum.[31,83–86]

Noninvasive Positive-Pressure Ventilation

The role of noninvasive positive-pressure ventilation (NIPPV) remains controversial. In those with true life-threatening asthma (extremis), it should not be used with preference for endotracheal intubation. The aims of NIPPV are the same as those in patients with invasive mechanical ventilation. The usefulness of NIPPV in improving breathing cycle synchrony and in reducing airway pressures is largely unproven. Several small studies have demonstrated that NIPPV can be safely used in asthmatic patients with acute exacerbations and can even help avoid the need for intubation. A nonrandomized study by Meduri and associates reported a reduction in $PaCO_2$ and improvement in dyspnea with the use of NIPPV in 17 episodes of asthma with acute respiratory failure. Ram and colleagues, however, countered that NIPPV in status asthmaticus, despite some promising preliminary results, remains controversial. A most recent investigation by Stefan and colleagues failed to demonstrate a reduction in the need for invasive ventilation or a mortality benefit, although the hospitals that used NIPPV the most frequently trended toward a shorter length of stay. If NIPPV is used, initial setting should be an expiratory positive airway pressure (continuous positive airway pressure or PEEP) of about 5 cm H_2O and inspiratory pressure (or pressure support) of approximately 8 cm H_2O. If tidal volumes are shallow (<7 mL/kg), inspiratory pressure can be increased gradually by 2 cm H_2O every 15 minutes to a goal to reduce the respiratory rate to less than 25 breaths/min[87–93] (also see Chapter 10).

The Future for Those With Life-Threatening Asthma

As population health efforts shift into high gear, there is increasing recognition of the need for better knowledge of risk factors for severe asthma and what outpatient strategies might ameliorate readmissions, the severity of exacerbations, and mortality. Obesity in the United States has reached epidemic levels and its impact on new adult-onset asthma and the severity of the disease is well known. Koebnick and colleagues demonstrated the following compared with patients with a body mass index (BMI) of 25 kg/m^2 or less. Adult patients with a BMI ranging from 25 to 29.9 kg/m^2 had a 12% increased risk of adult-onset asthma. BMIs in excess of 50 kg/m^2 conferred a 250% increase in adult-onset asthma.[94]

A recent investigation by Pakhale and colleagues revealed that even mild reductions in BMI and waist circumference were associated with reduced asthma severity, improved FEV_1 and forced vital capacity, and improved symptom control and quality of life.[95] Although these findings cannot yet be extrapolated to the critical care experience for patients with severe asthma, we might surmise that the benefit would extend to that population as well.

Concomitant mental illness and gastroesophageal reflux disease have been demonstrated to worsen asthmatic symptoms and to make control more challenging. In addition to other risk factors, such as prior hospitalizations and intubations, gastroesophageal reflux disease and mental illness were associated with increased utilization of health care resources and increased 30-day readmission rates.[96–98]

After a near-fatal episode of asthma exacerbation, strategies can be implemented to reduce the likelihood of another event or the severity of subsequent episodes. Examples include asthma education, follow-up phone calls, assistance and facilitation of primary and specialist follow-up appointments, and more. Gibeon and colleagues developed 11 asthma centers around the United Kingdom that used standardized treatment approaches and reported into a national database. This intervention reduced steroid use and improved quality-of-life scores but, again, the impact on life-threatening asthma remains unknown.[99]

Two recent studies assessed the impact of healthy environments and in-home assistance as mechanisms to control severe asthma in low-income, minority patients with social and economic barriers. Bryant-Stephens and colleagues made home visits and found high-risk dwellings with mite and cockroach infestations, mold, overcrowding, and chronic exposure to tobacco smoke and unhealthy diets.[100] Reddy and colleagues expanded these findings in a study from 2007 to 2011 recently published. Investigators partnered with New York housing administration to identify at-risk patients and to optimize opportunities to maximize modification of risk—dwelling updates and reduction of onsite triggers as examples. Considerable reductions in morbidities were achieved as predicted.

Summary

Asthma is a complex and comprehensive disease and its severity exists along an extensive spectrum. Life-threatening asthma in adult patients is more common in those with previous serious exacerbations, those who are female, obese, and African American. Corticosteroids and inhaled bronchodilators remain the cornerstones of rescue treatment, and invasive mechanical ventilation may be required for those with refractory airflow obstruction. Immune-modulating drugs are increasingly recognized as possible adjunctive or replacement agents. Efforts to modify risk factors such as obesity, mental illness, and comorbidities and efforts to maximize disease management and avoidance of triggers continue to be fundamental to the success of asthma care and the avoidance of life-threatening episodes.

Key Points

- The prevalence of asthma in the United States continues to steadily decrease and mortality is highest in African American women older than 65 years of age.
- Severe asthma may be characterized as type 1 (slow onset) or type 2 (rapid onset) and the majority of mortalities are related to type 1.
- Bronchodilators and corticosteroids remain the cornerstones of severe asthma treatment but are not being supplemented with nontraditional inhaled therapies and immune modulators.
- In a patient with severe asthma, signs of impending respiratory failure requiring invasive mechanical ventilation may include central cyanosis, paradoxical breathing, altered mentation, hemodynamic instability, a silent chest, and a "normal" $PaCO_2$.
- Reducing risk factors, triggers, and comorbidities is likely the most effective strategy to sustainable improvement in mortality from severe asthma.

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Review Questions

1. Which of the following is the best predictor for a life-threatening asthma attack?
a. Age >45 years
b. African American heritage
c. A prior near-fatal attack
d. Male gender
Answer: c. Advanced age, female gender, and African American heritage all predispose to adult-onset severe asthma, but the best predictor of mortality is having had a prior near-fatal episode.

2. Which of the following should prompt the practitioner to immediately intubate and provide mechanical ventilation to the severe asthmatic patient?
a. Partial pressure of arterial carbon dioxide ($PaCO_2$) of 45 with respiratory rate of 26 breaths/min
b. Diaphoresis
c. Diffuse bilateral wheezing on auscultation
d. H1N1 infection
Answer. a. All of the symptoms listed are serious and have the potential to lead to mechanical ventilation. However, a patient with an elevated respiratory rate and a simultaneously elevated $PaCO_2$ is demonstrating severely impaired ventilation and an insufficient ability to overcome this derangement.

3. Which of the following treatments has the most clear and undisputed role in the treatment of severe acute asthma?
a. Bronchial thermoplasty
b. Anti–immunoglobulin E antibodies like omalizumab
c. Leukotriene inhibitors
d. β-agonist bronchodilators
Answer: d. Each of the therapies listed shows promise in the management of chronic asthma, but only β-agonists bronchodilators have a well-established role in rescue from acute severe disease.

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Chronic Obstructive Pulmonary Disease

GUILLERMO DOMÍNGUEZ-CHERIT, CARMEN M. HERNÁNDEZ-CÁRDENAS, AND EDUARDO RIVERO SIGARROA

CHAPTER OUTLINE

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Terminal Care for the Patient With End-Stage COPD

The most recent 2017 iteration of the Global Initiative on Obstructive Lung Disease (GOLD) guidelines defines chronic obstructive pulmonary disease (COPD) as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients.[1] Its pulmonary component is characterized by chronic airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles and gases. The 2017 GOLD classifies COPD based on spirometric staging (1–4) and symptoms/exacerbations (A–D). The new classification predicts mortality more accurately than previous symptoms.[2]

Definitions

Although controversies remain over the definition of exacerbation, how they should be monitored, and their underlying mechanisms, acute exacerbations of COPD (AECOPD) are major and increasingly recognized events in the disease course. They typically occur one to three times per year. Exacerbations are associated with an increase in economic burden[3] and a decline in health-related quality of life.[4] Those patients with more than two exacerbations per year have significantly worse health-related complications and decline in lung function than those with two or fewer exacerbations.[5] As mentioned earlier, there is no general agreement on the definition of AECOPD, but it has been defined according to the presence of specific signs and symptoms, worsening in symptoms, and the need for medical intervention; each of these approaches has positive and negative connotations. It is well recognized, however, that the presence of increased shortness of breath, increased sputum volume, and increased purulence are the three specific symptoms that represent an exacerbation.[6]

Background

COPD affects more than 200 million people worldwide and is the fourth leading cause of death. COPD is a disease that is both preventable and treatable. COPD is a major cause of morbidity and death in the world, with an increasing burden as a result of epidemiologic changes that expose more of the population to COPD risk factors. Although the major environmental risk for COPD is tobacco smoking, only 20% of smokers develop COPD. Indoor air pollution from burning biomass fuel is associated with increased risk of COPD in developing countries. In the United States, COPD is the fourth leading cause of death[7] and is exceeded only by heart attacks, cancer, and stroke. COPD has had a similar effect on health and mortality rate throughout the developed and underdeveloped sectors of the world, and many of the important issues surrounding COPD in the United States apply elsewhere.[8]

The real prevalence is masked by the burden of undiagnosed COPD; a population-based Spanish sample of 4274 adults (age 40–80 years) who answered a questionnaire and underwent prebronchodilator and postbronchodilator spirometry found that the prevalence of COPD was 10.2% (4.4% with GOLD II disease or worse) with only 27% having a prior diagnosis.[9]

Pathophysiology

The main pathophysiologic feature in COPD is the limitation to expiratory flow.[10] Chronic expiratory flow limitation and

hyperinflation are the mechanical hallmarks of COPD.[11] Expiratory airflow limitation results from many factors; among them, narrowing of the peripheral airways,[12] mucus hypersecretion,[13] and impaired ciliary clearance[14] are the most important factors.

Several mechanistic concepts have been implicated in the pathogenesis of COPD. First is the development of exaggerated chronic inflammation in the lung in response to inhalation of cigarette smoke compared with smokers without lung disease.[15] Host factors including genetic susceptibility, epigenetic changes, and oxidative stress contribute by amplifying inflammation induced by cigarette smoke. Second, patients with deficiency of α_1-antitrypsin, the main inhibitor of neutrophil elastase, develop emphysema early in life owing to an increase in proteolytic activity.[16] Third, an imbalance between oxidants and antioxidants in the lungs of patients with COPD, resulting in excessive oxidative stress, not only amplifies airway inflammation in smokers but also induces cell death of structural cells in the lung. Disruption of the balance between cell death and replenishment of structural cells in the lung contributes to the destruction of alveolar septa, leading to emphysema.[17] Autoimmunity has been proposed as a late pathogenic event in the progressive course of the disease.

COPD is characterized by a specific pattern of inflammation involving increased numbers of $CD8^+$ cytotoxic T-cell lymphocytes present only in smokers in whom the disease develops. These cells as well as neutrophils and macrophages release inflammatory mediators and interact with epithelial cells in the airways, lung parenchyma, and pulmonary endothelium; all these relationships and interactions produce structural changes in the lungs by activation of growth factors.[18] Changes in the airway architecture, endothelium, and lung parenchyma lead to the characteristic physiologic abnormalities and symptoms of COPD.

In acute exacerbations there is an increase in sputum neutrophil numbers as well as an increase in neutrophils in bronchial biopsies, which rarely are seen in the stable state.[19] Interestingly, virally induced exacerbations are associated with increased expression of eosinophils in sputum. Viral infections induce the expression of chemokine (C-C motif) ligand 5 (CCL5) in airway epithelial cells,[20] and CCL5 may act synergistically with $CD8^+$ cells to enhance the apoptosis of virally infected cells, thus leading to increased tissue destruction.[21] Also, an increase in the concentration of the elastolytic enzyme matrix metalloproteinase-1 during exacerbations is consistent with evidence of elastolysis, which may provide a causal link between exacerbations and accelerated decline in lung function.[22]

Changes in the microbiome also lead to exacerbations. During these episodes, changes in the taxonomy of the microbiome (i.e., increases in Proteobacteria and decreases in *Acinetobacter,* Clostridia, and Bacteroidia) could contribute to the development of exacerbations. Additionally, treatment with steroids influences the diversity of the microbiome, and antibiotic therapies result in a reduction in the number of colonies.[23]

Data from patients with AECOPD who required mechanical ventilation indicates the presence of increased central drive, dyspnea, tachypnea, reduced tidal volume, and development of hypercapnic respiratory failure, but ventilation-perfusion ($\dot{V}/\dot{Q}$) match remains relatively preserved.[24] AECOPD appears to be characterized by increased central drive, decreased inspiratory capacity, and decreased inspiratory muscle force, perhaps secondary to dynamic hyperinflation. There is an association between increased serum levels of interleukin 6 (IL-6) and leukotriene B4 and the magnitude of dyspnea, respiratory rate, and inspiratory capacity, suggesting that it may be possible to detect serum changes that reflect the inflammatory burden of the exacerbation.[25]

Although hypercapnia depends on the severity of airflow limitation, there is considerable variability in the relationship of partial pressure of arterial carbon dioxide ($PaCO_2$) to forced expiratory volume in 1 second (FEV_1) and total lung resistance, best explained by contribution of dead space and minute ventilation.[26] In stable COPD patients with severe airflow obstruction, shallow breathing is the main factor associated with carbon dioxide (CO_2) retention. In this circumstance the diaphragm is less effective than in normal subjects, and with increasing airflow obstruction and hyperinflation, the contribution of the rib cage muscle to the generation of ventilatory pressure increases.[27] Abdominal muscles are recruited during expiration in patients with severe COPD, and the expiratory rise in gastric pressure is directly related to intrinsic positive end-expiratory pressure (iPEEP). During acute exacerbation, patients with severe airflow obstruction increase the inspiratory recruitment of the rib cage muscles relative to the diaphragm. This recruitment is associated with abdominal muscle contraction and a reduction in abdominal volume at end expiration, which contributes to iPEEP. Dynamic hyperinflation can be overestimated during chronic and acute airway obstruction if abdominal muscle function is not evaluated.[28]

Hypercapnic respiratory failure is associated with a worsening of the lung mechanics, including an increased inspiratory load as indicated by the integral pressure/time of the diaphragm and other respiratory muscles (respiratory load). These factors are related to a worsening of muscle strength and the ability to generate pressure and can translate into an imbalance of capacity/load, resulting in a superficial and rapid respiratory pattern that can lead to acute respiratory failure.[29]

The worsening gas exchange and the deterioration of the arterial blood gas values during acute exacerbations in patients with severe COPD can be explained by several factors. These factors are, in no particular order, respiratory muscle fatigue,[30] increases in dead-space ventilation, and alveolar hypoventilation.[31] Minute ventilation may be normal early in an exacerbation, but the respiratory rate is generally increased. There is an associated increase in physiologic dead space that impairs CO_2 elimination and may result in acidemia.[32] The hypoxemia seen during exacerbations results from the combination of two factors: alveolar hypoventilation and, later, worsening of $\dot{V}/\dot{Q}$ matching. Increases in $\dot{V}/\dot{Q}$ heterogeneity are attributed to (1) a reduction in the effectiveness of hypoxic vasoconstriction as a protective mechanism as pulmonary artery pressure rises and vasodilatory inflammatory mediators are released, and (2) the failure to redirect perfusion away from inadequately ventilated regions because of the reduction in cross-sectional area of the pulmonary vascular bed.

Clinical Manifestations

An exacerbation of COPD is a sustained deterioration of the baseline condition in a patient that begins acutely and requires additional treatment over and above the usual care.[33,34] However, defining the characteristics of the clinical picture is essential. Much effort has been exerted to standardize the diagnosis of "COPD exacerbation," but because of the variability in the symptoms that characterize each case, reaching a consensus has been challenging. The following symptoms may be present: breathlessness, wheezing, chest tightness, increased cough, fever, and changes in sputum color or volume; these symptoms may be accompanied by malaise, insomnia, fatigue, depression, and confusion. Spirometric variables,

• BOX 38.1 Clinical Signs of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Increasing cough
Worsening dyspnea
Increased sputum production
Purulent sputum

such as the peak expiratory flow rate (PEFR), FEV_1, and forced vital capacity may worsen (Box 38.1). The symptoms may slowly intensify over several days or appear acutely, partially depending on the severity of the underlying disease. Additionally, patients often have a recent history of an upper respiratory tract infection. The vital signs typically show tachycardia and tachypnea, and blood pressure can be reduced in response to the effect of iPEEP. The use of accessory inspiratory muscles may be observed as the severity of the exacerbation increases. Because of diaphragmatic fatigue, the diaphragm no longer functions as a primary muscle of inspiration, but instead it assists the inspiratory effort of the intercostal muscles by fixing the rib cage. This action is associated with a rise in the diaphragm, and the abdomen moves inward instead of outward as it does in normal inspiration. This sign is called *paradoxical breathing* and is indicative of respiratory muscle fatigue and often imminent ventilatory failure and respiratory arrest.[31,32] Wheezing and other auscultatory signs of obstruction are also often present. Cyanosis is an insensitive manifestation, but its presence indicates severe hypoxemia. Patients with severe acute CO_2 retention may present in a coma. The classic clinical signs of imminent respiratory failure include an inability to speak complete sentences, the use of accessory muscles, the absence of wheezing, a paradoxical pulse, lethargy (common in hypercapnia), cyanosis, and hemodynamic instability.

Precipitating Factors

The most common precipitant factor is respiratory infection, either bacterial or viral.[35,36] Air pollution can also precipitate exacerbations of COPD[37,38]; however, the cause of one-third of AECOPD events cannot be identified. Some other conditions that can either mimic or induce an exacerbation include pneumonia, arrhythmia, pneumothorax, pulmonary embolism,[39] and pleural effusion. Medication failure and lack of compliance have also been shown to lead to exacerbations.

Infections

Bacteria and viruses account for the vast majority of episodes of exacerbation. Respiratory viruses are associated with 30% of exacerbations with or without a superimposed bacterial infection.[40] Another study reported that up to 78% of the patients admitted to the hospital with severe AECOPD had evidence of viral or bacterial infection.[20]

Several studies have been conducted to investigate airway bacterial infections as etiologic factors involved in COPD exacerbations.[41–43] Bronchoscopic sampling of the distal airway has demonstrated the presence of pathogenic bacteria in 50% of exacerbations. Acquisition of new strains of bacterial pathogens has been associated with more than a twofold increase in the risk of AECOPD.[44] At present, there appears to be an agreement that the major pathogens isolated from sputum during acute exacerbation are *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis*[45]; however, all of these bacteria can be isolated in patients during the stable phases of COPD.[46,47] Atypical bacteria, mostly *Chlamydia pneumoniae,* have been implicated in approximately 10% of acute exacerbations.[48,49] Other potential microorganisms that should be considered include other *Streptococcus* species, enteric gram-negative bacilli, and *Legionella.*[50] Bacterial colonization may be a factor increasing airway inflammation.[51] There is an association between bacterial colonization and increased markers of inflammation in sputum and in the frequency of exacerbations.[52]

Approximately 50% of AECOPD events are associated with upper respiratory tract virus infections. Infections with rhinovirus, respiratory syncytial virus, and influenza virus have been associated with AECOPD.[53] COPD patients with a history of frequent exacerbations may be more susceptible to respiratory viral infections. There is increasing recognition that many patients with exacerbations have concomitant viral and bacterial infection. Approximately a quarter of patients admitted to hospital with AECOPD have coinfection with viruses and bacteria, and those patients have more severe exacerbations.[53]

Environmental Factors

Environmental factors are among noninfectious causes of COPD exacerbation that should be investigated as precipitating causes.[37,54,55] Epidemiologic studies have shown that hospital admissions with AECOPD increase slightly with a rise in atmospheric levels of sulfur dioxide, ozone, nitrogen dioxide, and particulates. There is convincing evidence that exposure to particulates with a 50% cutoff aerodynamic diameter of 10 μm is associated with increased hospital admissions for AECOPD.[56] Air pollution is implicated as a trigger of exacerbations[57]; however, a direct cause-and-effect relationship has been difficult to establish.[58] From an epidemiologic viewpoint, definitive evidence exists regarding a role of air pollutants in the increased death rates seen in cities during periods of heavy pollution.[59] The recent dramatic increase in motor vehicle traffic has produced a relative increase in the levels of newer pollutants, such as ozone and fine-particulate air pollution. Elucidation of the mechanisms of the harmful effects of these pollutants should allow improved risk assessment for the patients with airway diseases who are susceptible to the effects of these air pollutants.

Pulmonary Thromboembolism

Pulmonary thromboembolism (PTE) can precipitate acute COPD exacerbations through either impairment of gas exchange or increases in pulmonary vascular pressures.[60,61] Some evidence suggests that deep venous thrombosis occurs in more than 5 million people each year. More than 500,000 people eventually develop PTE, which is the primary cause of death in more than 100,000 patients annually in the United States.[62] The precise incidence of PTE in COPD is unknown. Studies in COPD patients have found pulmonary embolus in up to 50% of autopsies and in patients admitted to the hospital with severe AECOPD of unknown cause; 25% had pulmonary embolism confirmed by spiral computed tomography (CT).[63] PTE risk factors inherent to COPD are sedentary lifestyle, right ventricular failure, right ventricular mural thrombi, and secondary polycythemia.[64] Patients with COPD have also been shown to have increased platelet aggregation and increased plasma β-thromboglobulin.[65]

Up to 30% of patients with untreated thromboembolism die. The necessity of diagnosing PTE as the precipitating factor in acute COPD exacerbation is crucial. However, the diagnosis of PTE is extremely difficult in COPD exacerbation. Nonetheless, the approach to diagnosis is similar to that used with other patients.[66] Unfortunately, most patients with COPD have an indeterminate $\dot{V}/\dot{Q}$ scan, usually making this scan unhelpful in evaluation for PTE.[67] For patients with such indeterminate results (low or intermediate probability), noninvasive testing of the lower extremity should be conducted.[68–70] If positive results for deep venous thrombosis are obtained, anticoagulation therapy must be initiated. It has been proposed that use of newer D-dimer assays may also have a role as a diagnostic tool; however, even with a sensitivity of 98%, specificity is problematic, with a value of 39%.[71] When the diagnosis is still in doubt (intermediate-probability scan and negative leg study or low-probability scan and negative leg study with intermediate clinical probability of PTE), helical CT or conventional pulmonary angiography may be required. Even though the safety of pulmonary angiography in patients with cor pulmonale has been questioned, data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study support both safety and accuracy in patients with COPD.[66] Helical CT has become an increasingly accepted technique and is the method of choice for direct visualization of pulmonary emboli. The quantitative assessment of tissue perfusion may yield more important information for patient management than the direct visualization of emboli by CT alone. Enhanced multislice helical CT with thin collimation can be used to analyze precisely the subsegmental pulmonary arteries and may identify even more distal pulmonary arteries. Recent data suggest that spiral CT may be an alternative to angiography, particularly when results are not discordant with pretest clinical probability of pulmonary emboli and when combined with other tests that support CT findings (D-dimer, leg ultrasound, lung scanning), and may have adequate sensitivity and specificity in the COPD population.[67]

Medication Failure or Noncompliance

Many acute COPD exacerbations can be explained in terms of inadequate pharmacologic therapy or noncompliance with pharmacologic therapy. These factors are likely underestimated causes of exacerbation in COPD patients. It is also possible that patients have toxic drug effects of cardiac, gastrointestinal, or metabolic nature. Certain pharmacologic drug interactions can precipitate toxicity or loss of effect of one drug, and the physician must ascertain whether newer medications for other conditions have recently been added to the patient's therapeutic regimen.[72,73]

Other Causes

Clinical decompensation in patients with stable COPD may also occur as a result of acute congestive heart failure (CHF) or cardiac arrhythmia. One study found that 27% of COPD patients die as a result of coronary disease,[74] likely related to risk factors such as smoking, diabetes mellitus, and vasculopathy. Heart failure may also lead to a symptomatic exacerbation of COPD; however, it may be difficult to differentiate the symptoms of CHF from those of AECOPD.[75]

Other causes of exacerbation include sleep-disordered breathing,[76–78] vocal cord paralysis, tumor or scarring from prior intubations, and the development of spontaneous pneumothorax.[79,80]

• BOX 38.2 General Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Adjust O_2 to Spo_2 goal 88% to 92%
Initiate and maintain β-agonist and anticholinergic agents combined
Start prednisone 50 mg/day for 7 days
Start antibiotics if signs of infection

O_2, *Oxygen;* Spo_2, *oxygen saturation measured by pulse oximetry*

Finally, pleural effusion can also produce respiratory deterioration, especially in patients with poor respiratory reserve.[81]

Initial Management

Because chronic airflow obstruction cannot be reversed, acute management of COPD is directed at reversible pathogenic mechanisms, including pulmonary infection, airway tissue inflammation, bronchoconstriction, and support of failing muscular function. Box 38.2 summarizes initial general management.

Oxygen

Enhancing blood oxygenation by increasing the concentration of inspired oxygen compensates for a major physiologic consequence of COPD with hypoxemia.[82] Oxygen remains the mainstay of initial therapy in most COPD exacerbations. Relief of hypoxemia, and consequently of hypoxemic pulmonary vasoconstriction, decreases pulmonary vascular resistance, with variable effects on the ventilation/perfusion ratio.[83,84] Oxygen delivery may increase as a result of increases in oxygen arterial content and anticipated improved right-sided heart function. However, one study demonstrated that relief of hypoxemia did not increase cardiac output.[85]

Hypercapnia is well tolerated when it is chronic.[86–88] However, oxygen should be administered cautiously in patients who are chronically hypercapnic because it is known to lead to clinically significant rises in $PaCO_2$ in select patients with COPD as a result of changes in the physiologic dead space and perhaps suppression of the respiratory drive.[89,90] Acute increases in $PaCO_2$ are more likely to occur in patients with elevated baseline $PaCO_2$. A randomized study has shown that, although oxygen administration worsened hypercapnia and respiratory acidosis, these changes were well tolerated in most patients.[91] Oxygen therapy should not be withheld in acutely ill hypoxemic patients because tissue hypoxia can lead to acute organ dysfunction. However, oxygen should be initiated at a low fraction of inspired oxygen (FIO_2) and slowly titrated up as necessary with vigilant monitoring to document improvement and stabilization in the partial pressure of arterial oxygen (PaO_2), with special attention paid to maintaining the oxyhemoglobin between 88% and 92% or greater without producing dangerous falls in pH as a result of rises in CO_2. These dangerous rises in $PaCO_2$ are typically associated with worsening mental status. Nasal cannulas or Venturi masks can be used to initiate a low FIO_2. Either nasal cannula at a flow rate of 1 L/min or a Venturi mask initially at the lowest setting (25%) is appropriate for initiating oxygen in patients known or suspected to be chronic CO_2 retainers. However, in the presence of acute severe hypoxemia in patients with impending respiratory failure, high-flow oxygen therapy may be in the patient's best interest regardless of the risk for CO_2 retention.[92]

Drug Treatment

Bronchodilators

Bronchodilator therapy has important roles in both the prevention and treatment of AECOPD. Bronchodilators are the primary treatment to alleviate patient symptoms, improve physiologic state, and prevent or reverse respiratory failure; however, their use has not been shown to improve survival. Systematic reviews have demonstrated that inhaled delivery of short-acting β_2-selective agonists and anticholinergic agents has greater effect on spirometry and is the therapy of choice for AECOPD over parenteral bronchodilators.[93] Bronchodilator treatment in acutely ill COPD patients has been shown to decrease inspiratory muscle loading, with an increase in FEV_1 and a decrease in functional residual capacity and dynamic hyperinflation.[94] In mechanically ventilated patients, a reduction in expiratory resistance and dynamic hyperinflation (measured as a decrease in iPEEP) has been described.[95]

There is no evidence supporting the use of one inhaled β_2-selective agonist over another. There is no difference in outcome between β_2-agonist compared with ipratropium bromide and no evidence that the combination of these two drugs is any more effective in AECOPD; these results are in contrast with the greater efficacy of these combinations in stable COPD.[93] The widespread use of inhaled β-agonists has been accompanied by clinical concern of cardiac complications in elderly patients and those with coronary artery disease. However, in a study performed with clinically stable COPD or asthmatic patients with a history of myocardial ischemia, no ischemic events or dysrhythmias were observed when commonly used doses of salbutamol were administered.[96] To date, no clinical studies have evaluated the use of inhaled long-acting bronchodilators (either β_2-agonist or anticholinergic agents) with or without inhaled corticosteroids during AECOPD.

Several studies have suggested that the combination of β_2-agonists and anticholinergic agents, particularly long-acting agents, prevent exacerbations.[97–101] It is possible that these agents reduce exacerbation frequency as a result of the effect on reduction of dynamic hyperinflation at rest and exercise,[102] as well as nonbronchodilator mechanisms such as antiinflammatory effect.[103]

Intravenous methylxanthines (theophylline or aminophylline) are considered second-line therapy, to be used only in selected cases when there is insufficient response to short-acting bronchodilators. Side effects of methylxanthines are significant and the clinical response is inconsistent.

Corticosteroids

COPD is recognized as an inflammatory disorder, and the severity of airway inflammation correlates with the severity of the underlying COPD. During exacerbations, there is a large increase in concentration of proinflammatory cells, including neutrophils. Systemic corticosteroids improve lung function significantly, shorten hospital stay, and reduce the risk for relapses compared with placebo in patients with AECOPD.[104] In the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) trial, the median exacerbation rate was reduced by 25%, and there was also a reduction in the health status deterioration.[105] In the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial, treatment with prednisone administered at 40 mg/day for 5 days[105] was not inferior to the administration of prednisolone 30 mg/day for 14 days in terms of the length of hospitalization, improved FEV_1 by 60 mL/day, and accelerated recovery from symptoms.[106] The use of oral steroids has not been shown to be different from the use of intravenous steroids.[107] Corticosteroids halve the chance of treatment failure compared with placebo.[108] A meta-analysis demonstrated that the use of systemic corticosteroids was associated with significant reduction in treatment failure, defined as either clinical deterioration, withdrawal from the study owing to unsatisfactory clinical improvement, or relapse of exacerbation symptoms during the follow-up period.[109] It also showed beneficial effects in reducing the length of hospitalization by a weighted mean of 1.42 days.

Oral corticosteroids have beneficial effects in the management of AECOPD. Prednisolone, administered at 30 mg/day for 14 days, shortened the length of hospitalization by 2 days, improved FEV_1 by 60 mL/day, and accelerated recovery from symptoms.[110] The majority of patients with COPD probably require only 2 weeks with oral corticosteroids and therapy for 8 weeks produced no incremental benefits above those achieved at 2 weeks.[111] One of the most important concerns regarding the use of corticosteroids in AECOPD is the possibility of confusing it with community-acquired pneumonia. Nevertheless, there is no evidence that corticosteroid use worsened the prognosis of community-acquired pneumonia if appropriate antibiotics are used; moreover, systemic corticosteroids may reduce morbidity and mortality rates in community-acquired pneumonia.[112]

The use of inhaled corticosteroids is associated with a decrease in exacerbation events by 12% to 25%.[113] Studies involving inhaled corticosteroids and a long-acting β_2-agonist showed reduction in exacerbation frequency to a greater extent than using either corticosteroid or a long-acting β_2-agonist alone.[114,115] There is also a trend toward mortality rate reduction over 3 years of 17.5%, although without statistical significance.[116] There is no evidence that the addition of inhaled corticosteroids to systemic corticosteroids in AECOPD has any impact on either recovery or mortality rate.

Antibiotics

Use of antibiotics in AECOPD remains a controversial topic, with some authors recommending antibiotic therapy and others not, maybe in part because of the heterogeneity of the population studied.[117,118] Compared with placebo, antibiotic use during AECOPD reduced treatment failures by 46%; failures were defined as requiring additional antibiotics within the first 7 days or unchanged or deteriorated symptoms within 21 days. Antibiotics reduced treatment failures, particularly in those patients who were hospitalized, but not when they were used in ambulatory patients.[119] Three clinical trials involving 181 patients demonstrated that the in-hospital mortality rate can be reduced by 78% with the use of antibiotics during AECOPD.[120,121] Patients who present with dyspnea and increased sputum volume or purulence or patients who require mechanical ventilation benefit from a 3- to 7-day course of oral or parenteral antibiotics.[122]

Although routine sputum cultures are recommended in all patients with AECOPD, invasive techniques (transtracheal aspirates,[123,124] bronchoscopic aspirates, or protected specimen brushing[6,125–129]) are not indicated. Exceptions include culture-negative community-acquired pneumonia not responsive to therapy and ventilator-associated pneumonia.[130,131] Because many patients with COPD have airways colonized by bacteria, without clinical signs of infection and exacerbation, there is no clear significance of a positive culture result in a patient with COPD; however, in the presence of exacerbation associated with an alteration in sputum character or quantity, potentially pathogenic organisms grown from sputum should be covered with an appropriate antibiotic.[132] Thus the selection of empiric antibiotics to treat AECOPD should depend on the severity of underlying disease and severity of COPD exacerbation. Therapy for more severe exacerbations should include

coverage for antibiotic-resistant bacteria, such as *Pseudomonas* or methicillin-resistant *Staphylococcus aureus*.

Hemodynamic Support

Fluid Management

Patients with COPD often have chronic pulmonary hypertension, which may worsen with COPD exacerbation because of hypoxic vasoconstriction, dynamic lung hyperinflation, and in mechanically ventilated patients, iPEEP. This may lead to acute or worsening right ventricular failure. In one study, the prevalence of right ventricular failure in patients with terminal COPD was 66% and the prevalence of left ventricular failure was only 6%.[133] As in other patients with right ventricular failure, hemodynamic stability is related to maintenance of mean arterial pressure. Mean systemic pressure can potentially be increased in these patients by increasing intravascular volume or by selectively improving compliance of the pulmonary vascular bed.[134] Intravenous fluid challenge is the initial step in hemodynamic support in the presence of hemodynamic compromise. Despite the presence of peripheral edema, diuretics should be avoided, given the potential to induce loss of intravascular volume, decreased venous return, decreased cardiac output, and hypotension.

Likewise, because pulmonary hypertension produces chronically elevated right ventricular pressures, fluid challenge could potentially worsen the hemodynamic status of patients with cor pulmonale. Overzealous fluid administration may raise right ventricular pressure to the point that it produces a shift in the interventricular septum and a reduction in left ventricular compliance and filling. The central venous pressure (CVP) is no longer used to assess COPD patients; currently the global end-diastolic index has been proposed to achieve accurate measurements.[135] Currently no consensus or guidelines exist concerning invasive pulmonary artery catheterization in this group of patients; however, in patients who remain hypotensive after initial volume challenge or in patients with organ perfusion abnormalities and biventricular failure, invasive monitoring may be clinically useful.

Inotropes and Vasodilators

In patients who remain hemodynamically unstable despite fluid therapy, adrenergic therapy is advised. Although some literature recommends adrenergic therapy for right ventricular failure using norepinephrine or dobutamine,[136–138] we could find no controlled trials of adrenergic drug therapy in hemodynamically unstable COPD patients. However, patients with pulmonary embolism have a hemodynamic derangement similar to that of COPD patients with right ventricular failure, and as such, dobutamine seems a reasonable choice in attempts to increase right ventricular function and increase cardiac output in the normotensive patient with decreased tissue perfusion. In the presence of hypotension, dobutamine would be used in combination with a combined inotrope vasopressor such as norepinephrine or dopamine. Nitroglycerin has been shown in one study to enhance right ventricular performance when added to dobutamine.[139] Nitroglycerin should be administered cautiously in patients who may have suboptimal right ventricle filling. Digoxin has no anticipated clinical utility in right ventricular failure, unless it is associated with left ventricular failure or arrhythmias that respond to digoxin.[140–142]

Although vasodilators have been used in clinical trials of COPD with right ventricular failure,[143–150] there is no consistent evidence of clinical outcome benefit. Inhaled nitric oxide, a selective pulmonary vasodilator with a short half-life and no systemic vasodilator properties, has shown variable results in patients with AECOPD.[151–155]

Nutritional Support

Malnutrition has been recognized as a factor that increases mortality rate[156,157] in COPD. Weight gain has been associated with decreased mortality rate.[158] Nutritional status tends to decline markedly during acute illness in patients with COPD,[159–161] and they may not recover to their previous nutritional state during convalescence, with recurrent exacerbations leading to a stepwise decline in nutritional status over time.[162] Recent studies have shown that skeletal muscle mass is directly related to muscle dysfunction in patients with COPD.[163] Nutritional status has been correlated with weaning outcome.[164] Short-term studies of oral supplemental feeding or enteral feeding have demonstrated increases in body weight and improvement in immunologic markers and respiratory muscle function.[165–167] Nutritional support has been demonstrated to produce improvement in lung function in hospitalized patients with an acute exacerbation of COPD.[168]

Special care must be taken to avoid overfeeding patients with COPD exacerbation because excess calories, particularly if carbohydrate-rich, elevate total oxygen consumption and CO_2 production, which may complicate management in patients with hypercapnia.[169] In one study of mechanically ventilated patients, enteral nutrition was administered with a fixed carbohydrate content and an association between total caloric intake and CO_2 production when providing nutritional support to the COPD patient with acute respiratory failure (ARF) was noted. It has been recommended that enteral alimentation provide total calories from 1.25 to 1.3 times the resting energy expenditure of the patient with a respiratory quotient target of 0.7 to 0.8 and that carbohydrate calories be limited to 40% of total calories.[170]

Noninvasive Mechanical Ventilation

ARF in the setting of AECOPD is characterized by the worsening of hypoxemia and a variable degree of carbon dioxide retention and acidemia. Worsening in $\dot{V}/\dot{Q}$ ratio mismatching is probably the leading mechanism in the occurrence of the hypoxemia by the enlargement of physiologic dead space and the rise of wasted ventilation.[171] The increase in airway resistance and the need of a higher minute ventilation may result in expiratory flow limitation, dynamic hyperinflation, and related iPEEP with subsequent increased inspiratory threshold load and dysfunction of the respiratory muscles, which may lead to their fatigue.[172] Dyspnea, right ventricular failure, and encephalopathy characterize severe AECOPD complicated by ARF. Arterial pH reflects the acute worsening of the alveolar ventilation, and, regardless of the chronic level of $PaCO_2$, it represents the best marker of the ARF severity.[173]

Those patients with severe AECOPD develop ARF requiring ventilatory support. The frequency of this support varies among series, being as high as 74%.[174] Ventilatory support may be of two types: invasive and noninvasive. Noninvasive ventilation (NIV) using nasal masks or face masks has proved efficacious in ARF caused by COPD in several clinical studies, with success rates as high as 65% in some series.[175–177] As with invasive mechanical ventilation, the goals of NIV include respiratory muscle rest, ventilatory support during treatment of reversible conditions, and the correction of severe hypoxemia and hypercarbia.

Several prospective, randomized, controlled studies confirmed the clinical efficacy of NIV in the treatment of the ARF during AECOPD. Compared with standard medical therapy alone the application of NIV improves survival, reduces the need for endotracheal intubation and the rate of complications, and shortens length of stay in the hospital and intensive care unit (ICU).[174,177,178]

Indications

Although there are recommendations regarding the physiologic variables necessitating NIV or invasive ventilation in patients with respiratory failure, no studies have verified the efficiency of using these variables in the initiation of ventilatory support criteria. Patients with mild exacerbation, with normal or mildly reduced pH (pH > 7.35) and without clinical signs of respiratory failure, do not appear to benefit from a trial of NIV.[179]

In patients with moderate ARF, characterized by pH levels between 7.25 and 7.30, NIV is indicated for a few hours per day (<12 hours/day) to prevent endotracheal intubation, with low failure rates (15%–20%), and appears to have the greater benefit.[180]

In more severely ill patients (pH < 7.25), the rate of NIV failures is inversely related to respiratory acidosis. In this population, the use of NIV as an alternative to invasive ventilation does not affect the mortality rate or the duration of ventilatory support, but it is associated with a lower rate of complications (ventilator-associated pneumonia, difficult weaning). Despite the elevated rate of failure, it is worth a short trial of NIV if no contraindication is present (decreased level of consciousness, cardiac or respiratory arrest, severe gastrointestinal bleeding, severe hemodynamic instability, facial surgery or trauma, upper airway obstruction, inability to clear secretions).[181]

Implementation of Noninvasive Positive-Pressure Ventilation

NIV is usually delivered in assisted ventilation modality, but no differences in success rate were found when applied in controlled ventilatory modality.[182] Leak is a constant feature of NIV and may affect triggering of the ventilator, delivered FIO_2, and air humidification. As such, the choice of the interface is one of the crucial issues affecting NIV outcome; although a face mask is the standard interface to deliver NIV in patients with ARF, poor mask tolerance, skin lesions, and leaks are reported among factors causing NIV failure and intubation requirement.[183]

The nasal mask has less dead space, causes less claustrophobia, minimizes potential complications in case of vomiting, and allows both expectoration and oral intake of fluids without the need to remove the mask. However, face masks are preferable in severely dyspneic patients because the nasal resistance to breathing is decreased with combined nose and mouth air entry. Also, opening of the mouth during nasal noninvasive positive-pressure ventilation produces loss of tidal volume, which decreases effectiveness. In our opinion, the face mask is optimal for initial use in most patients with severe respiratory distress.

The use of pressure support ventilation (PSV) is the most common mode of ventilation for application of NIV. Nonetheless, bilevel positive airway pressure has become the preferred mode of NIV administration in COPD patients because it is generally as comfortable as PSV but produces greater improvement in gas exchange and reduces the work of breathing more effectively than PSV alone.[184–186] Specifically designed noninvasive bilevel ventilators have a better leak tolerance and adjust trigger and cycle sensitivity to improve patient-ventilator synchrony.[187]

The goal of NIV is to provide ventilatory support to rest fatigued respiratory muscles while the underlying illness is treated. The use of adequate ventilatory support is important regardless of the ventilator and modality chosen to deliver NIV. When using pressure-cycled modes, the recommended approach is to start at low pressures for patient comfort and titrate the pressure support or inspiratory positive airway pressure to achieve a tidal volume of at least 6 mL/kg, improvement in clinical signs (respiratory rate <25 beats/min, reduced accessory muscle use), and patient comfort.[188] In one clinical trial, spontaneous ventilation at higher pressures (inspiratory positive airway pressure >25 and <34 cm H_2O) with a higher ventilation frequency (two breaths more than the patient's frequency) decreased muscular work and asynchrony.[189] External PEEP, referred to as expiratory positive airway pressure in bilevel ventilators, may counteract iPEEP, and thus aid triggering, reducing oxygen consumption, and improving comfort. Although iPEEP can be as high as 15 cm H_2O in patients with severe AECOPD, expiratory positive airway pressure levels higher than 5 cm H_2O are rarely tolerated or necessary. Therefore slow titration to patient comfort is important to maximize the likelihood of NIV success. Improvements in pH, $PaCO_2$, and level of consciousness at 60 minutes are predictors of success in patients on AECOPD who respond to NIV.[185]

The British Thoracic Society recommended that patients with ARF who respond to NIV be maintained as continuously as possible during the first 24 hours. If the respiratory status has stabilized, then the duration of ventilatory support can be reduced on subsequent days. Masks are removed for meals, conversation, comfort, and respiratory treatment as necessary.[190]

The predictors of early failure include the lack of improvement in pH (7.25–7.29 odds ratio [OR] 4.7; <7.25 OR 20.9) and tachycardia (>120 beats/min OR 2.5)[191] An ultrasonographic evaluation of the diaphragmatic thickness during the respiratory cycle can also be used to predict failure of NIV. The following calculation is used where ΔTdi(%) is change in diaphragm thickness from inspiration to expiration as a percentage of end-expiration thickness as follows:

$$\Delta Tdi(\%) = \text{End-inspiration Tdi} - \text{End expiration Tdi} / \text{End-expiration Tdi} \times 100$$

The presence of diaphragmatic dysfunction is defined as a ΔTdi <20%, which is independently correlated with the failure of NIV.[192]

Weaning From Noninvasive Ventilation

Weaning from NIV may be accomplished either by progressively decreasing the levels of inspiratory positive-pressure support or by permitting the patient to be intermittently off NIV for increasing lengths of time. A combination of both strategies can also be used. In general, it is useful to wean patients by progressively increasing the period of spontaneous breathing without NIV. Once the acute process improves, many patients can be weaned relatively quickly. Unlike invasive ventilation, NIV can be reinstituted easily and quickly if the patient shows signs of fatigue or intolerance to spontaneous breathing.[193] The use of nocturnal NIV may be needed during the early weaning period and may be continued at home in some patients.

Some studies have analyzed weaning outcome in intubated patients with AECOPD, comparing NIV with conventional weaning methods. Results showed that NIV reduced weaning time, shortened intensive care days, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates.[194,195] NIV has also been used successfully in another study of patients with hypercarbia after extubation.[196] A meta-analysis concluded that, notwithstanding these results, the use of NIV to facilitate weaning in mechanically ventilated patients with predominantly COPD is associated with promising, but insufficient, evidence of clinical benefit at present.[197]

Invasive Mechanical Ventilation

Patients requiring immediate admission to the ICU are those (1) who presented with severe dyspnea that responds inadequately to initial emergency therapy, (2) with changes in mental status (confusion, lethargy, coma), (3) unable to clear respiratory secretions, (4) with severe arrhythmias, (5) persistent or worsening hypoxemia (PaO_2 < 40 mm Hg), and/or (6) severe or worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and NIV, and (7) with hemodynamic instability requiring the use of vasopressors.

Patients with AECOPD requiring invasive mechanical ventilation have a higher ICU mortality rate and in-hospital mortality rate compared with nonventilated patients.[198]

Complications

The main complication in patients with COPD exacerbations is the development of pneumonia associated with mechanical ventilation. The risk factors in COPD patients are similar to the risks in the general population and include age, male gender, the presence of a tracheostomy, hospitalization for more than 48 hours with invasive mechanical intubation or up to 14 to 15 days of intubation, and advanced stages of COPD.

Intubation is a major risk factor for lower respiratory tract colonization. At 72 hours after intubation in patients with COPD, the most commonly isolated organism is *Pseudomonas aeruginosa* (31%), followed by *Acinetobacter baumannii*.[199,200] The main prevention measure to avoid the development of an in-hospital infection in COPD patients is the use of noninvasive mechanical ventilations as an initial treatment option before intubation to reduce invasive mechanical ventilation days.

Intrinsic Positive End-Expiratory Pressure (Video 38.1)

The two primary pathophysiologic changes that contribute to the development of respiratory distress and ARF in patients with obstructive lung disease are increased expiratory airflow resistance and dynamic hyperinflation. In COPD, the alveolar attachments that normally keep the smaller airway open via radial traction are lost. This leads to airway narrowing and collapse, especially during expiration. In AECOPD the already narrowed airways may be further compromised by increased secretions, mucosal swelling, and peribronchial inflammation. The time constant for lung emptying is prolonged, and end-expiratory lung volume is dynamically increased. Therefore the next inspiratory effort occurs before the expiratory phase is completed, leading to air trapping, and the respiratory system is prevented from returning to its resting state at the end of the expiration and thus dynamic hyperinflation develops. Dynamic hyperinflation results in iPEEP.[201] Initially, PEEP is beneficial because it maintains open airways, thereby reducing the airway resistance.

iPEEP is typically not detected on the pressure gauge of the ventilator because it is open to the atmosphere except for a very brief moment at the end of expiration. If the expiration port of the circuit is occluded at end expiration in a relaxed patient with a delay of next inspiration, the pressure inside the lungs and in the circuit will begin to equilibrate; if occlusion is sufficiently prolonged, iPEEP may be recorded.[202]

iPEEP has numerous hemodynamic and mechanical consequences. When iPEEP is excessive, barotrauma may occur. Hemodynamic consequences of iPEEP effect are more common with decreased venous return, decreased stroke volume, and hypotension. iPEEP also increases the work of breathing, which is represented by an increase of workload during spontaneous inspiration and by an increase in the threshold of ventilator triggering. iPEEP is treated by increasing expiratory time and decreasing the minute ventilation, as well as reducing the airflow resistance by bronchodilators and corticosteroids. This effect is achieved by decreasing the respiratory rate and tidal volume.

In the past, PEEP was avoided in patients with AECOPD because of the concern of worsening dynamic hyperinflation. It is now recognized that the application of extrinsic PEEP below 75% to 85% of iPEEP may facilitate ventilator triggering, because alveolar pressure now needs to be decreased to only below the level of the external PEEP, instead of below the level of atmospheric pressure, decreasing the work required to trigger the inspiration.[203,204]

Weaning

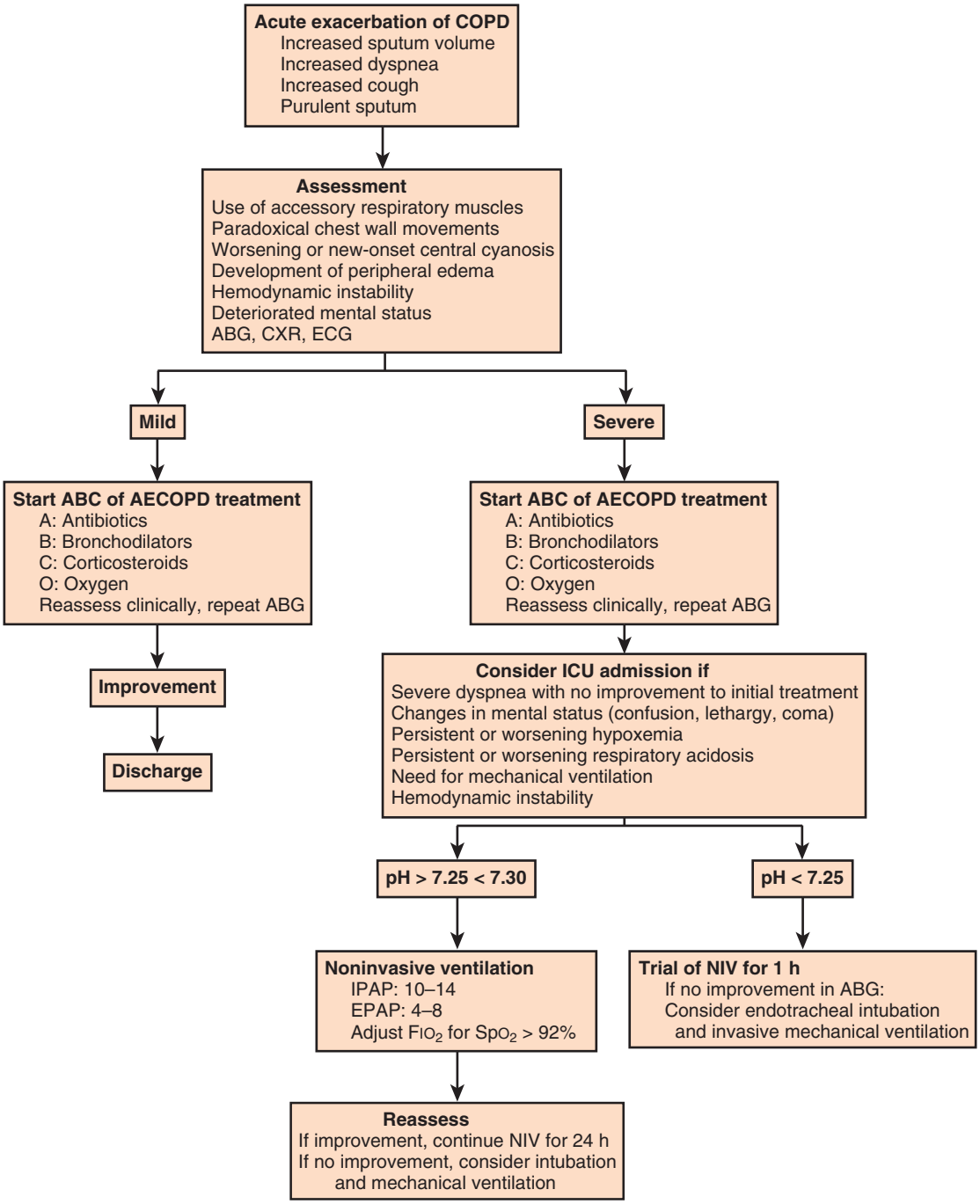
In general, restoration of respiratory muscle function requires approximately 24 to 48 hours of mechanical ventilation.[205–207] Before weaning patients with AECOPD from mechanical ventilation, the premorbid condition that triggered ARF should be corrected and an adequate neuromuscular competency/workload ratio achieved. Therefore the strategy for facilitating weaning from the ventilator should include an increase in inspiratory force and a decrease in the load on the respiratory system. See Chapter 43 for a comparison of various weaning techniques.

Extubation to Noninvasive Ventilation

COPD is classified as a major risk factor for the development of weaning-induced pulmonary edema (OR of 8.7).[208] Earlier studies supported the idea that NIV can facilitate weaning and improve outcomes in difficult-to-wean patients by avoiding the complications of prolonged intubation. There is evidence that the use of NIV as a method of weaning in patients with AECOPD and CHF resulted in shorter periods of intubation, decreased length of hospital and ICU stay, lower rate of nosocomial pneumonia, and improved ICU and 90-day survival. Fig. 38.1 shows a suggested algorithm for the management of AECOPD.

Patients with COPD are predisposed to prolonged weaning with the following risk factors: high $PaCO_2$ and tachycardia during the development of the first spontaneous breathing trial (SBT).[209] In general, studies support the development of noninvasive weaning.

The current proposal relates to the optimal time to withdraw invasive ventilation and develop noninvasive weaning by complying with the basic weaning criteria (i.e., neurologic status, oxygenation, coughing ability, and clinical condition) or choosing the moment



• **Fig. 38.1** Management of acute exacerbations of chronic obstructive pulmonary disease. *AECOPD,* Acute exacerbations of chronic obstructive pulmonary disease; *CXR,* chest x-ray; *ECG,* electrocardiogram; *EPAP,* expiratory positive airway pressure; *FIO_2,* fraction of inspired oxygen; *ICU,* intensive care unit; *IPAP,* inspiratory positive airway pressure; *NIV,* noninvasive ventilation; *SpO_2,* oxygen saturation measured by pulse oximetry.

of infectious control (i.e., temperature corporal, radiographic improvement, decrease in secretions, and normal leucocyte count) as the switching time for intubated COPD patients.

The use of a high-flow nasal cannula after extubation has been proposed as an alternative maneuver to the use of noninvasive mechanic ventilation. We demonstrated noninferiority by comparing noninvasive versus high-flow ventilation for weaning of patients with COPD who passed an SBT and by comparing reintubation and postextubation respiratory failure.[210] Patients at risk for reintubation are considered to have the following risk factors: absence of effective cough and the use of pre-extubation sedatives (OR 8.6).[211]

The British Thoracic Society recommends that patients with ARF who respond to NIV be maintained with NIV as continuously as possible during the first 24 hours. If the respiratory status has

stabilized, the duration of ventilatory support can be reduced on subsequent days. The masks are removed for meals, conversation, comfort, and respiratory treatment as necessary.[193]

Prognosis

The outcome for the patients with AECOPD with ARF depends on the severity of the COPD, the trigger for ARF, and avoidance of ICU complications. In patients who require mechanical ventilation for acute exacerbation, the overall in-hospital mortality rate is greater than 20%.[212] For elderly patients, the mortality rate is greater than 50%.[213] In a multicenter study of patients aged 65 years or older, the mortality rate was 30% at hospital discharge, 41% at 90 days, 47% at 180 days, and 59% at 1 year. The time course and recovery after COPD exacerbation in a cohort of 101 patients with a mean FEV_1 of 41.9% has been reported.[214] Patients recorded daily morning PEFRs after the onset of the exacerbation. Median recovery time for PEFR was 6 days. Recovery of PEFR to baseline values was complete in only 75.2% of exacerbations at 35 days, and 7.1% of patients with exacerbations had still not returned to baseline status at 91 days.[214]

A recently observed factor with a significant correlation with mortality is the presence of anemia at hospital admission, which was maintained for up to 2 years after the exacerbation.[215–217]

Terminal Care for the Patient With End-Stage COPD

All patients with severe end-stage COPD should be well educated about their prognosis and limitations of therapy. Some patients may elect not to be mechanically ventilated when the COPD is in the late stage and the likelihood of extubation is extremely low. Others may choose short-term ventilation only in the hope of a reversible cause. Others may choose long-term ventilation with tracheostomy and home or special facility mechanical ventilation. It is important that emotional and psychological support be given for the end-stage patient and his or her family.

Key Points

- Although hypercapnia depends on the severity of airflow limitation, there is considerable variability in the relationship of $PaCO_2$ to FEV_1 and total lung resistance, best explained by the contribution of dead space and minute ventilation.
- Abdominal muscles are recruited during expiration in patients with severe COPD. Dynamic hyperinflation can be overestimated during chronic and acute airway obstruction if abdominal muscle function is not evaluated.
- Although the precise cause of acute exacerbation is poorly understood, it has been associated with a number of precipitating factors, including infection, either bacterial or viral; environmental factors; pulmonary embolism; medication failure; and patient noncompliance.
- Acute increases in $PaCO_2$ with administration of supplemental oxygen are more likely to occur in patients with elevated baseline $PaCO_2$.
- The cornerstone of treatment of airway flow limitation in AECOPD is based on the ABCs: antibiotics, bronchodilators, and corticosteroids.
- A combination of inhaled short-acting β_2-agonists and inhaled anticholinergics is indicated during exacerbations to alleviate patient symptoms.
- Systemic corticosteroids shorten the recovery time, improve lung function (FEV_1) and arterial hypoxemia, and reduce the risk of relapse, treatment failure, and length of hospital stay. Treatment with corticosteroids should be maintained for 5 days.
- Antibiotics should be given to patients with AECOPD who have an increase in dyspnea, sputum volume, and sputum purulence or who require mechanical ventilation.
- The choice of antibiotics should be based on the local bacterial pattern, and the recommended length of antibiotic therapy is usually 5 to 10 days.
- Nutritional support has been demonstrated to produce improvements in lung function in hospitalized patients with AECOPD.
- NIV reduces the rate of intubation and mortality rate in selected patients with ARF secondary to AECOPD. The highest benefit occurs in patients with moderate ARF with pH between 7.25 and 7.3.
- Potential physiologic benefits of NIV in AECOPD include improvement in tidal volume, gas exchange, respiratory rate, heart rate, oxygenation, and diaphragm activity, as well as a reduction in arterial CO_2 with a concomitant improvement in pH. When these beneficial responses occur, they are typically seen in the first several hours after beginning NIV.
- ICU admission for patients with AECOPD is recommended in patients with severe dyspnea that responds inadequately to initial emergency therapy, changes in mental status, persistent or worsening hypoxemia or persistent or worsening respiratory acidosis despite NIV, the need for mechanical ventilation, and hemodynamic instability.
- If the expiration port of the circuit is occluded at end expiration in a relaxed patient with a delay of next inspiration, the pressure inside the lungs and in the circuit will begin to equilibrate; if occlusion is sufficiently prolonged, iPEEP may be recorded.
- iPEEP has numerous hemodynamic and mechanical consequences.
- To reduce dynamic hyperinflation and iPEEP, provide the longest expiratory time possible, reduce patient ventilatory demand and minute ventilation, and reduce airflow resistance by using bronchodilators and corticosteroids.

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Review Questions

1. What is the definition of Acute exacerbation of COPD (AECOPD)?
   Answer:
   - Much effort has been exerted to standardize the diagnosis of AECOPD, but because of the variability in the symptoms that characterize each case, reaching a consensus has been challenging.
   - It has been defined according to the presence and worsening of specific signs and symptoms such as: dyspnea, cough, sputum volume and purulence. It is also important to consider the need for additional treatment over and above the usual care.
   - The vital signs typically show tachycardia and tachypnea. Wheezing and other auscultatory signs of obstruction are also often present.
   - The use of accessory inspiratory muscles may be observed as the severity of the exacerbation increases. Because of diaphragmatic fatigue, the diaphragm no longer functions as a primary muscle of inspiration, but instead it assists the inspiratory effort of the intercostal muscles by fixing the rib cage, therefore producing a sign called paradoxical breathing.
2. Which factors can precipitate an AECOPD?
   Answer:
   - *Infections (bacterial or viral).*
     - Bacteria and viruses account for the vast majority of episodes of exacerbation. Bronchoscopic sampling of the distal airway has demonstrated the presence of pathogenic bacteria in 50% of exacerbations. Approximately 50% of AECOPD events are associated with upper respiratory tract virus infections. Approximately a quarter of patients admitted to hospital with AECOPD have coinfection with viruses and bacteria, and those patients have more severe exacerbations.
   - *Environmental factors*
     - Environmental factors are among noninfectious causes of COPD exacerbation that should be investigated as precipitating cause.
     - Epidemiologic studies have shown that hospital admissions with AECOPD increase slightly with a rise in atmospheric levels of sulfur dioxide, ozone, nitrogen dioxide, and particulates
   - *Pulmonary Thromboembolism*
     - Pulmonary thromboembolism (PTE) can precipitate acute COPD exacerbations through either impairment of gas exchange or increases in pulmonary vascular pressures.
   - *Medication failure or noncompliance*
     - Many acute COPD exacerbations can be explained in terms of inadequate pharmacologic therapy or noncompliance with pharmacologic therapy. These factors are likely underestimated causes of exacerbation in COPD patients
     - Certain pharmacologic drug interactions can precipitate toxicity or loss of effect of one drug, and the physician must ascertain whether newer medications for other conditions have recently been added to the patient's therapeutic regimen
   - *Unknown.*
     - The cause of up to one third of AECOPD events cannot be identified.
3. Studies have shown that in patients admitted to the hospital with severe AECOPD of unknown cause, up to 25% had pulmonary embolism confirmed by spiral computed tomography (CT). What are some of the Pulmonary thromboembolism (PTE) risk factors inherent to patients with COPD?
   Answer:
   - Sedentary lifestyle
   - Right ventricular failure
   - Right ventricular mural thrombi
   - Secondary polycythemia
4. What is the main principle of the initial management of AECOPD?
   Answer:
   Starting **ABCO**
   - Antibiotics
   - Bronchodilators
   - Corticosteroids
   - Oxygen
5. Why is it necessary to be cautious when administering oxygen therapy to a patient with AECOPD?
   Answer:
   - Although oxygen remains the mainstay of initial therapy in most COPD exacerbations, oxygen should be administered cautiously in patients who are chronically hypercapnic because it is known to lead to clinically significant rises in $PaCO_2$ in select patients with COPD as a result of changes in the physiologic dead space and perhaps suppression of the respiratory drive.
   - Oxygen should be initiated at a low fraction of inspired oxygen (FIO_2) and slowly titrated up as necessary with vigilant monitoring to document improvement and stabilization in the partial pressure of arterial oxygen (PaO_2), with special attention paid to maintaining the oxyhemoglobin between 88% and 92% or greater without producing dangerous falls in pH as a result of rises in CO_2.
   - However, in the presence of acute severe hypoxemia in patients with impending respiratory failure, high-flow oxygen therapy may be in the patient's best interest regardless of the risk for CO_2 retention.
6. It is recommended to obtain routine sputum cultures in all patients with AECOPD. Invasive techniques to obtain culture specimen are not generally indicated. What are the two exceptions to this recommendation?
   Answer:
   - Culture negative community acquired-pneumonia not responsive to therapy.
   - Ventilator associated pneumonia.
7. What are the goals of providing ventilatory support in patients with AECOPD who develop Acute Respiratory Failure (ARF)?
   Answer:
   - Provide respiratory muscle rest while the underlying illness is treated.
   - Correction of severe hypoxemia and hypercarbia.
8. What kind of patients with AECOPD and ARF should be considered for Non Invasive Ventilation (NIV)?
   Answer:
   - In patients with moderate ARF, characterized by pH levels between 7.25 and 7.30, NIV is indicated for a few hours per day (<12 hours/day) to prevent endotracheal intubation.

- In more severely ill patients (pH < 7.25), the rate of NIV failures is inversely related to respiratory acidosis. In this population, the use of NIV as an alternative to invasive ventilation does not affect the mortality rate or the duration of ventilatory support, but it is associated with a lower rate of complications (ventilator- associated pneumonia, difficult weaning).
- Despite the elevated rate of failure, it is worth a short trial of NIV if no contraindication is present (*decreased level of consciousness, cardiac or respiratory arrest, severe gastrointestinal bleeding, severe hemodynamic instabil- ity, facial surgery or trauma, upper airway obstruction, inability to clear secretions)*.

9. What are some strategies to reduce dynamic hyperinflation and iPEEP during MV in patient with ARF and AECOPD?
Answer:
- Provide the longest expiratory time possible.
- Reduce patient ventilatory demand and minute ventilation.
- Reduce airflow resistance by using bronchodilators and corticosteroids.

10. Which patients with AECOPD should be considered for admission to the ICU?
Answer:
- Patients with
  - Severe dyspnea that respond inadequately to initial emergency therapy.
  - Changes in mental statu (confusión, lethargy, coma)
  - Persistent or worsening hipoxemia.
  - Persistent or worsening respiratory acidosis despite NIV.
  - Need for mechanical ventilation.
  - Hemodynamic instability.

39

Hypoventilation and Respiratory Muscle Dysfunction

FRANCO LAGHI AND VEERANNA MADDIPATI*

CHAPTER OUTLINE

Decreased Neuromuscular Capacity
Decreased Respiratory Center Output
Respiratory Muscle Weakness
Respiratory Muscle Fatigue
Increased Load
Increased Mechanical Load
Increased Ventilatory Requirements
Hypercapnia-Induced Hypoventilation
Summary

Hypercapnic respiratory failure is conventionally defined as a state in which ventilation is insufficient to maintain an arterial tension of carbon dioxide ($PaCO_2$) of less than 45 mm Hg for the level of metabolic activity (measured by carbon dioxide [CO_2] production, $\dot{V}CO_2$).[1] Under steady-state conditions, the relationship among $PaCO_2$, alveolar ventilation ($\dot{V}A$), and $\dot{V}CO_2$ is given by the equation:

$$PaCO_2 = (\dot{V}CO_2 / \dot{V}A) \times K,$$

in which K (usually stated as 0.863) is a constant that converts measurement of $\dot{V}CO_2$ from standard conditions to body temperature conditions. The term $\dot{V}_A$ represents the portion of minute ventilation ($\dot{V}_E$) that reaches the terminal gas exchange units and is calculated as

$$\dot{V}A = \dot{V}E - \dot{V}D,$$

where $\dot{V}D$ equals dead-space ventilation. A reduction in $\dot{V}A$ may result from an inadequate $\dot{V}E$ or an increase in $\dot{V}D$ (resulting from an increase in true $\dot{V}_D$ or a functional increase in $\dot{V}D$ secondary to lung regions with high ventilation-perfusion ($\dot{V}A/\dot{Q}$) relationships).[a]

Hypercapnia is synonymous with alveolar hypoventilation for the patient's level of carbon dioxide production. Alveolar hypoventilation can result from decreased neuromuscular capacity and increase respiratory load (Fig. 39.1).[2] Isolated impairments in gas exchange—that is, conditions where the alveolar-arterial O_2 gradient[b] is increased—usually do not cause hypercapnia.[3] When gas exchange is impaired, however, the magnitude of neuromuscular derangements causing hypercapnia or the magnitude of increased respiratory loads causing hypercapnia is less than the corresponding derangements when gas exchange is normal. Conditions where gas exchange contributes to hypercapnia are usually characterized by ventilation-perfusion inequality. When gas exchange is impaired total $\dot{V}E$ may actually be increased despite a concurrent decrease in $\dot{V}A$.

Decreased Neuromuscular Capacity

Disease states that may result in decreased neuromuscular capacity and thus in alveolar hypoventilation include conditions characterized by decreased respiratory center output and conditions characterized by respiratory muscle weakness and respiratory muscle fatigue.

Decreased Respiratory Center Output

Isolated decreases in respiratory drive can produce ventilatory failure without distress. Potential causes include administration of sedatives,[1] hypothyroidism,[4] metabolic alkalosis,[5] semi-starvation,[6] and central alveolar hypoventilation syndrome. The latter can be either idiopathic (i.e., primary alveolar hypoventilation or Ondine curse) or

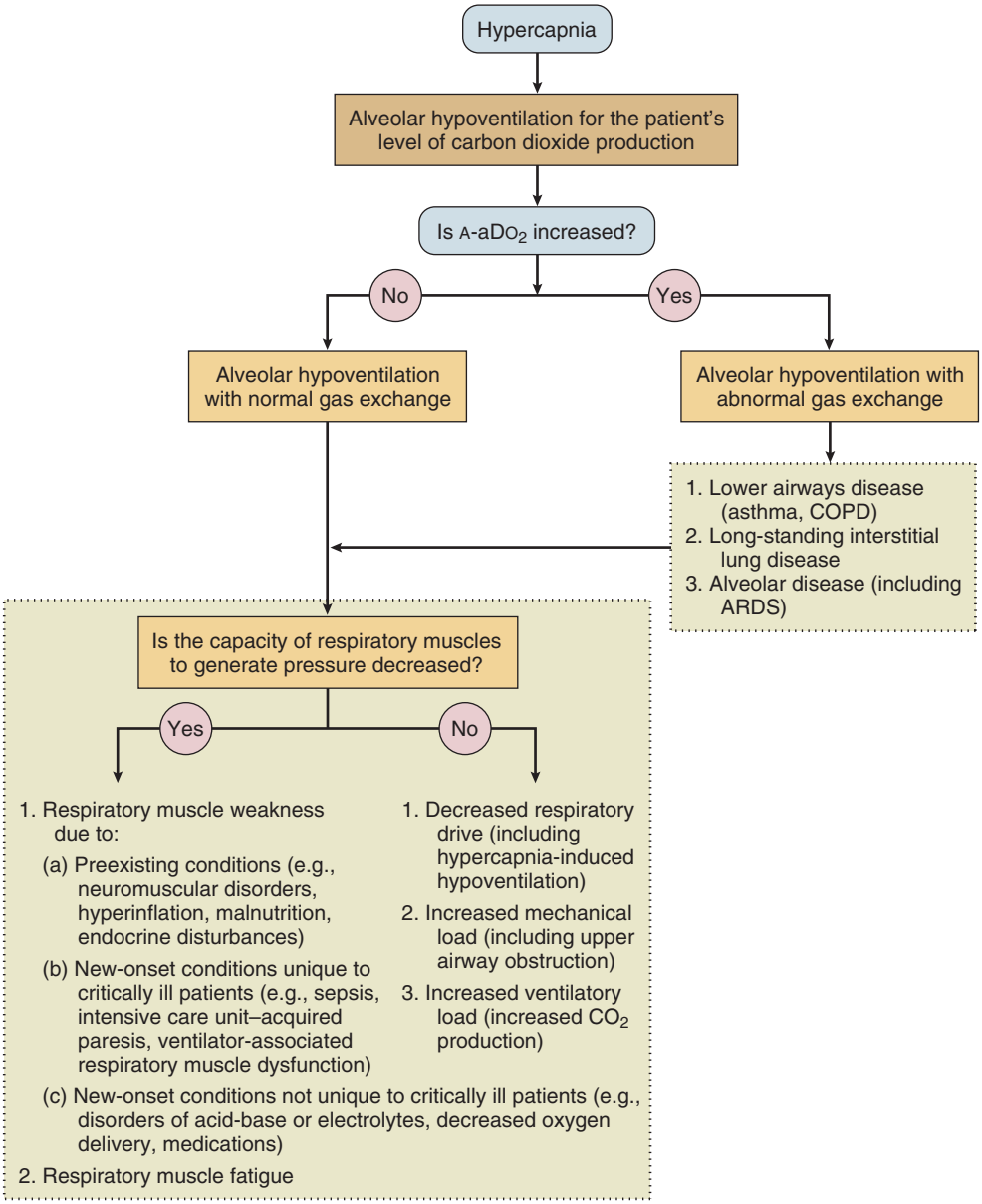
*Supported by a Merit Review Award from the Veterans Administration Research Service 1 I01RX001325-01A2.

[a]Terminology of dead space is confusing. *Anatomic dead space* is made up of the conducting airways (nose, mouth, pharynx, larynx, trachea, bronchi, and bronchioles). *Alveolar dead space* is made up of alveoli that receive some or no blood flow, which does not match ventilation (units with very high $\dot{V}A/\dot{Q}$ ratio). *Physiologic dead space* is the sum of anatomic dead space and alveolar dead space.[1]

[b]The alveolar-arterial oxygen (O_2) gradient ($A\text{-}aDO_2$) is calculated as $PAO_2 - PaO_2$, where PAO_2 (alveolar O_2 tension) can be estimated according to the simplified alveolar gas equation:

$$PAO_2 = FIO_2 \times (PB - PH_2O) - PaCO_2 / R,$$

where FIO_2 is the fractional concentration of inspired O_2 (about 0.21 when breathing room air), PB is barometric pressure (about 760 mm Hg at sea level), PH_2O is water vapor pressure (usually taken as 47 mm Hg at 37°C), and R is the respiratory exchange ratio of the whole lung. The respiratory exchange ratio (R) = CO_2 production/O_2 consumption ($\dot{V}CO_2/\dot{V}O_2$). R is normally about 0.8. In steady state, R is determined by the relative proportions of free fatty acids, protein, and carbohydrate consumed by the tissues. In this equation, it is assumed that alveolar PCO_2 and $PaCO_2$ are the same (usually they nearly are). In healthy young subjects (≤30 years of age) breathing air at sea level, $A\text{-}aDO_2$ is usually less than 10 mm Hg, but it increases to as much as 28 mm Hg in healthy 60-year-old subjects.[1]



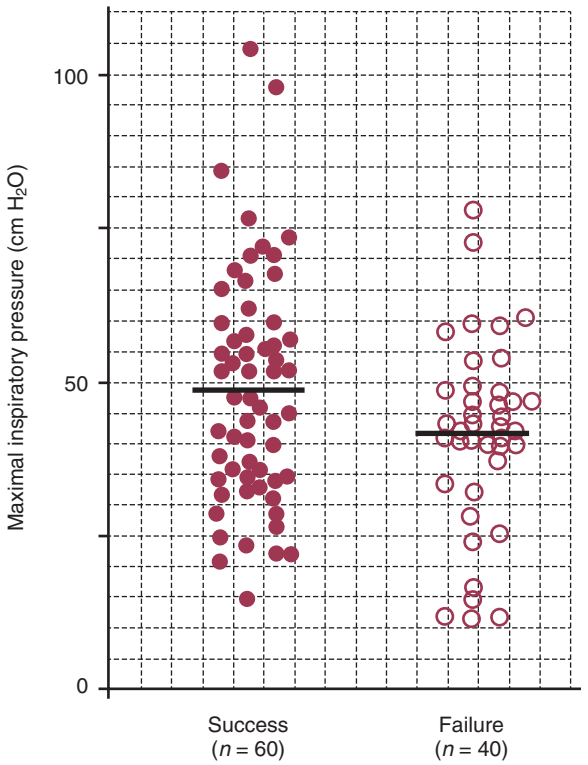
• **Fig. 39.1** Diagnostic approach to critically ill patient with hypercapnia. *A-aDO$_2$,* Alveolar-arterial difference in partial pressure of oxygen; *ARDS,* acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease.

secondary to neurologic lesions, such as trauma, infection (poliomyelitis), infarction, cervical laminectomy with the purported interruption of the reticulospinal fibers innervating the phrenic nerve nuclei,[7] and obesity hypoventilation syndrome.[4] Both hyperoxia and hypoxia can interfere with respiratory center output. Hyperoxia can worsen opiate-induced respiratory depression.[8] Hypoxia can cause respiratory instability by acting on the pre-Bötzinger complex.[9,10] The pre-Bötzinger complex is a neuronal premotor respiratory network located in the ventrolateral medulla of the brainstem that is critical for inspiratory rhythm generation.[9,10] In addition, hypoxia can cause incomplete transmission of inspiratory activity from the respiratory centers to the hypoglossus motor nucleus.[10] These phenomena have been attributed to oxidative stress.[9] Whether sleep deprivation decreases respiratory drive remains controversial.[11,12]

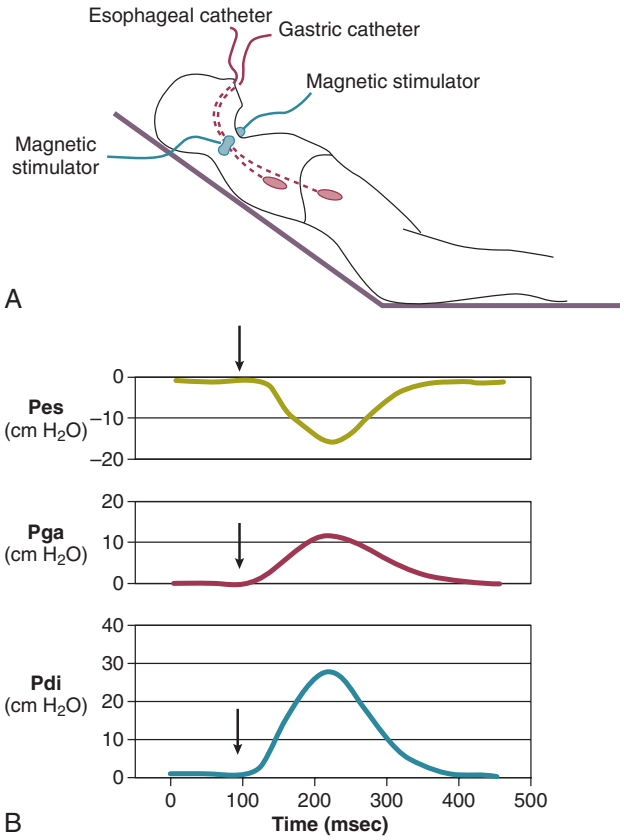
Respiratory Muscle Weakness

Detection of Respiratory Muscle Weakness in Critically Ill Patients

Measurements of airway pressure during maximal voluntary inspiratory efforts are used to evaluate global inspiratory muscle strength.[13] In healthy subjects, maximum inspiratory airway pressure is usually more negative than −80 cm H_2O.[13] In mechanically ventilated patients recovering from an episode of acute respiratory failure, maximum inspiratory airway pressure can range from less negative than −20 cm H_2O to about −100 cm H_2O.[14–16] Values of maximal airway pressure during voluntary maneuvers depend greatly on a level of motivation and comprehension of the maneuver (often not obtainable in critically ill patients).[17] Not surprisingly,



• **Fig. 39.2** Maximal inspiratory pressure recorded before a weaning trial in 60 patients who were successfully weaned *(solid circles)* and 40 patients in whom weaning failed *(open circles).* Maximal inspiratory pressure did not differ significantly between the groups. The *horizontal bars* represent mean values. (Data from Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med*.1991;324:1445–145, courtesy Martin J. Tobin.)



• **Fig. 39.3** Recording of transdiaphragmatic twitch pressure. A, An esophageal balloon and ca gastric balloon are passed through the nares. Magnetic stimulation of the phrenic nerves elicits diaphragmatic contraction. B, Continuous recordings of esophageal *(Pes)* and gastric pressures *(Pga)* and transdiaphragmatic pressure *(Pdi),* calculated by subtracting Pes from Pga. Phrenic nerve stimulation *(arrows)* results in contraction of the diaphragm with consequent fall in intrathoracic pressure (negative deflection of Pes) and rise in intraabdominal pressure (positive deflection of Pga). These swings in pressure are responsible for the transdiaphragmatic twitch pressure. The smaller the transdiaphragmatic twitch pressure, the smaller the force generation capacity of the diaphragm.

in patients requiring short-term mechanical ventilation, measurements of maximum inspiratory airway pressure commonly do not differentiate between patients with weaning successes and those with weaning failures (Fig. 39.2).[16–18]

In contrast to the voluntary nature of maximal voluntary inspiratory efforts, transdiaphragmatic pressures elicited by single stimulations of the phrenic nerves—or twitch pressure—are independent of patients' motivation and eliminate the influence of the central nervous system.[19] Activation can be achieved with either an electrical stimulator[20] or a magnetic stimulator,[20] although the latter is easier to use in mechanically ventilated patients (Fig. 39.3).[19]

In healthy volunteers, magnetic stimulation elicits twitch pressures that average from 31 to 39 cm H_2O.[13] In patients with severe chronic obstructive pulmonary disease (COPD), twitch pressures average 19 to 20 cm H_2O.[21,22] The value of transdiaphragmatic twitch pressure in patients recovering from an episode of acute respiratory failure is about one-third or even less of that recorded in healthy subjects (Fig. 39.4).[23,24] This marked reduction in twitch pressure[24–26] indicates the presence of respiratory muscle weakness in most of these patients. Respiratory muscle weakness in critically ill patients can result from preexisting conditions or from new-onset conditions.

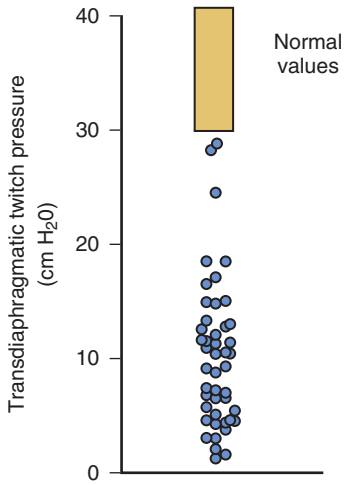
Weakness Caused by Preexisting Conditions

Neuromuscular diseases, malnutrition, endocrine disorders, and hyperinflation are some of the preexisting conditions that can cause respiratory muscle weakness. The existence of preexisting conditions can be recognized before acute ventilatory failure develops, when acute ventilatory failure develops, or when acute ventilatory failure is already established.[13]

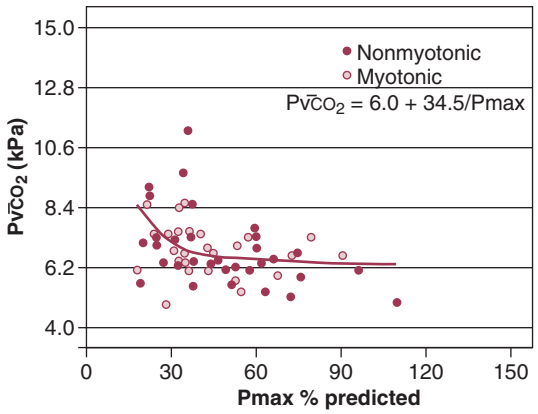
Neuromuscular Disorders

The capacity of the respiratory muscles to generate tension can be decreased in disorders, such as stroke, amyotrophic lateral sclerosis, spinal cord injuries, poliomyelitis, Guillain-Barré syndrome,[13] neuropathies caused by massive intoxications of arsenic or thallium, radiation-induced myopathy,[27] chronic inflammatory demyelinating polyneuropathy, axonopathy of acute intermittent porphyria, myasthenia gravis, acid maltase deficiency,[13] muscular dystrophies such as titin mutations,[28] idiopathic inflammatory myopathies (polymyositis, dermatomyositis, sporadic inclusion body myositis, necrotizing autoimmune myopathy),[29–31] and myotonic dystrophy (i.e., the most frequent adult form of muscular dystrophy).[4]

Hypercapnic respiratory failure usually occurs when respiratory muscle strength falls to 39% of the predicted normal value.[32]

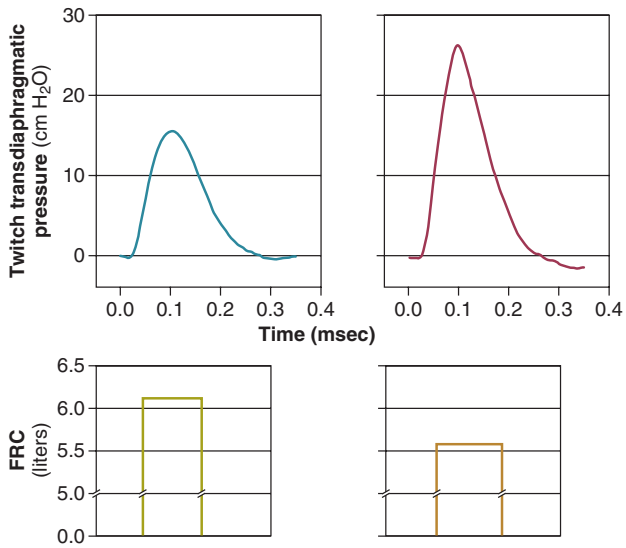


• **Fig. 39.4** Transdiaphragmatic pressure in response to single stimulations (twitch stimulation) of the phrenic nerves recorded in ventilated patients recovering from acute respiratory failure. The boxed area represents the 95% confidence interval of values obtained in healthy subjects. The decreased transdiaphragmatic twitch pressure in patients indicates the presence of diaphragmatic weakness. (From Laghi F. Ventilator-induced diaphragmatic dysfunction: is there a dim light at the end of the tunnel? *Crit Care Med*. 2011;39:903–905.)



• **Fig. 39.5** Relationship between muscle strength and mixed venous partial pressure of CO_2 *($PvCO_2$)* in patients with respiratory muscle weakness. Respiratory muscle strength is the arithmetic sum of maximum static inspiratory and expiratory mouth pressures (Pmax = PImax + PEmax). The *open circles* indicate patients with myotonic dystrophy, and the *solid circles* indicate patients with a variety of nonmyotonic muscle diseases. As respiratory muscle weakness became more severe $PvCO_2$ rose, although considerable variability was observed among patients. The regression lines were similar in the myotonic and nonmyotonic patients. (From Gibson GJ, Gilmartin JJ, Veale D, et al. Respiratory muscle function in neuromuscular disease. In: Jones NL, Killian KJ, eds. *Breathlessness*. The Campbell Symposium. Hamilton, ON: Boehringer-Ingelheim; 1992.)

However, Gibson et al.[33] described several patients with neuromuscular disease who had a normal partial pressure of CO_2 despite decreases in respiratory muscle strength to less than 20% of predicted. Conversely, some patients with only moderate respiratory muscle weakness displayed hypercapnia (Fig. 39.5).[33] In other words, reductions in muscle strength do not consistently predict alveolar hypoventilation in this setting.



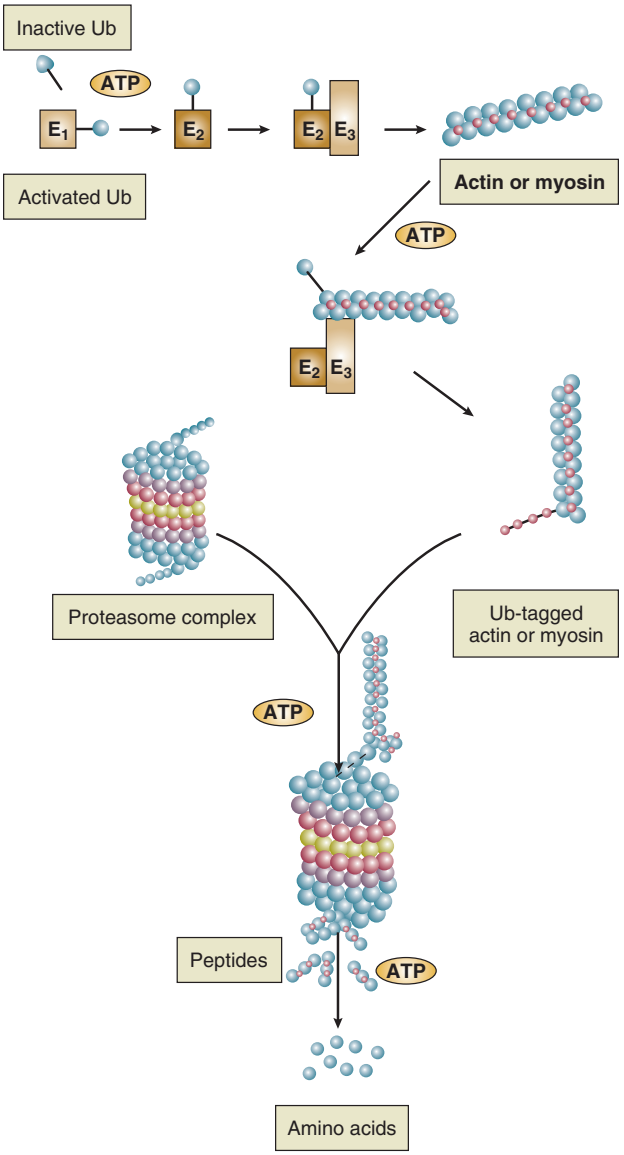
• **Fig. 39.6** Twitch transdiaphragmatic pressure elicited by phrenic nerve stimulation (*upper panel*) and functional residual capacity *(FRC)* (*lower panel*) in a patient with severe emphysema before *(left)* and after *(right)* lung volume reduction surgery. The increase in transdiaphragmatic pressure after surgery was in part due to a decrease in the operating lung volume as demonstrated by the decrease in functional residual capacity. (Data from Laghi F, Jubran A, Topeli A, et al. Effect of lung volume reduction surgery on neuromechanical coupling of the diaphragm. *Am J Respir Crit Care Med* 1998;157:475–483.)

Hyperinflation

Hyperinflation is a common preexisting condition in patients with obstructive lung diseases such as COPD,[4] cystic fibrosis,[34] bronchiolitis,[35] and lymphangioleiomyomatosis.[4] The severity of preexisting hyperinflation commonly worsens in patients experiencing an exacerbation of COPD.[36] Hyperinflation has a number of adverse effects on inspiratory muscle function. The inspiratory muscles operate at an unfavorable position of the length-tension relationship (Fig. 39.6)[37] and flattening of the diaphragm decreases the size of the zone of apposition with the result that diaphragmatic contraction causes less effective rib cage expansion.[4] Hyperinflation also has an adverse effect on the elastic recoil of the thoracic cage.[4] This means that the inspiratory muscles must work not only against the elastic recoil of the lungs but also against that of the thoracic cage. The functional consequences of dynamic hyperinflation are probably the main mechanisms of ventilatory failure in patients with COPD.[38] Hyperinflation can also occur de novo in patients with pneumonia, chest trauma, and acute respiratory distress syndrome (ARDS).[36,39] Impairment of inspiratory muscle function is less likely in patients with ARDS than in patients with obstructive lung disease because patients with ARDS breathe at a low lung volume despite dynamic hyperinflation.[39,40]

Malnutrition

Malnutrition is highly prevalent among critically ill patients requiring mechanical ventilation[41,42] and is associated with poor prognosis.[42] Malnutrition decreases muscle mass and respiratory muscle strength both in humans[43,44] and in laboratory animals.[45–47] Likely mechanisms contributing to decrease in respiratory muscle mass include proteolysis of myofibrillar proteins by the ubiquitin-proteasome proteolytic system (Fig. 39.7) and apoptosis.[4,48] Apoptosis can be triggered by local and circulating



• **Fig. 39.7** Ubiquitin-proteasome degradation of contractile proteins. The first step in degradation of actin and myosin is activation of ubiquitin *(Ub)* by a first enzyme, E_1—a process requiring adenosine triphosphate *(ATP)*. Activated Ub interacts with a second enzyme, E_2, a carrier protein. Ub and E_2 join a third enzyme, E_3. E_3 transfers activated Ub to actin and myosin. The cycle is repeated until a chain of Ub is bound to the contractile proteins. The chain of Ub binds to one end of a proteasome complex in a process requiring ATP. The Ub chain is subsequently removed (allowing reuse of Ub), and actin and myosin are unfolded and pushed into the core of the proteasome. Multiple enzymes within the core degrade actin and myosin into small peptides. The peptides are extruded from the proteasome and degraded to amino acids by peptidases in the cytoplasm. The ubiquitin-proteasome system degrades myofibrillar proteins only after they have been cleaved and released by other proteolytic pathways—that is, the ubiquitin-proteasome pathway cannot degrade intact myofibrillar proteins. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48. Reproduced with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.)

tumor necrosis factor α and by release of cytochrome c from the mitochondria.[49,50]

In patients with COPD, inspiratory muscle strength is about 30% less in poorly nourished patients than in well-nourished patients with equivalent airway obstruction.[51] Similarly, malnourished patients with anorexia nervosa can present with reduced inspiratory muscle strength to 35% to 50% predicted,[44] impaired respiratory muscle endurance,[52] impaired hypercapnic ventilatory response,[52] and, occasionally, with hypercapnia at rest.[44] In malnourished patients, inspiratory weakness,[44,51,52] fatigability,[51] and dyspnea[51] are partially reversible with nutritional support. The process is slow and, in laboratory animals, it can take months of refeeding for muscle mass to return to normal values.[53] To date, it remains unclear whether malnutrition by itself can cause sufficient respiratory muscle weakness to produce hypoventilation. It is more likely for malnutrition to be a contributory factor and not a sole cause of hypercapnic respiratory failure.

Endocrine Disturbances

Endocrine disturbances, such as hypothyroidism, hyperthyroidism, and acromegaly, can adversely affect respiratory muscle function.[54] Proteolysis of myofibrillar proteins by the ubiquitin-proteasome proteolytic system[48] (see Fig. 39.7) is probably responsible for respiratory muscle catabolism and weakness of hyperthyroidism.[50] This mechanism is implicated in muscle wasting associated with acidosis, renal failure, denervation, cancer, diabetes, AIDS, trauma, and burns.[48] In contrast to other endocrine disturbances, respiratory muscle weakness is unusual in patients with Cushing syndrome.[55]

Weakness Caused by New-Onset Conditions

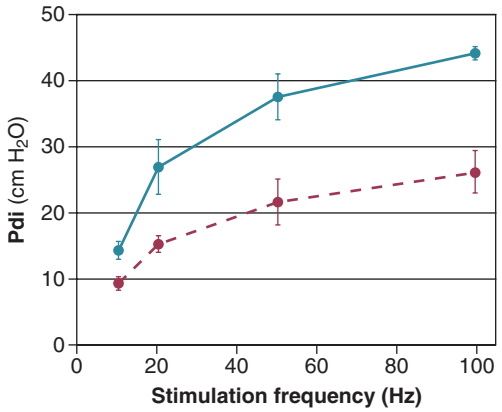
New-onset respiratory muscle weakness in critically ill patients may result from conditions that are unique to these patients. These include ventilator-associated respiratory muscle dysfunction, sepsis-associated myopathy, and intensive care unit (ICU)-acquired paresis. New-onset respiratory muscle weakness can also result from conditions that are not unique to critically ill patients. These include acid-base disorders, electrolyte disturbances, decreased oxygen delivery, and medications. Respiratory muscle weakness owing to conditions unique to critically ill patients are often associated with alterations in respiratory muscle structure, whereas the others are not necessarily associated with alterations in muscle structure. Recovery from respiratory muscle weakness (if it occurs at all) is slow when the weakness is caused by alterations in muscle structure. In contrast, recovery of respiratory muscle weakness in conditions that are not necessarily associated with alterations in muscle structure is usually quick once the underlying triggering factor has been corrected.

Ventilator-Associated Respiratory Muscle Dysfunction

Since the late 1980s, several groups have studied the effect of mechanical ventilation on the muscles of laboratory animals.[56] A seminal study Anzueto et al.[57] showed that 11 days of controlled mechanical ventilation (CMV) together with neuromuscular blocking agents produced a 46% decrease in respiratory muscle strength (Fig. 39.8). Subsequent studies have revealed that complete cessation of diaphragmatic activity with CMV—alone[58] or in combination with neuromuscular blocking agents[59]—results in atrophy and injury of diaphragmatic fibers (Fig. 39.9). Muscle fibers generate less force in response to stimulation, not simply because of a loss of contractile proteins, but also because of dysfunction of the remaining ones.[56,60–62] The decrease in diaphragmatic force ranges from 20% to more than 50%. The alterations in muscle function occur rapidly, within 12 hours of instituting mechanical ventilation,[63] and they appear to increase as ventilator duration is prolonged.[64,65] Of interest, long-term

CMV in rats causes the expected reductions in maximum force and specific force.[62] Paradoxically, however, it also produces an increase in myofiber cross-sectional area. Accordingly, investigators speculate that long-term CMV may trigger an ineffective compensatory hypertrophy of diaphragm myofibers.[62] In these rats, administration of a heat shock protein co-inducer (BGP-15) greatly improves diaphragm muscle fiber function without reversing diaphragm atrophy.[66]

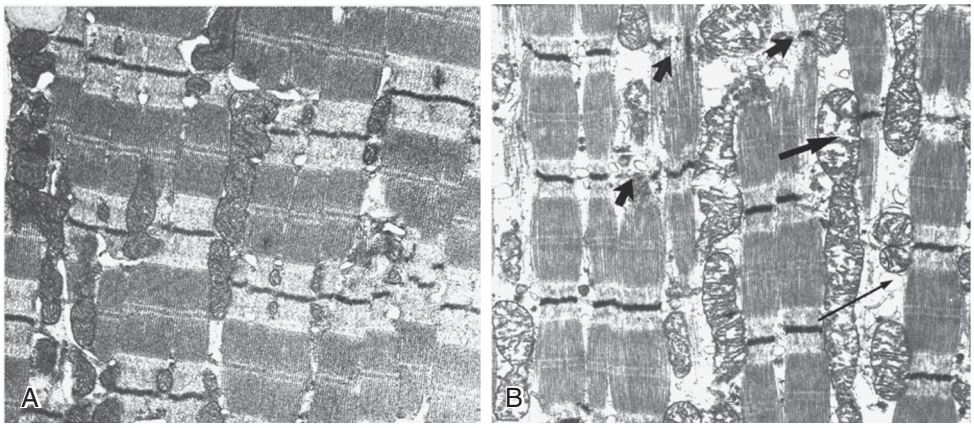
Mechanical ventilation may also harm the respiratory muscles of patients. In 1988, Knisely et al.[67] reported that the cross-sectional area of diaphragmatic fibers in infants who had died after receiving mechanical ventilation for 12 days or longer was much smaller than in infants who had received mechanical ventilation for 7 days or less (Fig. 39.10). Fibers taken from extradiaphragmatic muscles were similar in the two groups. Twenty years later Levine et al.[68] obtained biopsies of the diaphragm from 14 brain-dead organ donors who were maintained on CMV for 18 to 69 hours. They also obtained intraoperative biopsies of the diaphragms of 8 control patients who had received CMV for 2 to 3 hours. Histologic measurements revealed marked diaphragmatic atrophy in the brain-dead patients. Compared with the control group, the mean cross-sectional areas of muscle fibers were decreased by more than 50%. A number of these results have been corroborated by other investigators who also reported a progressive decrease in diaphragmatic contractility of mechanically ventilated patients.[61,65,69–71] The decrease in contractility correlated with the duration of ventilator support (Fig. 39.11).[65,69,70]



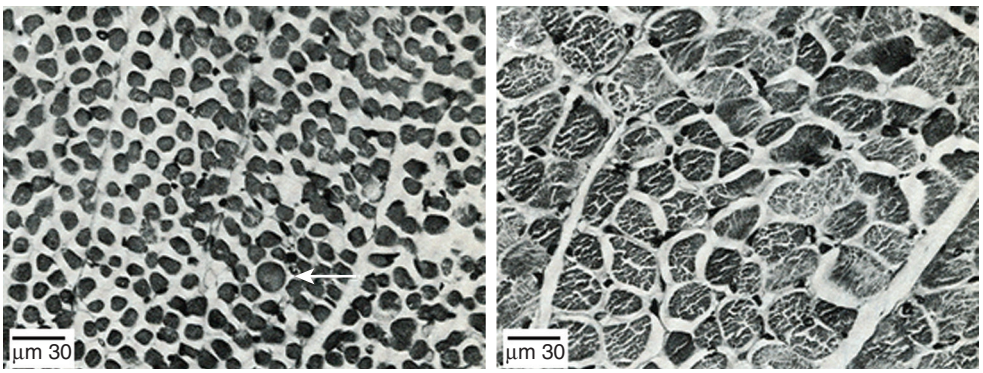
• **Fig. 39.8** Transdiaphragmatic pressure *(Pdi)* response to phrenic nerve stimulation before *(solid line)* and after 11 days *(dashed line)* of mechanical ventilation. That the transdiaphragmatic pressure recorded after 11 days of mechanical ventilation shows a decrease response to all stimulation frequencies is suggestive of ventilator-associated diaphragmatic dysfunction. (Modified from Anzueto A, Peters JI, Tobin MJ, et al. Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. *Crit Care Med* 1997;25:1187–1190.)

Biochemical and gene-expression studies in animals and humans[68,72] suggest that oxidative stress is a central factor in the biochemical cascade that leads to ventilator-induced muscle injury.[73] Oxidative stress decreases contractility through protein oxidation, increased proteolysis, and decreased protein synthesis,[73,74] including upregulation of the autophagy-lysosome pathway.[75] Activation of the JAK–STAT pathway (Janus kinase or JAK and signal transducer and activator of transactivation or STAT) is the likely proximal mechanism triggering oxidative stress in the ventilator-induced muscle injury reported in both animals and humans.[76]

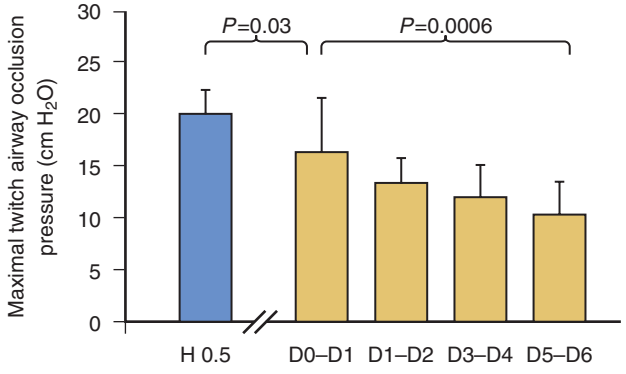
The synergism between ventilator-induced muscle injury and oxidative stress has caused investigators to explore whether early administration of antioxidants might minimize muscle injury.[77–79] In a study of more than 200 critically ill patients—80% of whom required acute ventilator support—duration of mechanical ventilation was nearly 3 days shorter in those who completed a 10-day antioxidant supplementation protocol (vitamin E and vitamin C) than in those who completed a 10-day course of placebo.[80] Similar results have been reported in critically ill surgical patients requiring mechanical ventilation.[81] Whether the decrease in duration of mechanical ventilation was, at least in part, due to the potential positive effects of antioxidants on the respiratory muscles remains



• **Fig. 39.9** Electron microscopy of the diaphragm (longitudinal section) of a rabbit under control conditions (A, specimen processed with 1100-mOsm fixative) and after 3 days of controlled mechanical ventilation (B, specimen processed with 500-mOsm fixative). The control rabbit has an intact ultrastructure. The mechanically ventilated rabbit shows several areas of disrupted myofibrils *(short thick arrows)*, the mitochondria are swollen *(long thick arrow)* and have abnormal cristae, and the intermyofibril space contains lipid droplets *(long thin arrow)*, indicating decreased lipid uptake by the mitochondria. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48. Electron micrographs provided by Dr. Catherine S.H. Sassoon, Long Beach VA Hospital and University of California, Irvine, CA.)



• **Fig. 39.10** Photomicrographs of transverse sections of diaphragm from an infant ventilated from birth until death at day 47 (A) and from an infant ventilated from birth until accidental death at day 3 (B). Prolonged mechanical ventilation was associated with reduction in myofiber cross-sectional area. (The *arrow* indicates a developing myofiber also known as Wohlfart myofiber.) (Modified from Knisely AS, Leal SM, Singer DB. Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. *J Pediatr* 1988;113:1074–1077.)



• **Fig. 39.11** Twitch airway pressure elicited by magnetic stimulation of the phrenic nerves in six patients who received mechanical ventilation (MV) for 30 minutes (short-term MV; *blue bar*) and in six patients who received MV for about six days (long-term MV; *gold bars*). On day 1 twitch airway pressure was already less in the long-term than in the short-term MV group. In addition, long-term MV was associated with a progressive decrease in twitch pressure over time, a mean reduction of 32% ± 6% after 6 days of MV. *D,* Number of days of mechanical ventilation; *H,* number of hours of mechanical ventilation. (From Jaber S, Petrof BJ, Chanques G, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med*. 2011;183: 364–371.)

to be demonstrated. Of concern, however, is the report that administration of the antioxidant N-acetylcysteine to critically ill patients with severe sepsis worsened sepsis-induced organ failure.[82]

In a study of 10 critically ill patients who had received mechanical ventilation for 28 to 603 hours, Hooijman et al.[60] reported that isolated fast-twitch diaphragm muscle fibers required more calcium to generate force than fibers obtained from 10 patients undergoing elective lung surgery. The investigators were able to restore the force output using CK-2066260, a troponin calcium sensitizer.[60] Despite this encouraging result, another study reported that administration of levosimendan, another troponin calcium sensitizer, to critically ill patients with sepsis was associated with a lower likelihood of successful weaning from mechanical ventilation.[83]

In animal models, ventilator settings can affect the extent of ventilator-associated respiratory muscle dysfunction.[84–87] In rabbits, assist-control mechanical ventilation causes a nonsignificant decrease in diaphragm muscle contractility, which contrasts with the 48% decrease recorded with CMV.[84] Similar results have been obtained when comparing CMV with adaptive support ventilation in piglets,[86] when comparing CMV with pressure support in rats,[74,87] or comparing CMV with intermittent spontaneous breathing in rats as well.[85] These observations raise the important question of whether maintenance of partial diaphragmatic activity or intermittent loading of the diaphragm could prevent the harm done to diaphragmatic function by mechanical ventilation.[88]

Considering that decreases in protein synthesis probably contribute to ventilator-associated respiratory muscle dysfunction,[89] it would seem biologically plausible that administration of anabolic factors—such as growth hormone—might be of benefit in ventilated patients. Unfortunately, when growth hormone has been administered to patients requiring prolonged mechanical ventilation, the duration of mechanical ventilation was not decreased nor was muscle strength increased.[90] Of concern was the report that recombinant growth hormone can increase mortality of critically ill patients.[91]

An even more fundamental point in regard to ventilator-associated respiratory muscle dysfunction has been raised by Hooijman et al.[92] These investigators measured the contractile properties of single diaphragmatic fibers obtained from nine brain-dead organ donors who had received CMV for 26 ± 5 hours (case subjects) and from 9 patients undergoing surgery for localized lung cancer who had received CMV for 1.7 ± 0.1 hour (control subjects). No difference was noted between the muscle fibers of the two groups of patients with respect to cross-sectional area, maximum force per unit area, calcium sensitivity of force generation, and rate constant of redevelopment of force. How to reconcile these results of Hooijman et al.[92] with the reduced calcium sensitivity of force generation reported by the same investigators[60] and with previous data obtained on muscle strips from animal models and by phrenic nerve stimulation in patients remains to be determined.

Finally, it is important to stress two additional points. Healthy rats submitted to CMV for 24 hours, followed by spontaneous

breathing for 1 to 7 hours, develop severe diaphragmatic dysfunction at the conclusion of CMV, yet diaphragm force starts to improve after only 3 hours of spontaneous breathing.[89] Complete recovery occurs by 4 to 7 hours of spontaneous breathing.[89] These findings are associated with increases in diaphragm muscle protein synthesis and type IIx/b fiber dimensions.[89] Such rapid reversibility has never been reported in critically ill patients, arguing that other mechanisms of diaphragm weakness and respiratory failure play a role in critically ill patients.[24] It follows that, in the ICU, ventilator-associated respiratory muscle dysfunction must always be a diagnosis of exclusion.[24]

Sepsis-Associated Myopathy

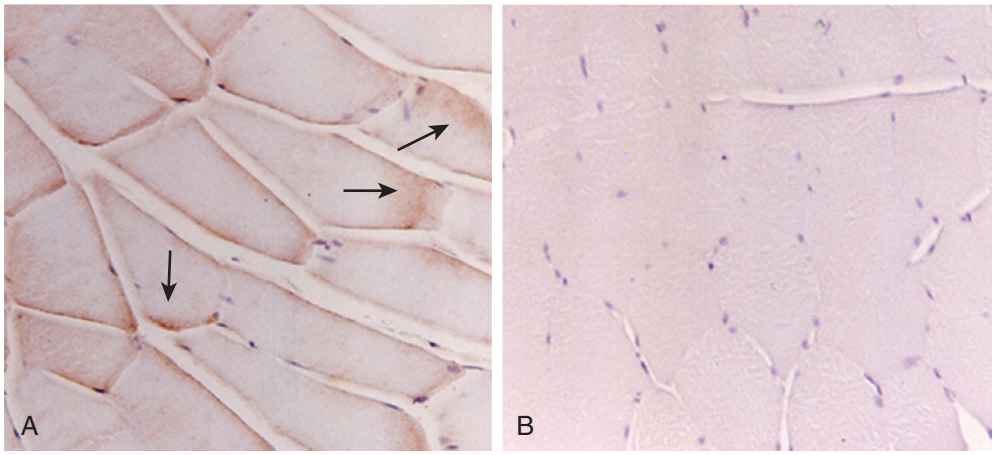
Sepsis, a common occurrence in critically ill patients, can produce ventilatory failure by causing respiratory muscle dysfunction and increased metabolic demands.[93] Septic animals develop failure of neuromuscular transmission (owing to increased sarcolemmal electric potential),[94–96] and failure of excitation-contraction coupling.[93,97] Mechanisms responsible for failure of excitation-contraction coupling include the cytotoxic effect of nitric oxide and its metabolites, free radicals, the activation of proteolytic pathways (including calpains, caspases, and the ubiquitin-proteasome[24]), and, possibly, decrease in nicotinic acetylcholine receptors.[98,99] Local dysregulation of the circulation and Krebs cycle may also contribute.[93] The result is a decrease in diaphragmatic strength by as much as 80% within 24 hours.[100,101]

Nitric oxide, a free radical that has a negative inotropic effect in the heart and skeletal muscle, is produced in large amounts during sepsis by a nitric oxide synthase inducible by lipopolysaccharide and several cytokines (Fig. 39.12).[102] Increased expression of inducible nitric oxide synthase in the diaphragm during sepsis is associated with widespread damage to the myofiber membrane, or sarcolemma (Fig. 39.13).[95] Whereas diaphragmatic contractions enhance this sepsis-induced sarcolemmal injury,[103] early mechanical ventilation decreases sarcolemmal injury and the associated diaphragmatic dysfunction.[104] The beneficial effects of resting the diaphragm with the use of mechanical ventilation are not coupled with a decrease in oxidative stress or with a decrease in the expression of inducible nitric oxide synthase in the muscle.[104] These observations suggest the existence of a detrimental interaction of two independent stressors (oxidative and biomechanical stresses) on the sarcolemma during sepsis.[104]

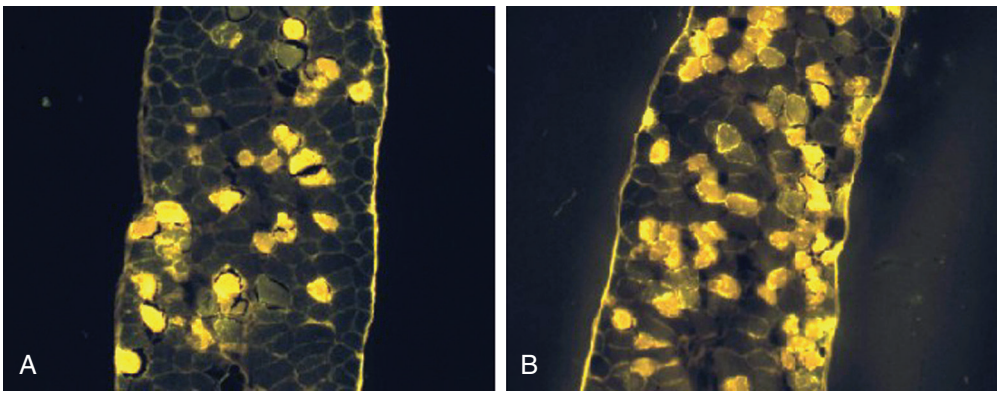
To determine whether the inducible nitric oxide synthase pathway contributes to impaired skeletal muscle contractility in humans, Lanone and coworkers[105] obtained samples of the rectus abdominis in 16 septic patients and 21 control subjects. The muscles of the patients had lower contractile force, and increases in inducible nitric oxide synthase expression (messenger ribonucleic acid and protein) and activity. Immunohistochemical studies revealed the generation of peroxynitrite (a highly reactive oxidant formed by the reaction of nitric oxide with superoxide anion). Exposure of control muscles to the amount of peroxynitrite found in patients caused an irreversible decrease in force generation. These data suggest that sepsis decreases muscle force through the production of nitric oxide and its toxic by-products.

Production of nitric oxide in sepsis may be protective and not solely deleterious.[103,106–108] In mice deficient in inducible[106] or constitutive (neuronal) nitric oxide synthase,[103] endotoxin caused a greater decline in diaphragmatic contractility than in nondeficient mice. This finding contrasts with the observation that nitric oxide synthase inhibitors prevent muscle dysfunction in septic rats.[95,102,109] Although the results may be species-dependent,[103] the data underscore that nitric oxide has both antioxidant and prooxidant actions.[110]

In addition to nitric oxide and its derivatives, several other oxygen-derived free radicals (superoxide anion, hydroxyl radicals, hydrogen peroxide) contribute to the decreased contractility of the diaphragm in sepsis.[108,111–113] This increased expression of oxygen-derived free radicals in sepsis is accompanied by enhanced activity of the antioxidant enzyme superoxide dismutase[111] and increased expression of the heme oxygenase-1 pathway.[113] The heme oxygenase-1 pathway is a powerful cellular system that protects against oxidative stress and contractile fatigue during sepsis.[113] Administration of an inhibitor (zinc protoporphyrin IX) or an



• **Fig. 39.12** A, A sample of gastrocnemius muscle obtained from an adult Sprague-Dawley rat injected 12 hours earlier with *Escherichia coli* endotoxin (20 mg/kg). The section was stained with an antibody to inducible nitric oxide synthase. Positive staining *(brown coloration, arrows)* is evident inside the fibers. B, A sample of gastrocnemius muscle obtained from a rat injected 12 hours earlier with normal saline solution. No positive staining is evident. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48. Photomicrographs provided by Dr. Sabah N. Hussain, Royal Victoria Hospital, Montreal, QC, Canada.)



• **Fig. 39.13** A, A strip of diaphragm obtained from a C57BL/6 mouse injected 12 hours earlier with normal saline solution. The strip was stimulated for 3 minutes (50 Hz, 300-msec duration) and then immersed for 90 minutes in Krebs solution containing a fluorescent probe, Procion orange 14 (0.15, wt/vol). B, A strip of diaphragm obtained from a C57BL/6 mouse injected 12 hours earlier with *Escherichia coli* endotoxin (20 mg/kg). Stimulation and staining were conducted as described in A. Sarcolemmal damage, indicated by *yellow staining*, was increased by endotoxin. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48. Photomicrographs provided by Dr. Sabah N. Hussain, Royal Victoria Hospital, Montreal, QC, Canada.)

inducer (hemin) of heme oxygenase activity, respectively, enhances or reduces the oxidative stress and contractile failure of the diaphragm in a rat model of sepsis.[113] In septic rats, decreased diaphragmatic contractility can also be improved by the administration of specific scavengers of superoxide ions, hydrogen peroxide, and hydroxyl radicals.[111]

According to some,[114,115] but not all, investigators,[70] sepsis is responsible for the development of severe diaphragm weakness in critically ill mechanically ventilated patients. In one study, septic patients had a transdiaphragmatic pressure (Pdi) of only 5.5 cm H_2O whereas nonseptic patients had a median twitch Pdi of 13.0 cm H_2O ($P < 0.001$). In a second study,[115] sepsis was an independent predictor of low twitch tracheal pressure (twitch Ptr) elicited by magnetic stimulation of the phrenic nerves, a surrogate for twitch Pdi (Fig. 39.14).[25,26] However, in a third study of 76 patients undergoing a first spontaneous breathing trial, diaphragmatic weakness was not associated with sepsis but was associated with longer ventilator duration, more frequent weaning failure, and higher mortality.[70] It remains unclear how to reconcile these contrasting reports.[116]

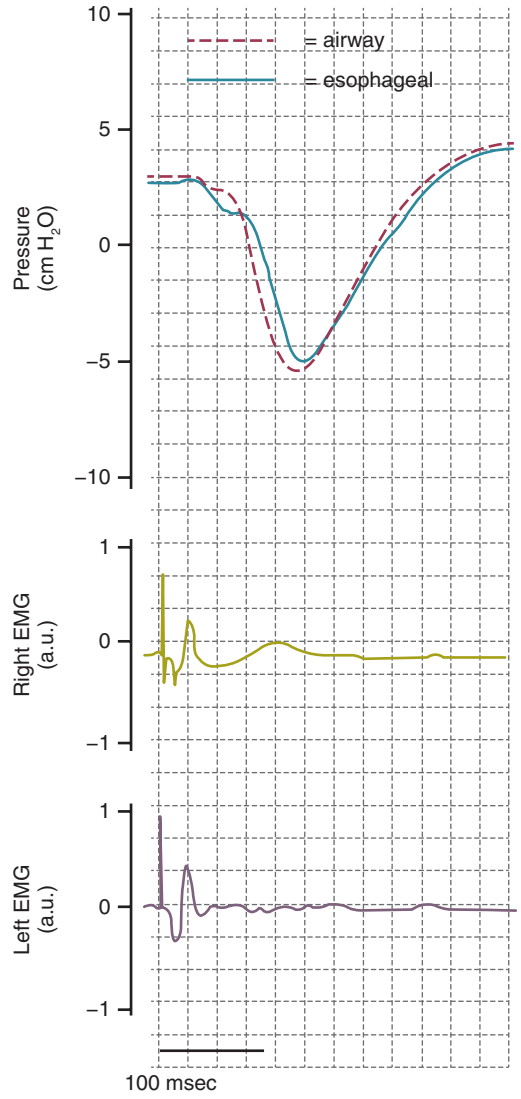
Agents that inhibit deleterious pathways (such as proteolytic pathways) and agents that alter upstream signaling pathways that improve muscle protein synthesis (e.g., mechanistic target of rapamycin [mTOR] activators, anti-myostatin receptor antibodies) are currently being tested in preclinical trials.[24] Clinically, however, aside from prevention and treatment of infections, there are no current available pharmacologic and nonpharmacologic strategies to minimize diaphragm weakness in ICU patients.

Intensive Care Unit–Acquired Paresis

While cared for in the ICU, critically ill patients can develop muscle weakness, reduced or absent deep tendon reflexes, and, occasionally, flaccid tetraparesis or tetraplegia.[117] Some of these patients have evidence for axonal degeneration and denervation atrophy (Fig. 39.15),[4] with nerve dysfunction (abnormal electrophysiologic studies) preceding structural abnormalities.[117] These constellation of findings are known as critical illness polyneuropathy (Table 39.1).[118] Cytokines[119] and low–molecular-weight neurotoxins[120] released during episodes of sepsis or when patients develop multiple organ failure are thought to be responsible for this axonal degeneration. Critical illness polyneuropathy has been considered one of the manifestations of multiple-organ failure syndrome.[117] Sepsis and multiple-organ failure, though, are not essential prerequisites for the development of critical illness polyneuropathy.[121,122] Tight control of hyperglycemia may reduce the risk of polyneuropathy and the duration of mechanical ventilation.[123]

In other patients, rather than axonopathy, there is evidence of isolated myopathy (i.e., critical illness myopathy).[4] Patients in whom isolated myopathy develops often have been treated with steroids and neuromuscular blocking agents (e.g., patients with status asthmaticus).[4] Muscle biopsies demonstrate a general decrease in myofibrillar protein content and a selective loss of thick filaments (myosin) within type I and type II fibers (Table 39.2 and Fig. 39.16). Animal models of critical illness myopathy suggest that medical denervation with paralytic agents cause an upregulation of glucocorticoid receptors in the muscle.[124] If the animal subsequently receives high-dose corticosteroids, it will develop depletion of thick myosin filaments.[124] Although a decrease in thick-filament proteins may be important for prolonged weakness,[125] this decrease is probably not the cause of the acute paralysis,[126] particularly in patients with compound motor action potentials of low amplitude.[127] Impaired muscle membrane excitability is probably more important during the acute stage.[126,128] An additional mechanism at play is an insufficient energy supply to the myocyte caused by insufficient translocation of the glucose transporter-4 (GLUT4) from the perinuclear spaces to the sarcolemma.[129] This, in turn, causes a decreased glucose availability in the cell. Failed activation of p-adenosine monophosphate–activated protein kinase (p-AMPK) is involved in these processes. Of interest, Weber-Carstens et al.[129] were able to prevent muscle-specific AMPK failure, restore GLUT4 disposition, and diminish protein breakdown in 5 critically ill patients by applying neuromuscular electrical stimulation to the quadriceps muscle for 12 consecutive days.

In the past few years it has become increasingly apparent that critical illness neuropathy and myopathy often coexist.[119,122,128,130–132] It has become common to refer to patients who become weak while in the ICU as a result of acquired neuropathy and/or myopathy (not associated with a known disorder) as simply having



• **Fig. 39.14** Airway pressures and electromyographic *(EMG)* signals of the right and left hemidiaphragm in an intubated patient. After phrenic nerve stimulation, muscle depolarization produces compound motor action potentials that are followed by the equivalent falls in airway pressure *(dashed line)* and esophageal pressure *(solid line). a.u.,* Arbitrary units. (From Laghi F, D'Alfonso N, Tobin MJ. A paper on the pace of recovery from diaphragmatic fatigue and its unexpected dividends. *Intensive Care Med.* 2014;40:1220–1226.)

ICU-acquired paresis.[128,130,132] In patients with ICU-acquired paresis duration of weaning from mechanical ventilation can be two to seven times longer than in patients without ICU-acquired paresis.[133]

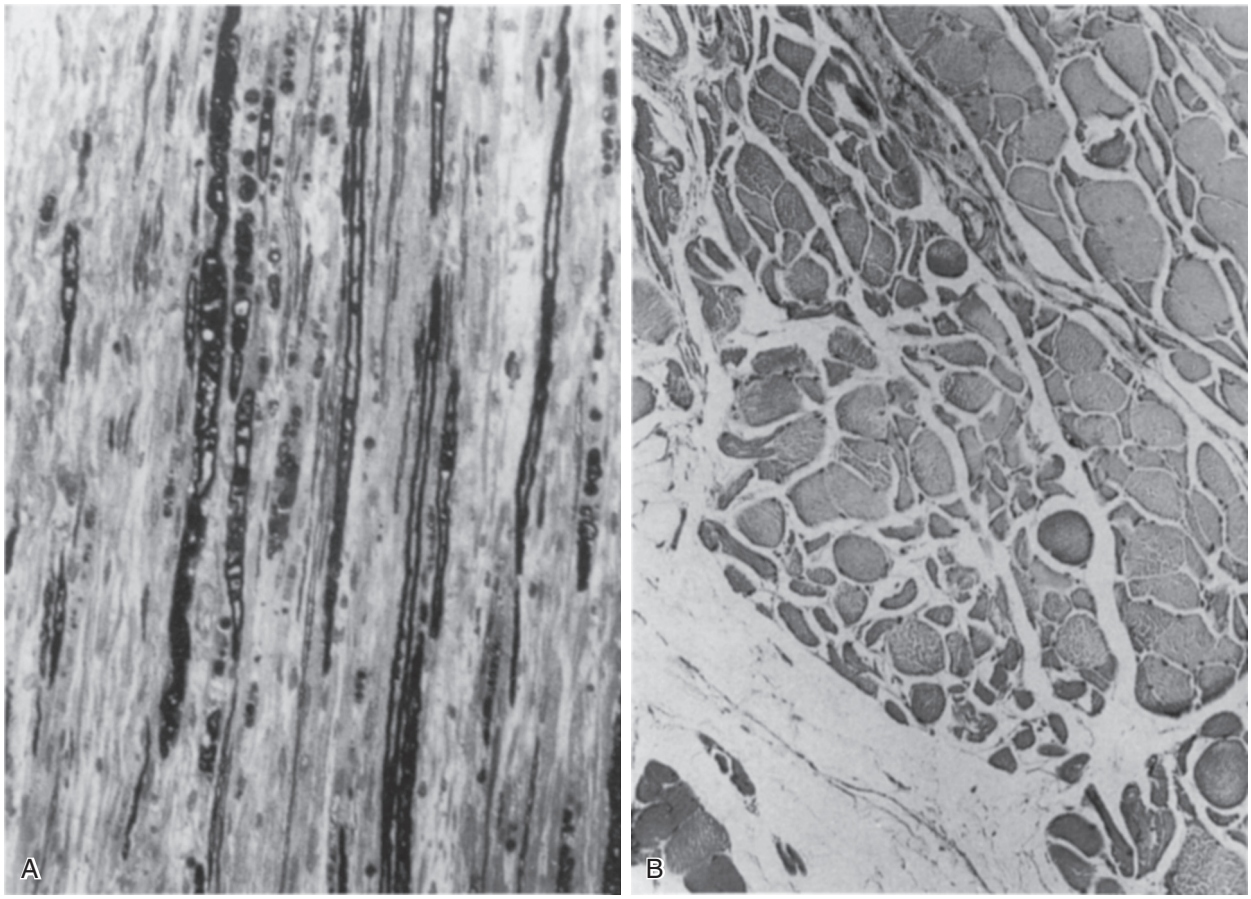
The functional outcome of ICU-acquired paresis is not uniform. Approximately 50% to 60% of patients experience complete recovery (ability to breathe spontaneously and to walk independently) over a period of 2 weeks to 6 months or longer.[125,133,134] About 30% experience severe persistent disability with tetraparesis, tetraplegia, or paraplegia.[133] Other investigators report even worse outcome: only 2 of 10 patients left the hospital in one study.[131] Whether it is possible to prevent ICU-acquired paresis in patients recovering from severe acute illness, and whether that would result in shorter duration of mechanical ventilation, remains unknown.

Acid-Base Disorders

Alkalosis, either metabolic or respiratory, does not affect skeletal muscle strength[135–137] and might improve endurance.[135] Whether acidosis, either metabolic or respiratory, impairs respiratory muscle function remains controversial. Because the contractile response to metabolic and respiratory acidosis is not necessarily the same,[138,139] metabolic acidosis and respiratory acidosis are separately discussed.

Metabolic Acidosis. Until recently, there was little doubt that metabolic acidosis could decrease muscle contractility.[140,141] Purported mechanisms included reduction of actin-myosin cross-bridge activation by hydrogen ion (H^+) competitive inhibition of calcium ion (Ca^{2+}) binding to troponin C, reduced transition of actin-myosin cross-bridges from low- to high-force state, inhibition of myofibrillar adenosine triphosphatase (ATPase), inhibition of glycolytic rate, inhibition of maximal shortening velocity, and inhibition of sarcoplasmic ATPase with reduction of sarcoplasmic Ca^{2+} reuptake, leading to reduced Ca^{2+} release from the sarcoplasmic reticulum.[142] Despite the biological plausibility, investigators have reported no effect[139,143] or marginal effect[144] of metabolic acidosis on respiratory muscle function. Yanos et al.[139] assessed maximal transdiaphragmatic pressure elicited by tetanic stimulation of the phrenic nerves in seven anesthetized dogs during respiratory acidosis (pH 7.1) and during lactic acidosis (pH 7.1). They observed a fall in maximal diaphragm strength with respiratory acidosis (−18%, $P < 0.05$), but not with lactic acidosis (+3%). Similarly, when Coast et al.[144] exposed isolated diaphragm strips of rats to different concentrations of lactic acid, they recorded decreases in force when the pH was lowered to 6.8—but only after the muscles strips were stressed with 75 contractions (25 Hz, 250-ms train duration, one train per second). Contractility was not affected when the pH was decreased to 6.8 to 7.2 at rest, and following the set of 75 contractions when delivered at a pH of 7.1 and 7.2.[144] These negative results are in line with some—but not all[145,146]—investigations questioning the inhibitory role of metabolic acidosis on limb muscle contractility at physiologic temperatures.[147–150] For instance, Nielsen et al.[150] reported that metabolic acidosis (pH 6.80) counteracts the detrimental effects of increased extracellular potassium ion (K^+) concentrations (which occurs with forceful contractions) on the excitability and force generation of the rat soleus muscle. In humans, Degroot et al.[148] measured intracellular H^+ concentration during sustained isometric foot plantar flexion. In contrast to what would be expected if acidosis caused decrease in contractility, Degroot et al.[148] reported a decrease in intracellular H^+ concentration during the first 10 seconds of exercise when force was declining and a rise in intracellular H^+ concentration immediately after exercise, when force partially recovered.[148] Whether severe metabolic acidosis in humans might impair skeletal function by causing a reduced central nervous system drive remains to be demonstrated.[140]

Acute Respiratory Acidosis. There are contrasting reports on the effect of acute respiratory acidosis on respiratory muscle contractility.[136,137,139,151] In anesthetized dogs, diaphragmatic contractility decreases pari passu with the severity of acute respiratory acidosis[136] (but has no effect on gastrocnemius muscle contractility).[139] Similarly, in healthy volunteers, acute increases of arterial carbon dioxide to 54 mm Hg (corresponding to a pH of about 7.29) reduces the capacity of the unfatigued diaphragm to generate pressure by 10% to 30% (Fig. 39.17).[137] Such reduction in pressure generation is even greater when arterial carbon dioxide is increased to 63 mm Hg (corresponding to a pH of about 7.22).[137] Acute respiratory acidosis can decrease respiratory muscle endurance[137,152]



• **Fig. 39.15** Transverse section of a peripheral motor nerve (deep peroneal nerve, A) and of a skeletal muscle (intercostal, B) in patients who developed profound weakness after a prolonged hospital course characterized by sepsis, multiple-organ failure syndrome, and inability to wean from mechanical ventilation. A, The long thin dark structures are myelin sheaths that contain axons. The axons are degenerating and dying; after death, they disintegrate. The myelin surrounding the disintegrating axons collapses around the axonal debris to form ovoids of myelin (seen better on the lateral portions of A). B, Amid muscle fibers that are normal in size and shape are atrophic ones that appear small and that have developed contours with acute angles. These findings are consistent with denervation atrophy secondary to axonal degeneration, so-called critical illness polyneuropathy. (From Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain.* 1987;110:819–841.)

and it can increase the extent of diaphragmatic fatigue at the conclusion of 2 minutes of maximal voluntary ventilation.[153] Despite greater voluntary activation of the diaphragm,[154] hypercapnic patients with COPD generate lower maximal static inspiratory pressures than patients with normocapnia.[155,156]

A direct inhibitory effect of acute respiratory acidosis[136,137,139,152,153] on respiratory muscle contractility and respiratory muscle endurance could provide a potential mechanism for the rapid clinical deterioration that can occur with severe asthma and during COPD exacerbations.[137] Yet, the human data suggesting a direct deleterious effect of acute respiratory acidosis on respiratory muscle function[137,152,153,155] are not uniform. Some investigators report no change in diaphragmatic contractility[151,153] (but decrease in force of the adductor pollicis)[151] when acute respiratory acidosis causes a decrease in pH to about 7.16 to 7.27,[151,157] no change in the maximum relaxation rate of the diaphragm,[157] and no effect in the extent of diaphragmatic fatigue 20 to 90 minutes after loading.[153]

For several reasons it is difficult to reconcile the conflicting data on the effects of acute respiratory acidosis on respiratory muscle contractility reported in the literature. First, the nonsignificant decrease in diaphragmatic contractility of 12% (twitch pressure) recorded during acute hypercapnia in 12 healthy subjects in one study[151] raises the possibility of type II error. Second, it is impossible to state that more severe acidosis was responsible for the different results in human investigations considering the comparable pHs of the studies with negative[151] and positive[137] findings. Third, it is unlikely that the different frequencies of stimulation used to assess the respiratory muscles[137,151,153] are responsible for the contrasting results because, when present, acidosis-associated decrease in contractility is frequency-independent.[136] Moreover, three additional considerations further cloud our understanding of any interaction (if present) between acute respiratory acidosis and respiratory muscle contractility. Respiratory acidosis (pH 6.50–6.88) may actually enhance and not depress skeletal muscle contractility.[150,158] It is unknown whether comorbidities, which often affect hypercapnic patients such as sepsis, decreased cardiac function, and impaired respiratory mechanics, could act synergistically with acute hypercapnia in worsening respiratory muscle function. Finally, it is unknown whether equivalent levels of pH occurring as a result of acute or

TABLE 39.1 Electromyographic Findings in Respiratory Muscle Weakness

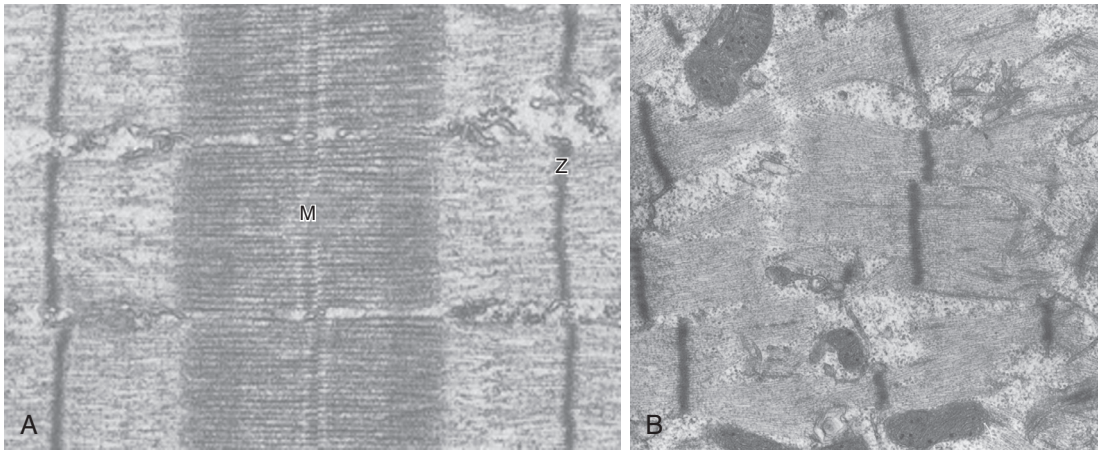
Electromyographic Feature	Axonal Injury	Myelin Injury	Neuromuscular Conduction Defect	Myopathy
Compound muscle action potential (amplitude)[a]	Reduced	Normal to slightly reduced	Normal[b]	Normal
Sensory nerve action potential (amplitude)[c]	Reduced	Normal to reduced	Normal	Normal
Conduction velocity	Normal to slightly reduced	Reduced	Normal	Normal
Spontaneous muscle depolarization[d]	Present	Absent	Absent	None to present
Amplitude of compound muscle action potential with stimulation at 3 Hz[e]	Unchanged	Unchanged	Decreased	Unchanged
Motor unit activation	Decreased	Decreased	Normal	Increased

Examples of injuries and deficits: *axonal injury,* critical illness myopathy; *myasthenia,* prolonged neuromuscular blockade; *myelin injury,* Guillain-Barré; *myopathy,* critical illness myopathy; *neuromuscular conduction defect,* myasthenia, prolonged neuromuscular blockade.
[a]Elicited by motor nerve stimulation.
[b]Decreased in the Lambert-Eaton syndrome.
[c]Elicited by sensory nerve stimulation.
[d]Spontaneous muscle depolarization (caused by denervation) is detected by presence of fibrillation potentials and positive sharp waves.
[e]Repetitive nerve stimulation is performed to exclude neuromuscular transmission defects such as prolonged neuromuscular paralysis.
Although features of myopathy can be recorded by electromyographic studies, electromyography cannot always distinguish critical illness myopathy from critical illness polyneuropathy, and muscle biopsies may be needed.
From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48.

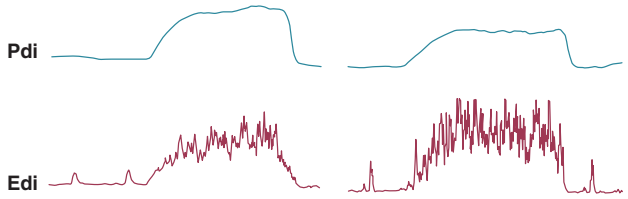
TABLE 39.2 Characteristics of Types of Muscle Fibers

Characteristic	Type I	Type IIa	Type IIx	Type IIb
Contractile Properties				
Velocity of shortening	+	++	+++	++++
Tetanic force	+	+	++	++
Endurance	++++	+++	++	+
Work efficiency[a]	+++	++	++	+
Histochemistry				
Mitochondrial volume density	+++	+++	++	+
ATP consumption rate	+	++	+++	++++
Oxidative enzymes	+++	+++	++	+
Glycolytic enzymes	+	++	+++	++++
Glycogen	+	++	++	+++
Capillary supply	+++	+++	++	+
Diameter	+	++	++	+++

[a]Amount of work performed per unit of ATP consumed.
A single myosin heavy chain isoform is typically expressed within an adult skeletal muscle fiber. Fibers classified as type I, IIa, IIx, and IIb express myosin heavy chain isoforms I (or slow), IIa, IIx, and IIb, respectively. Type IIx fibers have been reported in peripheral muscles of humans and animals and in the diaphragm of animals. Type IIx fibers have not been reported in the human diaphragm. More than one myosin heavy chain isoform is expressed in a few fibers (about 14% of adult rat diaphragm coexpresses myosin heavy chain isoforms IIb and IIx, and less than 1% coexpresses myosin heavy chain isoforms I and IIa).[244] Although the velocity of muscle contraction depends primarily on the myosin heavy chain isoform, the velocity of muscle relaxation is mainly determined by troponin C calcium binding and release and by calcium reuptake by the sarco-endoplasmic reticulum calcium-adenosine triphosphatase (SERCA). Several SERCA isoenzymes have been identified. SERCA 1 is expressed in type II fibers (fast calcium reuptake), and SERCA 2a is expressed in Type I (slow calcium reuptake).[245] The density of pumping sites largely accounts for different rates of calcium uptake in fast- and slow-twitch muscle fibers.[245] Despite this separation of tasks, velocity of contraction and velocity of relaxation tend to parallel each other. Type II fibers contract and relax with a greater velocity than type I fibers. Slower velocity of relaxation allows fusion of repetitive twitches at lower frequencies of stimulation as compared with fast relaxations. Impairment of SERCA activity has been implicated in the development of fatigue and in disease states including heart failure and corticosteroid myopathy.
ATP, Adenosine triphosphate.
From Laghi F, Tobin MJ Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48.



• **Fig. 39.16** Electron micrographs of normal skeletal muscle (A) and skeletal muscle from a patient who received steroids and the neuromuscular blocking agent vecuronium during a hospitalization with status asthmaticus followed by flaccid quadriplegia (B). Compared with the normal structure, the patient developed extensive loss of thick (myosin) myofilaments and relative preservation of thin (actin) filaments. Muscle strength returned to normal 2 months after discontinuation of vecuronium. *M,* M-line formed by myosin filaments and M-line proteins; *Z,* Z-disk formed by a lattice of filaments that join the actin filaments of one sarcomere with the actin filaments of the adjacent sarcomere. (From Eisenberg BR. Can electron microscopy distinguish fiber types? In: Bradley WG, Gardner-Medwin D, Walton JN, eds. *Recent Advances in Myology*. Amsterdam: Excerpta Medica; 1975;316–321; and Danon MJ, Carpenter S. Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. *Muscle Nerve* 1991;14:1131–1139.)



• **Fig. 39.17** Transdiaphragmatic pressure *(Pdi)* and electrical activity of the diaphragm *(Edi)* during a voluntary isometric contraction in a healthy subject during normocapnia *(left panel)* and during acute hypercapnia (end-tidal CO_2, 7.5%, *right panel*). For a given Edi during hypercapnia, the pressure output of the diaphragm was decreased. (From Juan G, Calverley P, Talamo C, et al. Effect of carbon dioxide on diaphragmatic function in human beings. *N Engl J Med.* 1984;310:874–879.)

acute-on-chronic respiratory acidosis may—or may not—have the same effect on respiratory muscle function.

Electrolyte Disturbances

Respiratory muscle function may be impaired by decreased levels of phosphate,[159] calcium,[160] magnesium,[161] and potassium.[162] Aubier et al.[159] studied the effects of severe hypophosphatemia (0.55 ± 0.18 mmol/L) on twitch Pdi in eight patients with acute respiratory failure who were mechanically ventilated. Correction of hypophosphatemia was accompanied by a significant increase in twitch Pdi—from 9.8 ± 3.8 cm H_2O before phosphate infusion to 17.3 ± 6.5 cm H_2O after phosphate infusion ($P < 0.001$). Changes in serum phosphorus concentration and changes in twitch Pdi were well correlated ($r = 0.73$). These results strongly suggest that hypophosphatemia can impair the contractile properties of the diaphragm during acute respiratory failure.

The same investigators assessed the effects of hypocalcemia on diaphragmatic function in 12 anesthetized dogs.[160] A continuous infusion of the chelating agent ethylene glycol-bis (B aminoethylether)-*N,N′*-tetraacetic acid (EGTA) was used to produce hypocalcemia. Over the 2 hours of observation, a progressive reduction in diaphragmatic force production paralleled the progressive reduction in ionized serum calcium.

Hypomagnesemia, a common occurrence in the ICU, can also cause respiratory muscle weakness. Dhingra et al.[161] reported improvements in maximal inspiratory and expiratory pressures in 17 hypomagnesemic patients after magnesium replacement therapy but not after placebo therapy.

Severe hypokalemia can be caused by several disorders, including posthypercapnic alkalosis,[163] renal tubular acidosis, primary hyperaldosteronism, gastrointestinal potassium losses, use of diuretics, thyrotoxic periodic paralysis, familial hypokalemic paralysis, β_2-adrenergic agonists, and licorice ingestion.[13] When the serum potassium concentration decreases below 2.0 to 2.5 mEq/L, patients may develop muscular weakness (including respiratory muscle weakness) and arrhythmias. Hypokalemia-associated respiratory muscle weakness can result in respiratory failure and death.[162,163]

Decreased Oxygen Delivery

Laboratory animals with cardiogenic shock[164] or with septic shock[93,165] die of respiratory failure. Death is not caused by pulmonary disease per se but by an inability of the respiratory muscles to maintain adequate ventilation. This inability to maintain adequate ventilation is caused by insufficient oxygen delivery to the respiratory muscles.[4]

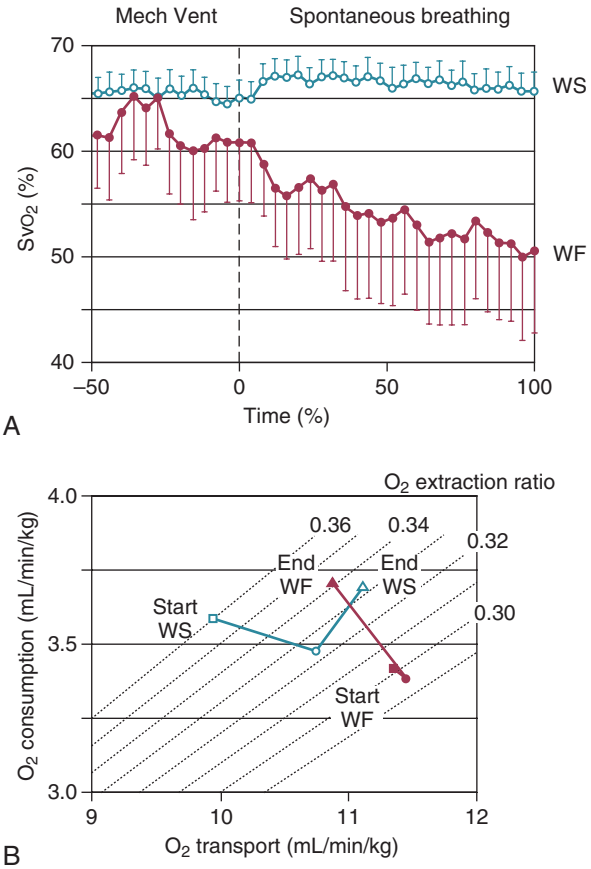
Whether the decrease in oxygen delivery to the respiratory muscles—or the respiratory centers—during shock is sufficient to decrease respiratory muscle performance and cause hypoventilation in patients, although likely,[166] remains to be determined. A nonrandomized study by Kontoyannis et al.[167] in 28 patients with cardiogenic shock supports the view that hemodynamic instability

could decrease respiratory muscle performance in patients with shock. Compared with nonventilated patients, ventilated patients were weaned from an intraaortic balloon pump more often, and their survival was greater.[167] These results are in line with the observation of Viires et al.,[168] who reported decreased metabolic requirements of the diaphragm after institution of mechanical ventilation in dogs with cardiogenic shock.

Hemodynamic situations less extreme than shock, which could still affect respiratory muscle performance, are failed attempts of spontaneous respiration during weaning from mechanical ventilation. Jubran et al.[169] investigated the importance of hemodynamic performance in determining weaning outcome in 8 ventilator-supported patients with a failed trial of spontaneous breathing and 11 patients who tolerated a trial and were successfully extubated. Immediately before the trial, mixed oxygen venous saturation was not different between the two groups. Mixed venous oxygen saturation progressively decreased over the course of the trial in the failure group, whereas it remained unchanged in the success group (Fig. 39.18A). Although the calculated oxygen demand was similar in the two groups, the manner in which it was met differed. In the success group, oxygen transport increased, mainly resulting from an increase in cardiac index; in the failure group, the increase in demand was met by an increase in oxygen extraction, resulting in a decrease in mixed venous oxygen saturation (see Fig. 39.18B). Although increased, the oxygen extraction ratio at the end of the trial in the failure group was close to the ratio reported to signify the onset of anaerobic metabolism (0.60)[170] in only two patients who had ratios of 0.50 and 0.56, respectively.

The ability of the failure group to deal with respiratory muscle energy demands through aerobic pathways is probably related to the capacity of the diaphragm to achieve higher blood flow than most other skeletal muscles.[171] During loading, the diaphragm rapidly increases oxygen extraction to a plateau of about 55% to 65%; further increases in oxygen demand are achieved by increases in blood flow.[172,173] The diaphragmatic musculature appears to be extremely resistant to hypoxic stress, and animals can maintain a ventilation that is sufficient to avoid hypercapnia until phrenic vein partial pressure of oxygen (P_{O_2}) falls to 12 mm Hg.[171] Likewise, investigators have found that an oxygen tension of about 10 mm Hg in the phrenic vein is the threshold associated with the onset of diaphragmatic lactate production[174] and the development of fatigue.[175] The lowest mixed venous oxygen tension recorded by Jubran et al.[169] was 26 mm Hg, which is above the threshold for onset of diaphragmatic lactate production. This association needs to be interpreted with caution, however, because mixed venous blood contains effluents from many tissue beds other than the diaphragm. The investigation of Jubran et al.[169] is the first documentation that when challenged by an increase in mechanical load,[15] the respiratory muscles of critically ill patients do not appear to switch from aerobic to anaerobic metabolism.

High variability in hemodynamic response during failure to wean has been reported by Zakynthinos et al.[18] Similar to Jubran et al.,[169] Zakynthinos et al.[18] recorded a decrease in mixed venous oxygen saturation and an increase in oxygen consumption (met mainly by an increase in oxygen extraction) in 9 of 18 patients in whom weaning failed. In the remaining 9 failures, however, mixed venous oxygen saturation and oxygen consumption were not affected by the weaning trial. It is unclear whether the absent interaction between weaning failure and oxygen consumption was due to depression of the respiratory centers, limited capacity to extract oxygen, or limited cardiac reserve.[176]



• **Fig. 39.18** A, Mixed venous oxygen saturation *(S_{VO_2})* during mechanical ventilation and a trial of spontaneous breathing in patients who were weaned successfully (*WS, open symbols*) and in 8 patients in whom weaning failed (*WF, solid symbols*). During mechanical ventilation, S_{VO_2} was similar in the two groups ($P = 0.28$). Between the onset *(dashed line)* and the end of the trial, S_{VO_2} decreased in the failure group ($P < 0.01$), whereas it remained unchanged in the success group ($P = 0.48$). Over the course of the trial, S_{VO_2} was lower in the failure group than in the success group ($P < 0.02$). The bars indicate the standard error. *B,* Oxygen transport, oxygen consumption, and isopleths of oxygen extraction ratio in the success (WS, *open symbols*) and failure (WF, *closed symbols*) groups during mechanical ventilation *(squares)* and at the onset *(circles)* and end *(triangles)* of a spontaneous breathing trial. See text for details. (Modified from Jubran A, Marthu M, Dries E, et al. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. *Am J Respir Crit Care Med.* 1998;158:1763–1769.)

Medications

Weakness can result from medications that have a direct myotoxic effect, such as uncoupling of the oxidative phosphorylation by propofol,[177] blockade of myocyte glycoprotein synthesis, and blockade of the electron transport by inhibitors of the hydroxy-methylglutaryl coenzyme A reductase or nucleoside analogs used in patients with human immunodeficiency virus,[178–181] and purported sarcolemma pore formation by daptomycin, the cyclic lipopeptide with bactericidal activity against gram-positive bacteria.[177] Weakness can also result with neuromuscular blocking agents and aminoglycosides, which interfere with neuromuscular transmission.[182,183]

Paralysis, including the respiratory muscles, can persist after discontinuation of neuromuscular blocking agents.[183–185] Prolonged neuromuscular blockade has been defined as 2,[183] 4,[185] or 6 hours[184]

of paralysis after discontinuation of neuromuscular blocking agents. Prolonged blockade is estimated to occur in 12% to 44% of patients receiving pancuronium or vecuronium for one or more days.[183–185] The risk with vecuronium is increased in patients with renal failure.[183,185] Accumulation of metabolites of the neuromuscular blocking agents is responsible for the prolonged blockade.[183] Recovery from prolonged neuromuscular blockade begins within 2 days of the last dose,[183,184] and this contrasts with the prolonged course of critical illness myopathy or neuropathy.[125,134,186,187] Train-of-four monitoring of the dose of a neuromuscular blocking agent with a peripheral nerve stimulator may hasten recovery.[185]

Acquired Diaphragm Weakness in Critically Ill Patients and Clinical Outcomes

Increasing experimental evidence suggests that, in critically ill patients, acquired diaphragm weakness is associated with excess morbidity and mortality.[70,114,115,188] First, duration of mechanical ventilation is about 6 days for patients without diaphragmatic weakness (twitch Pdi > 10 cm H_2O) and nearly 2 weeks for patients with diaphragmatic weakness (twitch Pdi < 10 H_2O; $P < 0.02$).[114] Second, in the same study, mortality was less than 10% for patients without weakness and it was nearly 50% for patients with diaphragmatic weakness ($P = 0.022$).[114] Third, in mechanically ventilated patients, diaphragm weakness was a far stronger predictor of ICU mortality than comorbidity index, extent of organ failure (including severity of lung functional abnormalities), age, gender, and steroid use.[189] Whether diaphragmatic weakness is a marker of disease severity or is causally related to worse outcomes in critically ill patients remains to be determined.[116]

Limitations in the Current Classification of Respiratory Muscle Weakness

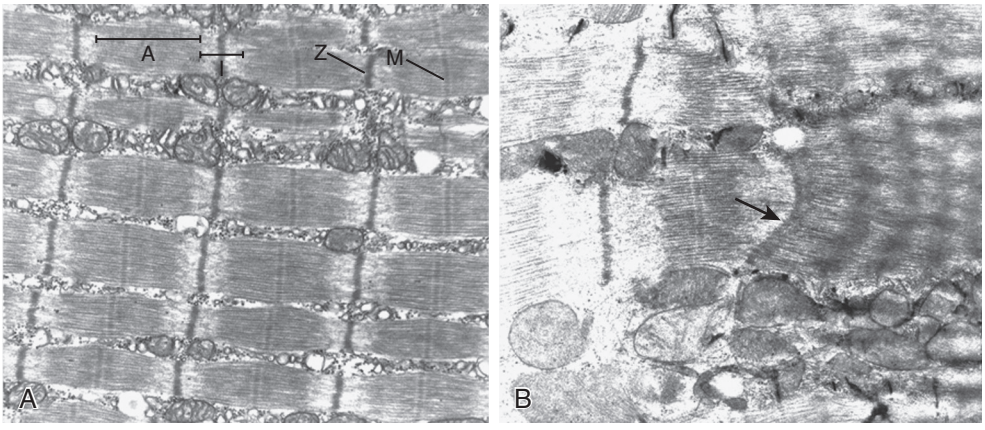
When one is studying respiratory muscle weakness leading to hypoventilation in critically ill patients, it is necessary to bear in mind the current limited understanding of the conditions, as follows:

1. The distinction between preexisting conditions and new-onset conditions can be arbitrary.
2. Conditions that are preexisting (malnutrition and hyperinflation) can worsen during the course of an unrelated critical illness.
3. The nosology is often unsatisfactory—see the nebulous distinction between ICU-acquired paresis and sepsis-associated myopathy or between ICU-acquired paresis and ventilator-associated respiratory muscle dysfunction.
4. Conditions in which respiratory muscle weakness is associated with muscle damage can also display some degree of muscle atrophy—see diaphragmatic atrophy in cases of ventilator-associated respiratory muscle dysfunction.
5. Laboratory specificity to differentiate the different conditions causing weakness in the ICU is limited.
6. In any given patient more than one mechanism may be responsible for respiratory muscle weakness.
7. Respiratory muscle weakness can be combined with depressed drive—for example, in the setting of hypercapnia-induced hypoventilation.

Respiratory Muscle Fatigue

Contractile fatigue occurs when a sufficiently large respiratory load is applied over a sufficiently long period.[20,190–198] Contractile fatigue can be brief or prolonged. Short-lasting fatigue results from accumulation of inorganic phosphate,[149,199,200] failure of the membrane electrical potential to propagate beyond T tubules,[201] and to a much lesser extent intramuscular acidosis.[202–204] Short-lasting fatigue appears to have a protective function, because it can prevent injury to the sarcolemma caused by forceful muscle contractions.[205] Long-lasting fatigue[191] is consistent with the development of, and recovery from, muscle injury (Fig. 39.19).[205,206]

Whether short-lasting or long-lasting contractile fatigue of the respiratory muscles develops in critically ill patients is not clear. Patients who fail a trial of weaning from mechanical ventilation are at particular risk of developing fatigue because they experience marked increases in respiratory load.[14,15,36] The addition of a new injury to the respiratory muscles (secondary to the development of contractile fatigue) might be the ultimate determinant of whether

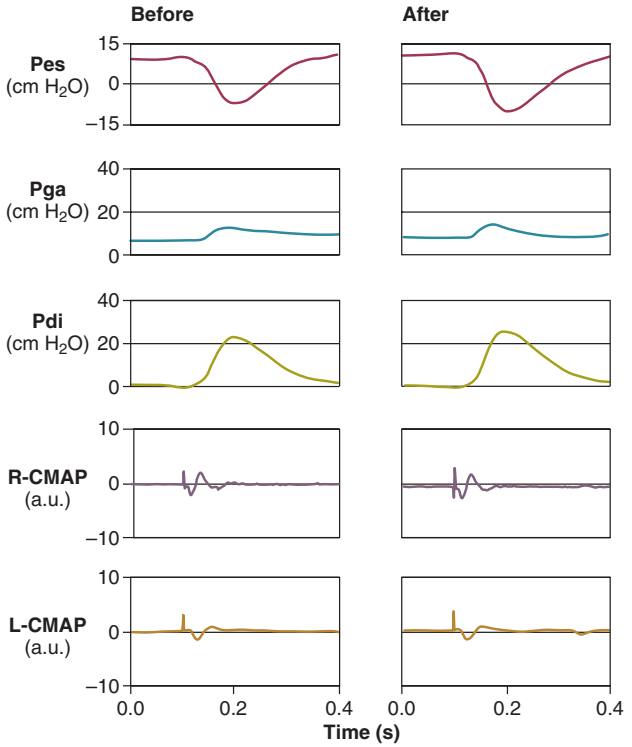


• **Fig. 39.19** Electron micrographs of longitudinal sections from the costal diaphragm of a healthy control hamster (A) and a hamster exposed to 6 days of resistive loading (B). A shows normal sarcomeres with distinct A-bands, I-bands, Z-bands, and M-lines that are aligned between adjacent myofibrils. B shows load-induced damage recognizable by Z-band streaming *(arrow)* and disruption of sarcomeric structure *(right section of B)* with loss of distinct A-bands and I-bands. Z-band streaming is attributed to a loss of cytoskeletal protein elements such as desmin, α-actinin, and vimentin. Magnification for both micrographs: ×16,500. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48. Electron micrographs provided by Drs. David C. Walker and Darlene W. Reid, University of British Columbia, Vancouver, BC, Canada.)

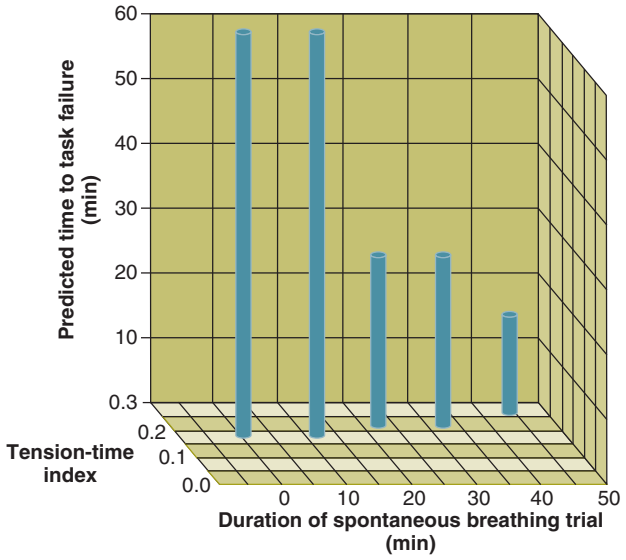
or not some patients ever achieve successful weaning. Circumstantial evidence of contractile fatigue in patients experiencing respiratory distress has been reported.[15,207–209] Because of technical limitations,[207–209] these early data did not provide proof of contractile fatigue.[13,19]

The most direct method for detecting fatigue in patients is to measure twitch Pdi over time (see Fig. 39.3).[20,191] When this technique is used in critically ill patients, it is especially challenging to ensure that successive stimulations are all generated at the same end-expiratory lung volume, that a constant degree of neural depolarization by the stimulator is achieved and that twitch potentiation (the transient increase in pressure that occurs with a recent forceful contraction) does not occur.[20,191] Controlling for these factors, Laghi et al.[17] studied 11 patients in whom weaning failed and 8 patients with weaning success before and after a T-tube trial. Twitch Pdi was 8.9 ± 2.2 H_2O before and 9.4 ± 2.4 H_2O after the trial in the weaning-failure group (Fig. 39.20). The respective values in the weaning-success group were 10.3 ± 1.5 and 11.2 ± 1.8 cm H_2O. Not a single patient developed a decrease in twitch Pdi. The absence of fatigue was surprising because seven of the nine patients in whom weaning failed had a tension-time index (the product of two fractions: [mean pressure per breath/maximum transdiaphragmatic pressure] × [inspiratory time/total time of respiratory cycle]) above the threshold reported to lead to task failure and fatigue (0.15).[210]

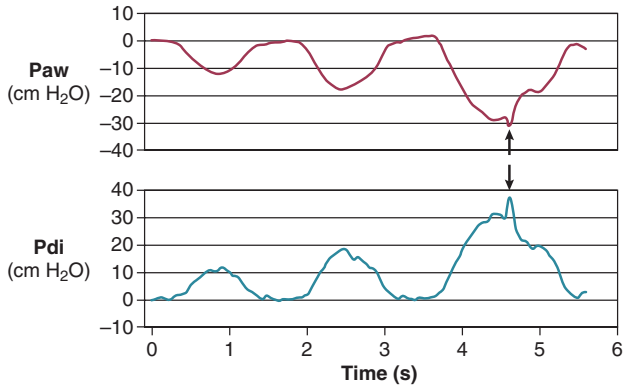
One of the most likely reasons patients did not develop fatigue is because physicians reinstituted mechanical ventilation before there was enough time for its development. The relationship between tension-time index and the length of time that a load can be sustained until task failure follows an inverse-power function. Bellemare and Grassino[210] expressed the relationship as time to task failure = 0.1 (tension-time index)$^{-3.6}$. The increase in the tension-time index over the course of the weaning trial[17] and predicted time to task failure[210] are shown in Fig. 39.21. At the point that the physician reinstituted mechanical ventilation, patients were predicted to be an average of 13 minutes away from task failure. Moreover, the time to task failure was underestimated because diaphragmatic recruitment during maximal voluntary contractions was incomplete (Fig. 39.22).[17] In other words, patients display clinical manifestations of severe respiratory distress for a substantial time before they would develop fatigue. In an intensive care setting, these clinical signs lead attendants to reinstitute mechanical ventilation before fatigue has time to develop. Other factors that might have protected the respiratory muscles from contractile fatigue include development of dynamic hyperinflation (susceptibility to fatigue is greater when fatiguing protocols are conducted at optimum muscle length rather than when a muscle is shortened)[211] and activation of extradiaphragmatic muscles of respiration.[212]



• **Fig. 39.20** Esophageal pressure *(Pes)*, gastric pressure *(Pga)*, transdiaphragmatic pressure *(Pdi)*, and compound motor action potentials *(CMAPs)* of the right and left hemidiaphragms after phrenic nerve stimulation before *(left)* and after *(right)* a failed trial of weaning. The end-expiratory value of Pes and the amplitude of the right and left CMAPs were the same before and after the trial, indicating that the stimulations were delivered at the same lung volume and that the stimulations achieved the same extent of diaphragmatic recruitment. The amplitude of twitch Pdi elicited by phrenic nerve stimulation was the same before and after weaning. *a.u.,* Arbitrary units. (From Laghi F, Cattapan SE, Jubran A, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? *Am J Respir Crit Care Med.* 2003;167:120–127.)



• **Fig. 39.21** The interrelationship between the duration of a spontaneous breathing trial, tension-time index of the diaphragm, and predicted time to task failure in nine patients who failed a trial of weaning from mechanical ventilation. The patients breathed spontaneously for an average of 44 minutes before a physician terminated the trial. At the start of the trial, tension-time index was 0.17, and the formula of Bellemare and Grassino[210] (see text for details) predicted that patients could sustain spontaneous breathing for another 59 minutes before developing task failure. As the trial progressed, tension-time index increased and predicted time to the development of task failure decreased. At the end of the trial, tension-time index reached 0.26; that patients were predicted to sustain spontaneous breathing for another 13 minutes before developing task failure clarifies why patients did not develop a decrease in diaphragmatic twitch pressure. In other words, physicians interrupted the trial based on clinical manifestations of respiratory distress before patients had sufficient time to develop contractile fatigue. (From Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48.)



• **Fig. 39.22** Continuous recordings of airway pressure *(Paw)* and transdiaphragmatic pressure *(Pdi)* during airway occlusion in a patient with chronic obstructive pulmonary disease after an unsuccessful trial of spontaneous breathing. Phrenic nerve stimulation *(arrow)* during the maximal inspiratory effort resulted in a detectable superimposed twitch. That a twitch could be superimposed during the maximal effort indicates that diaphragmatic activation was incomplete.

Studies in animals[202,213–215] support the finding that patients do not develop long-lasting contractile fatigue of the respiratory muscles. Inspiratory loading in animals causes respiratory failure and acidosis before force output decreases or substrate is depleted in the diaphragm,[202,213–215] suggesting that central[216] and reflex mechanisms[217,218] affect the breathing pattern[203] and α-motoneuron firing rates[219] in response to loading. Two neural pathways may convey information from the respiratory muscles to the central nervous system.[220,221] One pathway transmits information from mechanoreceptors (Golgi tendon organs and muscle spindles)[217,222] in the dorsal column, relaying it to the brainstem and thalamus, before reaching the sensorimotor cortex.[223] This pathway may participate in proprioceptive control of the respiratory muscles, integrating movements originating in the motor cortex.[216] The second pathway consists of vagal[215,222] and possibly phrenic nerve afferents (group IV phrenic afferent fibers)[217] that reach the amygdala after relaying in the brainstem and then projecting to the mesocortex (cingulated gyrus).[222] This pathway may deal with respiratory nociception,[216,224] such as dyspnea (through the relay in the amygdala),[225] and with the ventilatory response to carbon dioxide (through the relay in the brainstem, ventral cerebellum, and limbic system).[216,224,226] In addition to these two pathways projecting to the central nervous system, there is evidence for the existence of a spinal pathway responsible for phrenic-to-phrenic reflex inhibition.[218] An increase in carbon dioxide during loading may also protect the respiratory muscles by decreasing reactive oxygen species production.[227]

In healthy subjects, inspiratory threshold loading to the point of task failure causes hypercapnia without necessarily affecting diaphragmatic force output.[228] Similarly, resistive breathing causes hypercapnia without affecting diaphragmatic force output or aerobic metabolism (assessed by phosphorus 31–nuclear magnetic resonance spectroscopy) in spontaneously breathing piglets.[15,203,229] The hypoxia combined with resistive breathing caused a decrease in diaphragmatic force and inadequate oxidative metabolism, as reflected by accumulation of inorganic phosphorus and decreased phosphocreatine.[203] Force output and oxidative metabolism returned to baseline values with normoxia despite persistent loading.[203] The investigators speculated that loading produces a decrease in central activation (to the point of ventilatory failure), which decreases metabolic demands and prevents peripheral fatigue; additional stress of hypoxia may overwhelm this defense mechanism and cause peripheral fatigue.[203] Hypoxemia can also induce degradation of myofibrillar proteins.[230]

Hypoxia impairs the respiratory centers at a higher oxygen tension than it impairs the respiratory muscles,[175,231] making it difficult to decipher the effects of hypoxemia on the respiratory muscles. Animals develop severe alveolar hypoventilation and respiratory arrest before the tension-generating ability of the diaphragm has begun to decrease.[175,231] As previously stated, in patients with shock[166] it is unknown whether decreases in oxygen delivery to the respiratory muscles[169,232] or respiratory centers can be sufficient to cause hypoventilation.

Increased Load

Increased respiratory load can result from increased mechanical load and/or increased ventilatory requirements.

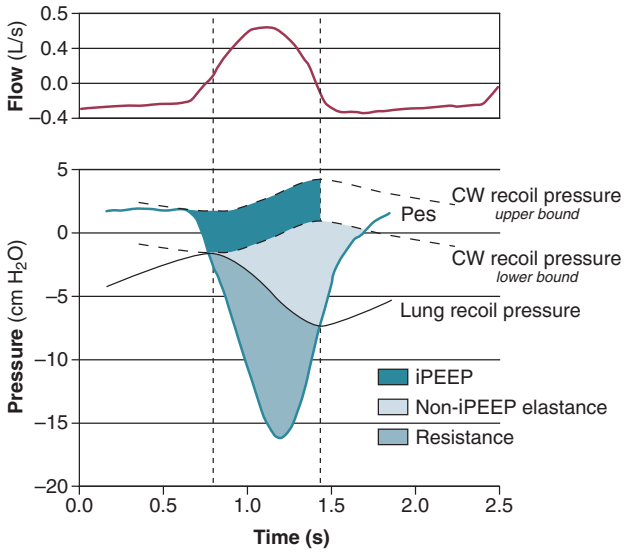
Increased Mechanical Load

Patients in acute respiratory failure usually experience an increased mechanical load.[†] The patients typically have a 30% to 50% greater inspiratory resistance,[15,17,36] 100% greater dynamic elastance,[14,15] and 100% to 200% greater intrinsic positive end-expiratory pressure (PEEP)[14,15,17] than do similar patients who are not in acute respiratory failure. Inspiratory effort—quantified by calculation of the *pressure time product* of the inspiratory muscles—is almost equally divided in offsetting intrinsic PEEP, elastic recoil, and inspiratory resistance (Fig. 39.23).[15,229] Abnormal mechanics arise from bronchoconstriction, bronchial edema, pulmonary edema,[15] and lung inflammation.[233,234] Rapid shallow breathing can aggravate the abnormalities in lung elastance, intrinsic PEEP, and carbon dioxide clearance.[15,36] Expiratory muscle recruitment can also increase intrinsic PEEP and breathing effort.[236] In some patients, increased mechanical load results from upper airway obstruction. The upper airway, which encompasses the passage between the nares and carina, can be obstructed by functional or anatomic causes. Among the first are vocal cord paralysis and laryngospasm. Among the second are trauma, burn, infections, foreign bodies, and tumors. Functional and anatomic obstruction can occur postoperatively in patients with redundant pharyngeal soft tissue (sleep apnea) and loss of muscle tone related to postanesthetic state.[1] Upper airway obstruction is one of the most urgent and potentially lethal medical emergencies.[1] Complete airway obstruction lasting for as little as 4 to 6 minutes can cause irreversible brain damage.[1]

Increased Ventilatory Requirements

Increased ventilatory requirements can result from increased carbon dioxide production, increased dead-space ventilation, and elevated respiratory drive. Carbon dioxide production can increase as a result of sepsis,[93] fever, shivering, drugs (salicylates), lipogenesis,[237,238] and a shift in utilization of fuels from lipids (respiratory quotient [RQ] = 0.7) to carbohydrates (RQ = 1.0).[239] An increase in carbon dioxide production can be only a contributory factor and not a sole cause of hypercapnic respiratory failure.[3]

[†]See references 14, 15, 17, 36, 229, and 233–235.



• **Fig. 39.23** Quantification of inspiratory effort with pressure-time product (PTP) of the inspiratory muscles. Flow (inspiration upward) and pressure tracings during spontaneous breathing. Recoil pressures of the chest wall *(CW)* and lung are calculated from dynamic elastances of the chest wall and lung, respectively, and lung volume. Upper bound inspiratory PTP is calculated using the integral of the difference between esophageal pressure *(Pes)* and upper bound CW recoil pressure from the onset of the rapid decrease in Pes to the transition from inspiratory to expiratory flow. The component of PTP owing to intrinsic positive end-expiratory pressure *(iPEEP)* is computed using the integral of the difference between the upper and lower bound of CW recoil pressure from the onset of rapid decrease in Pes to the transition from inspiratory to expiratory flow. The component of PTP owing to non-iPEEP elastance is computed using the integral of the difference between lung recoil pressure and lower bound CW recoil pressure from the onset of inspiratory flow to the moment of transition from inspiratory to expiratory flow. The resistive fraction of PTP is computed using the integral of the difference between Pes and lung recoil pressure. The *vertical interrupted lines* represent points for zero flow. (From Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1997;155;906–915.)

The ratio of dead space to tidal volume is normally 0.30. The ratio increases up to 0.65 in patients with severe COPD,[240] acute respiratory distress syndrome,[241] and other severe lung diseases.[3] Patients can compensate for such an increase in dead space by doubling $\dot{V}E$.[3] Such an increase in $\dot{V}E$ poses a minor challenge when respiratory mechanics and respiratory muscles are normal; for example, hypercapnia is uncommon with pulmonary vascular disease.[3] Accordingly, an increase in dead-space ventilation should never be considered the primary mechanism responsible for hypercapnic respiratory failure unless there is a concurrent abnormality in the control of breathing, or in the mechanical load of the respiratory muscles or in their contractile performance.[3]

Stimulation of pulmonary irritant or J receptors, neurologic lesions, sepsis, and toxins can inappropriately increase respiratory drive. Whether an inappropriately heightened drive places sufficient stress on the respiratory muscle to cause respiratory muscle fatigue and, consequently, hypoventilation remains to be determined.

Hypercapnia-Induced Hypoventilation

Severe hypercapnia depresses the central nervous system and decreases respiratory motor output.[238] A viscous cycle can arise, whereby hypercapnia causes depressed drive leading to more hypercapnia.[242,243] The possibility of hypercapnia-induced hypoventilation is supported by reports of successful resolution of hypercapnic respiratory failure in some patients after short-term infusion of the respiratory stimulant, doxapram.[242,243]

Summary

A relative or absolute decrease in respiratory muscle output is responsible for alveolar hypoventilation and hypercapnic respiratory failure. The number of distinct clinical entities that result in hypercapnia is vast and often more than one disease process may coexist (e.g., hyperinflation-associated respiratory muscle weakness and ventilation-perfusion inequality in patients with COPD). The relative or absolute decrease in respiratory muscle output in patients with hypercapnia may stem from a decrease in respiratory drive, excess mechanical load on the respiratory muscles and respiratory muscle weakness (see Fig. 39.1). Whether respiratory muscle fatigue is responsible for hypercapnic respiratory failure is an important issue that has yet to be resolved.

Key Points

- Hypercapnia is synonymous with alveolar hypoventilation (for the patient's level of carbon dioxide production).
- A relative or absolute decrease in respiratory muscle output is responsible for alveolar hypoventilation.
- Isolated impairments in gas exchange usually do not cause hypercapnia.
- When gas exchange is impaired the magnitude of neuromuscular impairment or increased respiratory load conducive to hypercapnia can be less than the corresponding derangements when gas exchange is intact.
- Respiratory drive is elevated in many patients with acute ventilatory failure. This finding does not necessarily exclude the possibility that during episodes of ventilatory failure the central nervous system is not fully recruiting the respiratory muscles and may be contributing to carbon dioxide retention.
- In critically ill patients, respiratory muscle weakness is probably responsible for many cases of alveolar hypoventilation.
- Metabolic disturbances, such as hypophosphatemia, hypomagnesemia, hypokalemia, and hypocalcemia, can cause respiratory muscle weakness.

- Hyperinflation, typically described in patients with asthma and COPD, places the respiratory muscles in a mechanical disadvantage to generate the driving pressure of the respiratory system.
- Hyperinflation can occur during episodes of respiratory distress even in patients without a history of airway disease (e.g., pneumonia and chest trauma).
- The role of respiratory muscle fatigue in causing hypercapnic respiratory failure remains to be determined.
- Severe hypercapnia can in itself be conducive to alveolar hypoventilation by depressing respiratory drive.
- It is still unclear whether respiratory or metabolic acidosis has a clinically relevant direct effect on respiratory muscle contractility.

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Review Questions

1. A 73-year-old male presented to an outlying hospital after being found on the floor and drowsy at a rehabilitation facility where he was convalescing from uneventful bilateral cervical laminectomy at the C3 to C7 level. In the rehabilitation facility he was ambulating very little and was administered opiates as needed for postoperative back pain. Past medical history included chronic obstructive pulmonary disease (COPD), hypertension, and coronary artery disease requiring bypass surgery, biventricular implantable cardioverter defibrillator, and several lung nodules stable for more than a year.

On presentation to the outlying hospital the patient was reported to be drowsy but arousable and wearing a cervical collar. Periodic breathing with respiratory rate ranged from zero to 24 breaths/min. Remaining vital signs were normal and physical examination also was unremarkable. Oxygen saturatiion was 98% with 2 L/min oxygen administered by nasal cannula. Noteworthy laboratory results included creatinine of 1.85 mg/dL (baseline of 0.9 mg/dL), normal thyroid-stimulating hormone (TSH) concentration, and calcium of 10.8 mg/dL with an albumin of 2.5 gm/dL. A computed tomography (CT) scan of the head without contrast was unremarkable. CT scanning of the of chest without contrast demonstrated multiple stable pulmonary nodules, multiple vertebral lytic lesions, emphysematous changes, and an enlarged pulmonary artery suggestive of chronic pulmonary hypertension.

While at the outlying hospital, the patient has a right frontoparietal acute to subacute ischemic stroke. He is intubated for possible aspiration pneumonia and respiratory failure. He is then transferred to your tertiary center for further evaluation of his respiratory failure.

On arrival to the tertiary center, the patient is alert and awake, follows commands, and moves all four extremities despite mild weakness of the left arm and left leg. On days 2 and 3 of this latest hospital stay, he is disconnected from the ventilation and a T-piece trial is conducted, yet the trial of weaning fails within 10 minutes owing to respiratory distress with tachypnea and use of accessory muscles of respiration. Brain natriuretic peptide levels are normal and there are no signs of obstruction on ventilator mechanics. A repeat chest radiograph shows no infiltrates.

What is the best diagnostic test to perform at this time in evaluating the patient's respiratory failure?

a. Echocardiogram
b. Sniff test
c. Bilateral phrenic nerve electromyography (EMG)
d. Bronchoscopy and biopsy of lung nodules
e. Sural nerve biopsy

Answer: c. Paresis or paralysis of the phrenic nerves was suspected from the clinical presentation. EMG of bilateral phrenic nerves failed to elicit any appreciable motor response at the right and left hemidiaphragms and the same was confirmed with ultrasound of the diaphragm. This might be related to his prior cervical stenosis followed by surgical intervention. It has been hypothesized that patients undergoing cervical laminectomy may experience delayed-onset central apnea caused by interruption of the reticulospinal fibers innervating the phrenic nerve nuclei. Alternatively, the patient's prior coronary artery bypass grafting might have placed him in a compromised state with one phrenic nerve and the recent spine surgery affecting the other phrenic nerve. The multiple lytic vertebral lesions were attributed to multiple myeloma.

An echocardiogram (option a) might help, but brain natriuretic peptide levels are normal and the chest radiograph was negative for infiltrates. Sniff test (option b) might be useful in an outpatient setting to evaluate for an elevated hemidiaphragm but is impractical in an intubated patient. Biopsy of the lung nodules or sural nerve (options d and e) will not shed light on the mechanisms responsible for weaning failure.

2. A 64-year-old obese man is brought to the emergency department by his son for evaluation of altered mental status that has progressed over the past several weeks. The patient has a known history of moderate COPD, type 2 diabetes mellitus, and hypertension. He is a heavy smoker and has active alcohol use disorder. Home medications include lisinopril and glyburide. The patient's son denied that his father had any new rash, fevers, or sick contacts. Within the past few weeks the patient has been housebound, eating and sleeping in bed all day with little to no activity at all. The son thinks that his father has had no chest pain or dyspnea but was gaining weight.

On admission blood pressure was 160/84 mm Hg with a regular hear rate of 60 beats/min, respiratory rate of 10 to 12 breaths/min, oxygen saturation of 96% with 5 L/min of oxygen delivered by nasal cannula. Physical examinations shows an obese male, with a full face, arousable but falling asleep during the interview with no distress. His neck was thick and short with no jugular venous distension, no lymphadenopathy, or thyromegaly. Auscultation revealed distant breath sounds, no active wheezing, and regular heart sounds. Results of the abdominal examination were benign. A neurologic examination was nonfocal except for sluggish reflexes and delayed relaxation phase at the ankle.

Laboratory tests on admission revealed hyponatremia (130 mEq/L), bicarbonate 37 mEq/L, slight transaminitis, and normal bilirubin, international normalized ratio (INR), and ammonia levels. Lipid panel results were as follows: high-density lipoprotein cholesterol 45 mg/dL; low-density lipoprotein cholesterol 203 mg/dL; and triglycerides 356 mg/dL. Urine drug screen results were negative for opiates and benzodiazepines. Brain natriuretic peptide (BNP) levels were normal. Arterial blood gas on one liter oxygen by nasal cannula gas shows pH of 7.28, partial pressure of carbon dioxide (P_{CO_2}) of 80 mm Hg, and arterial partial pressure of oxygen (P_{aO_2}) of 50 mm Hg. Chest radiographic findings were positive for emphysematous changes, and the head CT was unremarkable.

I. What is the cause of hypoxemia in this patient?
- **a.** Alveolar hypoventilation
- **b.** Intracardiac shunt
- **c.** Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch caused by COPD
- **d.** Diffusion limitation as the result of occult interstitial lung disease

II. What testing is most likely to reveal the cause of respiratory failure in this patient?
- **a.** CT angiography to rule out pulmonary embolism
- **b.** Echocardiogram with bubble study for shunt
- **c.** Magnetic resonance imaging (MRI) of the brain to look for brainstem pathology
- **d.** TSH with free triiodothyronine (T_3) and thyroxine (T_4) levels, treat the patient while waiting for results
- **e.** There is no need to do further testing and patient should be intubated

Answers: I: a. The alveolar-arterial (A-a) oxygen gradient is normal. The other choices of shunt, $\dot{V}/\dot{Q}$ mismatch, and diffusion

limitation would result in an elevated A-a gradient and hence are incorrect answers.

II: d. There are several findings suggestive of hypothyroidism and one could argue that the patient is in myxedema coma, a medical emergency. Physical examination findings are key. This patient is not in acute respiratory distress and this is not a COPD exacerbation (option e is incorrect). Arterial blood gas and BNP results are reflective of chronic respiratory acidosis and normal A-a gradient reflecting possibly hypoventilation. Hyponatremia and lipid panel are supportive of hypothyroidism.

3. A 33-year-old woman in her second trimester of pregnancy and with no significant past medical history presented to the emergency department with a 1-month history of dyspnea and proximal limb muscles weakness. She denied any history of skin rash, nausea, vomiting, diarrhea, or recent vaccinations. Her neurologic examination results were normal except for reduced strength in both upper and lower extremities (Medical Research Council [MRC] score, 3 of 5 for the proximal muscles and 4 of 5 for the distal muscles). Reflexes, sensations, cranial nerves, and cerebellar function were intact. Laboratory tests demonstrated elevated serum creatine kinase (2500 U/L; normal value 29–168 U/L) and elevated erythrocyte sedimentation rate (85 mm/h; normal value 0–42 mm/h). Arterial blood gas on room air was suggestive of acute on chronic respiratory acidosis (pH 7.32, $PaCO_2$ 59 mm Hg, PaO_2 78 mm Hg, bicarbonate (HCO_{3-}) 29 mEq/L) for which noninvasive ventilation was started. Further workup excluded any pulmonary infection, pulmonary emboli, and cardiac dysfunction as the underlying cause of her symptoms. Continuous fetal monitoring and obstetrical ultrasound were unremarkable. In the following 24 hours, despite noninvasive ventilation, respiratory acidosis markedly worsened (pH 7.12 and $PaCO_2$ 105 mm Hg), leading to carbon dioxide narcosis. The patient was intubated and mechanically ventilated. With resolution of hypercapnia, her mentation normalized. The following day, maximal inspiratory pressure was recorded at −14 cm H_2O. In addition, bedside needle EMG revealed electrophysiologic evidence of diffuse irritable myopathy including increased insertional activity, spontaneous fibrillation potential, and positive sharp waves, myopathic motor unit potentials, and early recruitment. What is the best testing choice at this time in evaluating the patient's respiratory failure?

a. MRI of the thighs
b. Sural nerve biopsy
c. Deltoid or quadriceps muscle biopsy
d. Bilateral phrenic nerve EMG
e. Lumbar puncture

Answer: c. This patient presents with symmetric proximal muscle weakness, elevated serum muscle enzymes, elevated erythrocyte sedimentation rate, and EMG abnormalities suggestive of a myopathy. The clinical course suggests an acquired myopathy. A muscle biopsy is needed to characterize the myopathy. The lack of skin rash would point away from dermatomyositis. An autoaggressive inflammatory exudate invading nonnecrotic muscle fibers (as was the case in this patient) would indicate polymyositis. A necrotizing pathologic picture would suggest a necrotizing autoimmune myopathy.

MRI of the thighs (option a) might demonstrate muscle edema, yet this finding is insufficient to make any definitive diagnosis. Sural nerve biopsy (option b) and bilateral phrenic nerve EMG (option d) are unlikely to be contributory considering that EMG demonstrated no neuropathic findings. Lumbar puncture (option e) would be a useful test to make a diagnosis of Guillain-Barré syndrome—not uncommon during pregnancy. In this patient, despite the markedly elevated serum creatine kinase, the EMG findings make this an unlikely possibility.

4. A 58-year-old thin alcoholic woman with known COPD was admitted to the medical intensive care unit (ICU) after new-onset grand mal seizure. She ran out of money to buy whiskey after drinking heavily for several days. On physical examination, she was communicative but incoherent, her lungs were clear, and her deep tendon reflexes were 2+ and symmetric. She was cachectic with a body mass index (BMI) of 19. Initial laboratory values included serum sodium 138 mEq/L, potassium 2.6 mEq/L, chloride 90 mEq/L, serum total CO_2 of 15 mmol/L, serum inorganic phosphate of 3.2 mEq/L, albumin 2.4 g/dL, and blood urea nitrogen of 7 mg/100 mL. An arterial blood sample collected while the patient was breathing room air was significant for metabolic acidosis and hypoxemia (pH of 7.24, carbon dioxide tension of 33 mm Hg, and oxygen tension of 55 mm Hg). Head CT was unremarkable and the chest radiograph was free of infiltrates.

Initial management in the ICU unit included intravenous glucose, potassium, thiamine, soluble multivitamins, and phenytoin. The patient was also given aluminum hydroxide, magnesium hydroxide (Maalox) by mouth. During the following day the patient's mentation improved and she started an oral diet. On the fourth hospital day, however, the patient was found to be obtunded. Her respiration was rapid and shallow. An arterial blood sample collected while the patient was using a nonrebreather oxygen mask was significant for mixed metabolic and respiratory acidosis (pH of 7.01, carbon dioxide tension of 71 mm Hg, and oxygen tension of 107 mm Hg). The patient was endotracheally intubated. The postintubation chest radiograph was free of infiltrates. No seizures, focal neurologic deficits, abnormal pupillary reflexes, or arrhythmias were noted. The only change was the presence of generalized areflexia and muscular weakness. A nasogastric feeding tube was placed and the patient was eternally fed. Over the next 2 days she was unable to voluntarily generate a vital capacity greater than 400 mL. Her maximum inspiratory pressure was −12 cm H_2O. She continued invasive ventilation.

What testing should be done next in evaluating the patient's respiratory failure?

a. Head CT
b. Continuous electroencephalographic (EEG) monitoring
c. Quadriceps muscle biopsy
d. Serum electrolytes
e. Lumbar puncture

Answer: d. This patient initially presents with presumed withdrawal seizures. Her admission laboratory test demonstrated hypoxemia and metabolic acidosis, a common finding after generalized tonic-clonic seizures. The clear chest radiograph and the history of COPD suggest that the patient's underlying COPD was responsible for hypoxemia. The patient's clinical course is initially one of neurologic improvement. She quickly starts with oral alimentation. The patient is known to be a heavy drinker and is malnourished. These factors make her at high risk of hypophosphatemia owing to refeeding syndrome. Indeed, on the sixth hospital day when the patient had already been intubated for 48 hours, all laboratory studies were within normal limits except for a serum inorganic phosphate level of 0.5 mEq/L. Potassium phosphate, 60 mEq, was administered intravenously over 16 hours. By the next morning the muscular

weakness was much improved, and forced vital capacity had doubled to 800 mL. Serum inorganic phosphate was 1.2 mEq/L (normal values 1.1–1.5 mEq/L). Later that afternoon, the patient self-extubated and remained extubated thereafter. The rest of the hospital course was uneventful.

A CT scan of the head (option a), continuous EEG monitoring (option b), and lumbar puncture (option e) are wrong choices because this patient has low yield. The patient has no focal neurologic deficit (option a), no evidence of seizure (option b), and no signs suggestive of meningitis (option e). Quadriceps muscle biopsy is not indicated as it would be unlikely for a patient to develop such a severe myopathy leading to hypercapnic respiratory failure within a matter of few days.

5. A 48-year-old woman with a remote history of mastectomy for noninvasive ductal carcinoma in situ of the breast was admitted and emergently intubated for respiratory distress. Arterial blood gas analysis revealed severe hypercapnia ($PaCO_2$ 102 mm Hg). According to family members, for the past 3 weeks the patient had been complaining of progressive dyspnea. In addition, 2 months before admission she started experiencing progressive, symmetric weakness of neck, arms, and leg muscles. One week before admission, she could not walk without support. After intubation, her physical examination revealed neck flexor weakness, mild symmetric proximal arm and leg weakness (MRC score 4 of 5), and weakness of the anterior tibial muscles (MRC grade 3). Deep tendon reflexes and sensation were normal. Her maximal inspiratory pressure was −15 cm H_2O. No skin abnormalities were observed. Creatine kinase was increased (5000 IU/L; upper limit of normal 145 IU/L). Routine blood examination showed no abnormalities. Tensilon test result was negative. EMG exhibited extensive myopathic changes consisting of spontaneous muscle activity and polyphasic motor unit action potentials of small amplitude and short duration in all muscles. CT imaging of the chest and abdomen ruled out overt malignancy and was not suggestive of interstitial lung disease. Repeated weaning trials from mechanical ventilation failed owing to recurrent hypercapnic respiratory failure with respiratory distress.

What is the best testing choice to evaluate the patient's respiratory failure?

a. Head CT
b. Anti–muscle-specific receptor tyrosine kinase (MuSK) antibody titers
c. MRI of the thighs
d. Anti-Hu antibody titers
e. Quadriceps muscle biopsy

Answer: e. This patient is affected by necrotizing autoimmune myopathy (NAM), a rare variant of idiopathic inflammatory myopathies that also include polymyositis, dermatomyositis, and sporadic inclusion body myositis. NAM is characterized pathologically by necrotic muscle fibers with absent or minimal inflammation and with some regeneration. It can be accompanied by statin therapy, connective tissue diseases, cancer, and signal recognition particle (SRP) autoantibodies or 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR) autoantibodies. Clinically patients usually present with lower extremity weakness (73%). Less often patents experience distal weakness (41%), dysphagia (35%), and dyspnea (37%). Respiratory insufficiency as a presenting symptom of NAM is unusual. Prednisone monotherapy is generally insufficient to control the disease. Accordingly, most patients require a second agent such as azathioprine, methotrexate alone, mycophenolate mofetil, and intravenous immunoglobulins. During immunosuppressant taper or discontinuation, 55% of patients experience a relapse of the disease process.

Options a through d are incorrect because the patient has no focal neurologic deficit (option a), her Tensilon test was negative (option b), CT and abdomen were negative (option c), and thus a workup for malignancy would not be the first diagnostic step to take. MRI of the leg muscles may show hyperintensity, consistent with edema, yet this would not be sufficient to make a diagnosis of NAM.

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Pneumonia: Considerations for the Critically Ill

RICHARD G. WUNDERINK AND MARCOS I. RESTREPO

CHAPTER OUTLINE

Definitions

Pathogenesis
- Acquisition of Pathogens
- Host Defense
- Resolution

Community-Acquired (Community-Onset) Pneumonia
- Etiologies
- Diagnosis
- Management

Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia
- Etiologies
- Diagnosis
- Management

Pneumonia is the presence of an abnormal collection of microorganisms in the alveolar space that induces a consequent acute systemic host immune response. The recent discovery of a normal lung microbiome has forced reconsideration of prior definitions of pneumonia.[1] Previously the alveolar space was thought to be sterile and pneumonia resulted from invasion and proliferation of microorganisms, which by definition were not "normal." The mere presence of microorganisms was thought to be enough to induce the inflammatory response that characterizes clinical pneumonia. Studies on the lung microbiome document not only that bacteria are normally present at the alveolar level, but also that certain interacting bacterial populations are antiinflammatory and actually prevent progression of chronic lung diseases.

Definitions

A variety of classifications for acute pneumonias have been used. The critical issue for attempts at discriminating between types of pneumonia is the spectrum of usual pathogens. Because most antibiotic therapy currently is empirical, separating cases of pneumonia into those in which the usual spectrum of pathogens, and therefore resultant appropriate empirical antibiotic, are very similar is important for optimizing care.

Community-acquired pneumonia (CAP) is pneumonia with onset that occurs outside an acute medical care setting.[2] Pneumonia that occurs within the first 48 hours of hospital admission is also considered CAP in most studies, with the assumption being that the pneumonia was incubating at the time of hospitalization. Given difficulties in radiographic diagnosis and confusion with other acute illnesses requiring hospitalization, this assumption is usually reasonable.

Advances in medical care have blurred the distinction between CAP pathogens and those usually found in hospital settings. Attempts to identify CAP patients at risk for hospital pathogens resulted in the health care–associated pneumonia (HCAP) classification.[3] Unfortunately, the initial definition used criteria developed for bacteremia. Although the negative predictive value was very high for pathogens resistant to the usual CAP treatment, the criteria were overly sensitive, resulting in excessive antibiotic therapy. This excess was especially driven by use of broad-spectrum antibiotics even when only a single criterion was present, and it was not associated with any clear improvement in outcomes. The HCAP term has therefore been abandoned and specific high-risk profiles for specific pathogens are now more commonly used. Although most important criteria of recent hospitalization—prior colonization or infection with resistant bacteria, recent antibiotic use, and poor functional status—define a high-risk group,[4] the criteria do not discriminate among pathogens.

Hospital-acquired pneumonia (HAP) is pneumonia with onset more than 48 hours after hospital admission or after a period of hospitalization.[5,6] Many patients previously classified with HCAP were in less traditional hospital settings such as long-term acute care facilities (LTACs) or acute inpatient rehabilitation facilities.[7] The risk of HAP pathogens is maintained and possibly even increased in these environments. Patients from more chronic nursing home situations are more difficult to classify. Probably the easiest ways to assess risk for multiple-drug–resistant (MDR) pathogens are to determine whether the patient entered from the community versus a hospital or LTAC, the degree of limitations in normal daily activities, and prior antibiotic exposure.

Ventilator-associated pneumonia (VAP) is a subgroup of HAP, occurring in patients who have been endotracheally intubated for at least 48 hours. Once again, the assumption is that the pneumonia was not incubating at the time of intubation. Aspiration pneumonitis and secondary infectious pneumonia compromise this criterion.[8] Chronically ventilated patients from LTACs or acute rehabilitation hospitals should be considered to have VAP for purposes of empirical

antibiotic therapy. The increasing number of patients with long-term tracheostomy and home ventilatory support are not easily classified; once again, frequency of hospitalization, prior pathogen infection/colonization, and exposure to antibiotics are likely the best criteria.

Pneumonia in the immunocompromised host is a subgroup of both CAP and HAP. The major issue is risk for pathogens rare for CAP and HAP, such as *Pneumocystis jirovecii*, nonendemic fungi such as invasive *Aspergillus* and other molds, cytomegalovirus and other opportunistic viruses, and so on. Infections in the immunocompromised host are covered separately in Chapter 50. However, the separation between immunocompetent and immunosuppressed is somewhat arbitrary. Many patients with pneumonia have some form of immunocompromised state that may not be self-evident. Even 20 mg prednisone equivalent for 30 days or less can increase the risk of sepsis. A variety of immunosuppressive agents are being used for nonmalignant medical problems, most prominently solid organ transplant, but also collagen vascular diseases and other immunologic diseases. Conversely, pneumococcal pneumonia is still the most common pathogen in patients with acute leukemia before induction therapy as well as patients with human immunodeficiency virus (HIV) infection receiving highly active antiretroviral therapy.

Pathogenesis

Prior pathogenesis theories for pneumonia were based on the concept of a sterile alveolar space and acquisition of a foreign pathogen.[1] These concepts generally still apply but are more nuanced with the awareness of a normal alveolar microbiome.

Acquisition of Pathogens

The pathogen's mode of entry into the lower respiratory tract has usually been divided into aspiration, inhalation, hematogenous spread, and contiguous spread.

Inhalation

Inhalation of infectious particles is particularly important for inspection of viruses and tuberculosis. In these situations, pneumonia is not necessarily preceded by upper respiratory tract colonization. Inhalation is the major mechanism for CAP. Rarely, bacteria can be inhaled through aerosols from contaminated respiratory therapy equipment.

Aspiration

Aspiration is the major mechanism for HAP/VAP and for bacterial pneumonia in general. The lower respiratory tract is in constant communication with the upper tract and aspiration likely occurs continuously. When the normal flora in the oropharynx are replaced by bacteria that are not usually present, such as occurs with gram-negative pathogens in HAP/VAP, the new microorganisms can then cause replacement of the normally diverse flora of the lower respiratory tract, especially when under antibiotic pressure.

Hematogenous Spread

Hematogenous spread was thought to be a relatively rare cause of pneumonia, mainly limited to pneumonia resulting from right-sided endocarditis or a septic thrombophlebitis. Recent data from patients with acute respiratory distress syndrome (ARDS) suggest that the microbiota of the gut may translocate into the portal circulation and spread into the pulmonary circulation, from which they can alter the normal alveolar microbiome.[9] Deep sequencing of bronchoalveolar lavage (BAL) specimens from patients with ARDS finds marker pathogens suggesting a gastrointestinal (GI) tract source. This mechanism may also play a role in immunocompromised patients undergoing chemotherapy-related diffuse mucositis.

Contiguous Spread

Contiguous spread of pathogens from an adjacent extrapulmonary infection is an uncommon mechanism for pneumonia. However, primary empyema without pneumonia clearly occurs.[10] If so, then the possibility of secondary pneumonia from the infected pleura is logical but the frequency is somewhat unclear. However, the management is not different than if the pneumonia was primary. Other rare causes include spread from serious neck infections or subdiaphragmatic infections. In each of these cases, infectious invasion through other tissue planes is required before pneumonia occurs, limiting the spectrum of potential pathogens.

Overgrowth of Normal Flora

Discovery of the presence of a normal lung microbiome offers a fifth potential source of pathogens causing pneumonia overgrowth of the normal resident lower respiratory tract flora. Many pathogens associated with pneumonia can be part of the normal lung microbiota, including *Mycoplasma*, the pneumococcus species, and many other *Streptococcus* species.[11] Changes in conditions of the microbiome may result in overgrowth of one of these bacteria. The most obvious example may be an upper respiratory tract viral infection. This possibility may explain the consistent association between low-pathogenicity viruses, such as human rhinovirus, with radiographic pneumonia.[12,13] Further research is clearly needed in this area.

Host Defense

The overwhelming majority of infectious challenges to the lung are handled by the complex, highly effective host defense mechanisms of the upper and lower respiratory tracts.[14] Upper airway mechanisms include the branching anatomy of the conducting airways, mucociliary clearance, cough, and local airway defenses, including antimicrobial peptides such as lysozyme, lactoferrin, and other defensins, as well as secretory immunoglobulin (Ig) A and IgG. Alveolar macrophages are the main cellular component of host defense at the alveolar level, although alveolar epithelial cells also play a role.[15] Multiple antimicrobial peptides and other cells can participate in handling an infectious challenge. For example, surfactant proteins SP-A and SP-D are important for opsonization of bacteria and particles for ingestion by alveolar macrophages.

When local host defenses are inadequate to control an infectious challenge, the innate immune system is activated. This activation results in many other clinical manifestations of pneumonia. Release of endogenous pyrogens, such as tumor necrosis factor and interleukin (IL)-1, cause fever. Granulocyte colony-stimulating factor and IL-8 result in both peripheral and alveolar leukocytosis. A variety of cytokines result in a localized alveolar capillary leak in the area of infection, resulting in radiographic infiltrates and increased secretions. This inmate immune response is often adequate to control infection, even without antibiotic therapy. Microbial antigens are recognized by a variety of pathogen recognition receptors, such as the Toll-like receptors, and transported to regional lymph nodes where they are taken up by specialized dendritic cells and presented to responding lymphocytes to initiate adaptive immune responses. Humoral immunity can prevent development of clinical pneumonia but also facilitate resolution.

Invading microorganisms can overwhelm host defense for several reasons. The patient's immune response may be inadequate from underlying comorbid illness, anatomic abnormalities (endobronchial obstruction, bronchiectasis), disease-associated immune impairment, or therapy-induced dysfunction of the immune system (corticosteroids, endotracheal intubation). Pneumonia in patients with an adequate immune system can result from a large inoculum of bacteria (massive aspiration) or by a particularly virulent organism. Hereditary or acquired deficits in the immune system can be somewhat subtle or be first manifested in a patient who has developed pneumonia.

Antiinfective therapy of pneumonia only partially compensates for problems in the normal host defense mechanisms. Severely immunocompromised patients may still succumb to pneumonia despite provision of optimal antibiotics or other antiinfectives. Conversely, activation of intrinsic host defense mechanisms can cure pneumonia caused by even highly virulent pathogens, even without antibiotic therapy.

Resolution

Resolution of pneumonia is an active process, rather than simply discontinuation of the host immune response. Specific molecules, such as resolvins and protectins,[13] are needed to return the alveolus to its normal structure and function. In addition, antibiotic therapy may induce a significant change in the resident microbiota with long-lasting effects. An overexuberant inflammatory response may result in a persistent inflammatory state despite complete clearance of the original inciting pathogen. This aberrant resolution may result in well-defined syndromes, such as bronchiolitis obliterans organizing pneumonia, or fibroproliferative ARDS. However, a larger adverse effect may be in nonpulmonary organs, including delirium and critical care encephalopathy, increased risk of acute cardiovascular events,[16] and persistent acute kidney injury. These other adverse effects result in excess mortality within a year of hospitalization for pneumonia, compared to matched controls.

Community-Acquired (Community-Onset) Pneumonia

"Severe CAP" is used to define a group of critically ill patients affected with pneumonia, with a disease severe enough that requires hospitalization and most likely a higher level of care in the intensive care unit (ICU). The disease process is better understood as a continuum of complex interactions that go beyond the care delivered in the ICU setting. This continuum of care involves patients with severe CAP that could be initially suspected and recognized at the office, emergency department, or hospital ward and may progress to require ICU level of care. This view is important owing to the impact on poor clinical outcomes associated with severe CAP, such as pneumonia-related complications, longer hospital stay, high health care costs, and death.

CAP and influenza are the leading causes of death from infectious diseases in the United States and accounts for about 50,000 deaths a year.[17] In addition, the World Health Organization considers pneumonia the most relevant of the lower respiratory tract infections and the third leading cause of death globally and the number one cause of death in low-income countries.[18] The incidence of CAP is variable around the globe because of geographic variation, circulating pathogens, and host factors. In Europe the estimated incidence of CAP is 1.1 to 1.7/1000 patient-years and tends to be much higher in the elderly (≥65 years) with an estimate of 8/1000 patient-years. From 10% to 60% (higher rates in the elderly) may require hospitalization owing to CAP and, among the ones hospitalized, 10% to 20% required ICU admission. The main reasons for care in the ICU setting are need for mechanical ventilation (44%–53% of the patients) and vasopressor support for CAP patients with septic shock (50%). These patients with severe CAP tend to stay longer in the hospital compared with ward patients (23 days vs. 6 days) and have higher costs of care ($21,144 for ICU vs. $7500 for ward patients).[19] Despite advances in antimicrobial therapy and supportive measures, the mortality in this group of patients remains unacceptably high (21% to 58%). The main reasons associated with death in patients with severe CAP include refractory hypoxemia, refractory shock, other pneumonia- and cardiovascular-related complications, worsening or exacerbation of comorbid conditions, and multiorgan failure. Early recognition of patients with severe CAP is critical to rapidly institute strategies attempting to minimize the poor clinical outcomes.

Etiologies

The most common etiologic agents causing CAP are bacteria and viruses. Several studies evaluated the etiology of patients with severe CAP but, despite extensive laboratory testing, the causative pathogen is found in only about one-third of the patients, leaving two-thirds of patients without a presumptive etiologic agent.[12] However, ICU patients tend to have higher rates of causative pathogen recognition compared with patients on ward services.[20] This results from more testing in the ICU, the ability to reach the lower respiratory tract in patients requiring invasive mechanical ventilation, and likely higher pathogen loads,[21] making isolation more feasible.

The most common bacterial pathogen causing severe CAP is *S. pneumoniae*. However, many other bacterial pathogens are identified in severe CAP patients (Table 40.1). Mixed infections with typical and atypical pathogens occur in 5% to 40% of cases, and should always be considered to ensure patients are treated with appropriate empiric antimicrobial therapy. In addition, respiratory viral infection or coinfection is important, with involvement documented to be as high as 50%. Over the past decades, outbreaks and case reports of pneumonia caused by less commonly found viruses, such as avian influenza virus, enterovirus, severe acute respiratory distress coronavirus,[22] or Middle East respiratory syndrome coronavirus[23,24] have been increasingly reported.

The most common pathogens implicated with mortality are *S. pneumoniae*, *S. aureus* (particularly community-acquired methicillin resistant strain [CA-MRSA]), *Legionella pneumophila*, and *Pseudomonas aeruginosa*. The severity of pneumonia may be linked to multiple factors, including bacterial burden, virulence factors, geographic exposure, exposure to vectors or infected hosts, impairments of the immune system, and preexisting conditions (Table 40.2). Multiple conditions and patient populations are more vulnerable to acquire severe CAP, such as those with chronic illnesses, including pulmonary, cardiovascular, renal, neurologic, and liver diseases (Table 40.3).

Extensive interest previously focused on CAP cause by drug-resistant *S. pneumoniae* (DRSP). However, multiple studies were unable to confirm an association between drug-resistant *S. pneumoniae* and poor clinical outcomes. Rates of pneumonia owing to *S. aureus* have been increasing in the past 2 decades. CA-MRSA pneumonia has been linked to prior influenza infection.[25]

TABLE 40.1 Pathogens Associated With Severe Community-Acquired Pneumonia

Common	Less Common	Endemic Areas
Gram-Positive Cocci	*Mycoplasma pneumoniae*	*Mycobacterium tuberculosis*
Streptococcus pneumoniae (including DRSP)	*Chlamydia pneumoniae*	Nontuberculous mycobacteria
Staphylococcus aureus (including MRSA)	*Chlamydia psittaci*	*Coccidioides* spp.
Gram-Negative Bacilli	*Coxiella burnettii*	Histoplasmosis
Haemophilus influenzae	*Moraxella catarrhalis*	*Blastomycosis*
Klebsiella spp.	*Bordetella pertusis*	**Bioterrorism/Exposure**
Enterobacteriaceae	*Acinetobacter* spp.	*Francisella tularensis*
Pseudomonas aeruginosa	*Burkholderia pseudomallei*	*Yersinia pestis*
Legionella spp.	Anaerobic bacteria	*Bacillus anthracis*
Influenza virus	Other respiratory viruses	

DRSP, Drug-resistant *S. pneumoniae*; *MRSA,* methicillin-resistant *S. aureus.*

TABLE 40.2 Risk Factors Associated With Selected Pathogens in Patients With Severe Community-Acquired Pneumonia

Pathogens	Risk Factors
Common Pathogens	
Streptococcus pneumoniae	Smoking, COPD, influenza infection, low socioeconomic status, sulfur dioxide air pollution, alcoholism, dementia, seizures, congestive heart failure, CVD, HIV infection
DRSP	Alcoholism, β-lactams within 3 months, presence of more than one coexisting disease, immunosuppressive illness
Staphylococcus aureus	Decreased functional status, CVD, intravenous drug use, diabetes mellitus, renal failure, influenza
CA-MRSA	Skin infections, prior influenza infection
Haemophilus influenzae	COPD, smoking, bronchiectasis
Legionella spp.	Chronic steroid use, hematologic malignancy, humid weather, smoking, diabetes mellitus, cancer, ESRD, HIV infection, epidemic events
Influenza virus	Air pollutants (nitrogen oxide, ozone, and particulate matter), winter season
Anaerobes	High dental plaque index, poor dental hygiene, periodontal disease, alcoholism, aspiration
Less Common Pathogens	
Francisella tularensis	Exposure to rabbits
Coxiella burnetti (Q fever)	Exposure to farm animals or parturient cats
Chlamydia psittaci	Exposure to birds
Histoplasma capsulatum	Exposure to bats, soil contaminated with bird droppings
Coccidioides spp.	Travel to southwestern areas of the United States

CA-MRSA, Community-associated methicillin-resistant *S. aureus; COPD,* chronic obstructive pulmonary disease; *CVD,* cerebrovascular disease; *DRSP,* drug-resistant *S. pneumoniae; ESRD,* end-stage renal disease; *HIV,* human immunodeficiency virus.

P. aeruginosa has been reported in severe CAP patients with specific risk factors, such as chronic or prolonged use of broad-spectrum antibiotic therapy, bronchiectasis, malnutrition, HIV, and immunosuppression.[26]

Diagnosis

Clinical and Radiologic

The most common symptoms are fever, chills, nonproductive or productive cough, pleuritic chest pain, and shortness of breath. Less frequently patients may present with diarrhea; new-onset or worsening confusion, particularly in elderly patients; and headache. On physical examination, patients are hyperthermic or hypothermic, tachypneic, and tachycardic. Lung examination reveals dullness on percussion, increased tactile and vocal fremitus, bronchial breath sounds, and egophony. Auscultation findings include crackles, whispering pectoriloquy, egophony, and pleural friction rub. Distant manifestations of pneumonia include involvement of the joints with arthritis, heart with endocarditis, and meninges with meningeal signs. Infections caused by "atypical pathogens," such as *Mycoplasma pneumoniae* or *Chlamydia pneumoniae,* can lead to complications such as bullous myringitis, skin rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis.

In the elderly or those with comorbid conditions, elevated respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days.[27] Respiration rates more than 30 breaths/min indicate an increased pneumonia severity and are usually included in severity of illness scores. Overall, the clinical diagnosis of pneumonia has moderate sensitivity (79%) and specificity (66%). Given this lack of specificity, clinical characteristics suggestive of a pneumonic process require further confirmation by imaging.

TABLE 40.3 Risk Factors Associated With Severe Community-Acquired Pneumonia

Demographics
Age
Genetic polymorphisms
Male gender
Humid weather
Low socioeconomic status
Winter season

Cardiovascular Conditions
Coronary artery disease
Congestive heart failure

Pulmonary Conditions
Asthma
COPD
Chronic systemic or inhaled corticosteroids
Bronchiectasis

Neurologic Conditions
Cerebrovascular disease
Decrease functional status
Dementia
Seizure

Immunosuppressive Conditions
HIV/AIDS
Malignancies
Chemotherapeutic agents
Endocrine conditions
Diabetes mellitus

Renal Conditions
Acute renal failure
Chronic renal failure and ESRD
Need for dialysis

Liver Conditions
Chronic liver disease
Cirrhosis

Exposures
Alcohol
Air pollutants
Intravenous drug use
Prior antibiotic therapy
Smoking
Influenza and other viral infection
Proton pump inhibitors
Skin infections
Prior MRSA colonization
Prior *Pseudomonas aeruginosa* colonization
Severe dental plaque/periodontal disease

COPD, Chronic obstructive pulmonary disease; *ESRD*, end-stage renal disease; *HIV*, human immunodeficiency virus.

The classic imaging includes alveolar filling densities with air bronchograms or peribronchial infiltrates; diffuse ground-glass changes are also common. The chest radiograph may be suboptimal in patients with early infection (especially with volume depletion), severe granulocytopenia, bullous emphysema, and obesity. In those instances, a repeat chest radiograph in 24 to 48 hours is reasonable. CAP severity correlates radiologically with multilobar and bilateral infiltrates, cavitation, or a loculated pleural effusion (suggesting an empyema). Chest radiographic patterns are generally not useful for identifying the cause of CAP, although findings such as pleural effusion (*Pneumococcus, Haemophilus influenzae, M. pneumoniae,* pyogenic streptococci) and cavitation (*P. aeruginosa, S. aureus*, anaerobes, tuberculosis) can suggest certain groups of organisms.

Chest computed tomography (CT) scan has better sensitivity in diagnosing pulmonary infiltrates suggestive of pneumonia, as well as excluding pneumonia in patients with borderline findings.[28,29] In emergency department patients with suspected CAP, chest CT scan results markedly affect diagnosis, treatment, and decision for site of care.[28] However, analysis of cost-effectiveness and actual implementation strategies in different resource settings are clearly needed before routine use.

Use of chest ultrasound for diagnosis of pneumonia has become more common and facilitates the diagnosis of parapneumonic pleural effusions and subsequent sampling of pleural fluid. Point-of-care ultrasound is frequently used in the ICU to avoid unnecessary chest radiographs and decrease radiation. Multiple systematic reviews and meta-analyses confirm that sensitivity and specificity are excellent.[30–33] The most common consolidation pattern on point-of-care lung ultrasound includes a large, compact mass without volume loss. On occasion, a "shred sign" appears at the interface between partially aerated alveoli and completely airless or fluid-filled alveoli from the pneumonic process. Pneumonic infiltrates often contain dynamic air bronchograms—mobile, hyperechoic, punctiform areas due to trapped air bubbles within the bronchi that move with respirations—which are rarely seen in atelectasis. The accuracy of lung ultrasound is limited by some patient factors but mainly the competence of the operator.

Laboratory Testing

A complete blood cell count, chemistry panel, lactic acid, and arterial blood gas analysis are recommended in all patients with severe CAP. Leukopenia and leukocytosis are seen in patients with severe CAP owing to *Pneumococcus* or gram-negative organisms.[34] Several abnormalities observed in the complete blood cell count, such as leukopenia, thrombocytosis, and thrombocytopenia, are associated with poor prognosis in patients with severe CAP.[2] Hyponatremia and hyperglycemia on admission are associated with poor outcome in CAP patients. Increased levels of blood urea nitrogen and creatinine are considered markers of severity in patients with CAP, indicate systemic organ dysfunction, and are associated with poor clinical outcomes. Elevated liver function test results can be seen in a variety of viral and bacterial pneumonias secondary to atypical agents such as *Legionella* spp. and *Mycoplasma* spp., Q fever, tularemia, and psittacosis, as well as in pneumococcal infection. Acidosis, hypoxemia, and alternations of carbon dioxide are frequently overlapping in patients with chronic comorbid conditions and are associated with high mortality.[35–39]

Microbiologic Testing

The American Thoracic Society (ATS)/Infectious Diseases Society of America (ISDA) 2007 guidelines recommend that patients with severe CAP should have two sets of blood cultures.[2] Culture results are more likely to be positive if the patient has not received antibiotics at the time of sampling or has any of the following risk factors: underlying liver disease, systolic blood pressure less than 90 mm Hg, temperature less than 35°C or greater than 40°C, pulse higher than 125 beats/min, blood urea nitrogen greater than 10.7 mmol/L (30 mg/dL), serum sodium less than 130 mmol, and leukocyte count less than 5000 or greater than 20,000 cells/mL.[40] Blood cultures should also be considered in patients with asplenia, cavitary infiltrates, or a history of ongoing alcohol abuse.[34] The presence of bacteremia may not indicate worse prognosis but does allow identification of drug-resistant organisms; most positive blood culture results in CAP reveal *Pneumococcus*.

Respiratory samples, including sputum Gram stain and culture, may assist clinicians in identifying the probable cause of severe CAP, but the results must be assessed carefully to distinguish between normal flora, colonization, or infection. Gram stain can be used to broaden initial empiric therapy to cover pathogens resistant to usual empiric therapy such as MRSA (presence of clusters of gram-positive cocci, particularly during influenza season). A sputum sample that contains less than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low-power field enhances the value of the sputum culture results in patients with severe CAP. Collection of invasive respiratory samples by bronchoscopic or nonbronchoscopic techniques is highly recommended in patients with severe CAP, who tend to have higher rates of microbial pathogens recovered at the time of pneumonia.[20] Respiratory sampling, including endotracheal aspirates obtained from patients with severe CAP requiring ventilation, assist with the diagnosis, direct changes of empiric antimicrobial therapy according to the culture results, and potentially alter duration of antibiotics. Open lung biopsy is rarely needed to diagnose severe CAP and is reserved principally for highly immunocompromised patients not responding to appropriate standard treatments or in patients with suspected pneumonia mimics, such as inflammatory lung disease, eosinophilic pneumonia, acute interstitial pneumonia, diffuse alveolar hemorrhage, or malignancy. The development of molecular diagnostic tests has largely obviated the need for open lung biopsy for diagnosis of *Aspergillus* spp., cytomegalovirus, *Cryptococcus* spp., *Blastomyces, Histoplasma, Nocardia* spp., and *Toxoplasma gondii* and other fastidious pathogens.

Serologic testing is not routinely recommended in patients with severe CAP. Serologic testing, requiring acute and convalescent collections several weeks apart with a fourfold increase in titers to confirm the diagnosis, is impractical at the site of care. In addition to the questionable value of a single acute result, uncertainty regarding whether the patient will survive to get the diagnosis-confirming convalescent sample and location of the patient at the time convalescent serology is needed create logistic barriers. Therefore routine serologic testing for atypical pathogens such as *C. pneumoniae, Coxiella burnetii* (Q fever), *Chlamydia psittaci*, *Legionella,* and *M. pneumoniae* is reserved for epidemiologic evaluations.

Patients with severe CAP at risk for *Legionella* infection should be tested with *Legionella* urinary antigen, which tends to be positive at the time of admission if the patient is infected with *L. pneumophila* serogroup I infection (which accounts for 70%–80% of legionella cases). A positive *Legionella* urinary antigen test result should be accompanied by culture confirmation on special charcoal-containing agar. Pneumococcal urinary antigen has a sensitivity of 50% to 80% and specificity of more than 90%.[41] False-positive test results are seen in patients who had pneumonia within the previous 3 months.

Polymerase chain reaction (PCR) assays are used for the detection of viruses (as was the case in the H1N1 epidemic) and other agents such as *M. tuberculosis*. They have now become the standard for diagnosis of respiratory viruses, as well as *Mycoplasma* and *Chlamydophila*.[12] PCR assays, usually performed on nasal or oropharyngeal swabs of lower respiratory tract samples, have additional sensitivity and increase the probability that the virus is causative of pneumonia rather than simple persistent shedding from an upper respiratory tract infection. Direct immunofluorescence or enzyme immunoassay can also be used to detect viral antigens such as influenza, parainfluenza, respiratory syncytial virus, and adenovirus. The impact of a positive test result on management of CAP is still unclear, but a negative test result is valuable in directing a focused antibiotic regimen.

Biomarkers

Inflammatory biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), midregional proadrenomedullin, midregional proatrial natriuretic peptide, proarginine-vasopressin, proendothelin-1, and the ILs have been used to distinguish bacterial infection from viral infection. Inflammatory biomarkers such as PCT, CRP, tumor necrosis factor α, and IL-6 levels tend to be higher in patients admitted to the ICU, including those with delayed ICU admission, compared with patients not needing ICU care. CRP is a biomarker that may be of use in patients with less disease to determine site of care. But CRP is nonspecifically elevated with any inflammatory state, such as severe CAP,[42] and therefore lacks discriminating value for complications, such as parapneumonic effusion or empyema. PCT, the peptide precursor of the hormone calcitonin, is a "hormokine" (a hormone with cytokine-like behavior) with a half-life of 25 to 30 hours. PCT is produced in response to bacterial microbial toxins but is inhibited by virus-related cytokines. Serum levels tend to be high in patients with severe bacteremic CAP, and serial measurements help guide the duration of antibiotic therapy.[43] All the other biomarkers remain in the investigational phase and the application in clinical practice is pending.

Management

Traditionally, antimicrobials have been considered the cornerstone of therapy against severe CAP. However, with the understanding of severe CAP as a systemic disease, other non-antimicrobial therapies should be considered for management of this group of patients.

Site-of-Care Decision

The site-of-care decision is critical for patients with CAP because it affects the diagnostic workup, the therapeutic interventions, and the clinical outcomes.[2] Therefore significant interest has been generated in this area of research over the past decades.

Several tools have been developed to predict mortality and determine the site of care for patients with severe CAP.[2] Two extensively studied and validated tools have been recognized and are recommended by the multiple clinical practice guidelines related to CAP (Table 40.4).[44] The Pneumonia Severity of Illness (PSI) score and the CURB-65 are the most frequently cited scores for aiding the decision for hospital admission. The PSI is based on 20 parameters that are evaluated at the time of clinical presentation and consists of three demographic, five comorbid conditions, five physical examination findings, and seven laboratory/imaging variables. The goal of this tool is to identify patients who can be discharged safely and receive home treatment with antibiotic therapy. However, the PSI score is heavily influenced by age, and it does not include certain comorbid conditions frequently found in patients with CAP, such as diabetes and COPD. In contrast, the second score—CURB-65, a six-variable tool that includes *c*onfusion, *u*rea, *r*espiratory rate, *b*lood pressure, and age above *65* years—is less complex.[45] An even simpler tool resulting from withdrawing the only laboratory value needed to calculate the score (blood urea nitrogen), named CRB-65, was validated with similar results. However, the CURB-65 score does not recognize any comorbid conditions previously associated as risk factors for CAP and does not include low oxygen levels as one of the criteria. Therefore these tools have value to designate low-risk patients but are not ideal to recognize patients at high risk of death.

TABLE 40.4 Different Systems Evaluated by the Most Relevant Severe Community-Acquired Pneumonia Severity Scores

Variable	IDSA/ATS 2007 Criteria[a]	PS-CURX080[b]	SMART-COP[c]	CAP-PIRO[d]	qSOFA[e]	SOFA[f]	PSI[g]	CURB-65[h]
Demographics	✓	✓	✓	✓			✓	✓
Neurologic dysfunction	✓	✓	✓		✓	✓	✓	✓
Respiratory dysfunction	✓	✓	✓		✓	✓	✓	✓
Circulatory dysfunction	✓	✓	✓	✓	✓	✓	✓	✓
Liver dysfunction						✓	✓	
Renal dysfunction	✓	✓	✓			✓	✓	✓
Hematologic dysfunction	✓					✓	✓	
Metabolic dysfunction	✓		✓			✓	✓	
Microbiologic				✓				

[a]IDSA/ATS score evaluates two major criteria (need for mechanical ventilation with endotracheal intubation and/or septic shock requiring vasopressors) and nine minor criteria: respiratory rate respiratory rate >30 breaths/min; arterial partial pressure of oxygen/fraction of inspired oxygen (Pa_{O_2}/F_{IO_2}) ratio <250; multilobar infiltrates, confusion/disorientation, uremia with serum blood urea nitrogen >20 mg/dL; leukopenia with white blood cell count <4000 cells/mm^3; thrombocytopenia (platelet count <100,000 cells/mm^3), hypothermia (core temperature <36°C); hypotension requiring agressive fluid resuscitation.

[b]PS-CURX080 predicts the diagnosis of severe community-acquired pneumonia and includes arterial pH < 7.30, *s*ystolic blood pressure <90 mm Hg, *c*onfusion (or altered mental status), blood *u*rea nitrogen >30 mg/dL, *r*espiratory rate >30 breaths/min, multilobar/bilateral lung infiltrates (by *x*-ray), *o*xygen arterial pressure <54 mm Hg or ratio of arterial oxygen tension to fraction of inspired *o*xygen <250 mm Hg, and age ≥*80* years.

[c]SMART-COP measures a low *s*ystolic blood pressure (1 point), *m*ultilobar chest radiography involvement (1 point), low *a*lbumin level (1 point), high *r*espiratory rate (age-adjusted) (1 point), *t*achycardia (1 point), *c*onfusion (1 point), poor *o*xygenation (age-adjusted) (2 points), and low arterial pH (<7.35) (2 points).

[d]CAP-PIRO score measures *Predisposition*: comorbidities (chronic obstructive pulmonary disease or immunocompromised) (1 point), age >70 years (1 point); *Infection:* bacteremia (1 point), multilobar opacities (1 point); *Response*: shock (1 point), severe hypoxemia (1 point); and *Organ dysfunction*: acute respiratory distress syndrome (1 point), acute renal failure (1 point).

[e]Quick Sequential Organ Failure Assessment (qSOFA) measures respiratory rate >22 breaths/min (+1 point); change in mental status (+1 point); systolic blood pressure <100 mm Hg (+1 point).

[f]Sequential Organ Failure Assessment (SOFA) score measure the following variables on a scales from 0 to 4, respiratory: Pa_{O_2}/F_{IO_2} (in mm Hg); coagulation (platelets ×103/μL); liver (bilirubin in mg/dL); cardiovascular hypotension and use of vasopressors (dopamine and norepinephrine at different dosages); central nervous system (Glasgow Coma Scale score); renal (creatinine in mg/dL or urine output, mL/day).

[g]PSI Score measures age (men [points = age in years] and women [points = age in years – 10]); nursing home resident (+10 points); coexistent neoplastic illness (+30 points); coexistent liver disease (+20 points); coexistent congestive heart failure (+10 points); coexistent cerebrovascular disease (+10 points); coexistent renal disease (+10 points); altered mental status (+20 points); respiratory rate ≥30 breaths/min (+20 points); systolic blood pressure <90 mm Hg (+20 points); temperature <35°C or ≥40°C (+15 points); pulse >125 beats/min (+10 points); arterial pH < 7.35 (+30 points); blood urea nitrogen ≥30 mg/dL (+20 points); sodium <130 mmol/L (+20 points); glucose ≥250 mg/dL (+10 points); hematocrit <30% (+10 points); Pa_{O_2} <60 mm Hg or oxygen saturation <90% (+10 points); pleural effusion (+10 points).

[h]CURB-65 is derived from *c*onfusion (altered mental status); serum blood *u*rea nitrogen >19.6 mg/dL; *r*espiratory rate >30 breaths/min; *b*lood pressure (BP) (BP – Systolic BP <90 mm Hg or diastolic BP <60 mm Hg); and age ≧*65* years.

Specific objective tools have been tested to identify patients with severe CAP with increased likelihood of need for ICU care when used in conjunction with clinician experience and clinical judgment. They all have in common the inclusion of parameters that assess organ dysfunction (see Table 40.4). These tools include the IDSA/ATS major and minor criteria,[2] PS-CURXO80,[39] SMART-COP,[37] PIRO-CAP,[46] qSOFA (quick Sequential [sepsis-related] Organ Failure assessment),[47,48] and SOFA scores.[48,49] The IDSA/ATS CAP guidelines in 2007 recommend the need for ICU admission for those patients with one of the major criteria (mechanical ventilation with endotracheal intubation and/or septic shock requiring vasopressors) or for patients with three of the nine minor criteria: hypotension requiring aggressive fluid resuscitation; confusion/disorientation; blood urea nitrogen greater than 20 mg/dL; respiratory rate greater than 30 breaths/min; multilobar lung infiltrates; ratio of arterial oxygen tension to fraction of inspired oxygen (Pa_{O_2}/F_{IO_2}) less than 250 mm Hg; leukopenia (<4000/mm^3); thrombocytopenia (<100,000/mm^3); or hypothermia (<36°C core).[2] Several minor criteria are uncommon and less helpful; conversely, a low pH may have additional discriminating value. Several studies have validated these criteria to admit patients to the ICU[50,51] and also applied them in other groups of patients, including elderly patients and patients infected with HIVs. The PS-CURXO80 predicts the diagnosis of severe CAP and includes these measures arterial pH < 7.30; *s*ystolic blood pressure less than 90 mm Hg; *c*onfusion (or altered mental status); blood *u*rea nitrogen greater than 30 mg/dL; *r*espiratory rate greater than 30 breaths/min; multilobar/bilateral lung infiltrates (by *x*-ray); *o*xygen arterial pressure less than 54 mm Hg or ratio of arterial oxygen tension to fraction of inspired *o*xygen (Pa_{O_2}/F_{IO_2}) less than 250 mm Hg; and age ≧*80* years.[39] The evaluation of severe CAP is based on the presence of one major criterion (PS) or two or more minor criteria (CURXO80). The model showed an area under the curve of 0.92 to accurately predict severe CAP. SMART-COP predicts the need of intensive respiratory and vasopressor support, by measuring low *s*ystolic blood pressure (1 point); *m*ultilobar chest radiography involvement (1 point), low *a*lbumin level (1 point); high *r*espiratory rate (age-adjusted) (1 point); *t*achycardia (1 point); *c*onfusion (1 point); poor *o*xygenation (age-adjusted) (2 points); and low arterial *p*H (<7.35) (2 points).[37] A SMART-COP score of 3 points or higher identified 92% of patients who received intensive respiratory care or vasopressor support, including 84% of patients who did not need immediate admission to the ICU. The CAP-PIRO score is based on the score suggested for the risk of sepsis and evaluates the following variables: *p*redisposition: comorbidities (COPD or immunocompromised) (1 point); age older than 70 years (1 point); *i*nfection: bacteremia

(1 point); multilobar opacities (1 point); *r*esponse: shock (1 point); severe hypoxemia (1 point); *o*rgan dysfunction: ARDS (1 point); and acute renal failure (1 point).[52] Based on the observed mortality with each PIRO score, the patients were stratified in four levels of risk as (1) low (0–2 points; (2) mild (3 points); (3) high (4 points); and (4) very high (5–8 points). Recent validation of qSOFA that includes a respiratory rate above or equal to 22 breaths/min, alteration of mentation, and a systolic blood pressure less than or equal to 100 mm Hg, lack specificity for pneumonia. In patients with pneumonia, qSOFA outperformed the systemic inflammatory response syndrome but was inferior to the PSI score.[53] In addition, a modified SOFA (mSOFA) may assist in predicting mortality and ICU admission, but more information is needed before changing practice. Although all severity criteria scores assess risk of death and the potential need for ICU care, because of the complexities in evaluating each one of them perhaps the most useful in clinical practice remains the IDSA/ATS major and minor criteria for severe CAP.

Empirical Antibiotics

Several professional organizations developed clinical practice guidelines with the objective of standardizing therapy for CAP following an evidence-based medicine approach.[2,54–56] Guidelines include specific recommendations for patients with severe CAP usually managed in the ICU. The guidelines emphasized the importance of appropriate, aggressive, and early management of patients with CAP who are cared for in the ICU. Combination antibiotics should be initiated as early as possible, as is recommended for patients with sepsis or septic shock, to prevent poor clinical outcomes (Table 40.5). Patients should be stratified according to the risk for *P. aeruginosa* infection.[26,57] If a patient has no risk factors for *Pseudomonas* infection, the treatment should always include two antibiotics: one β-lactam (such as cefotaxime, ceftriaxone, ceftaroline, ertapenem, a β-lactam/β-lactamase inhibitor combination) that will cover *Pneumococcus* (including drug-resistant isolates) and other likely respiratory pathogens; and therapy against atypical pathogens, especially *Legionella* spp., such as a macrolide (azithromycin or clarithromycin) or a respiratory fluoroquinolone (levofloxacin at the highest dose of 750 mg/day or moxifloxacin). Ceftaroline, a fifth-generation cephalosporin with anti-MRSA activity, shows higher cure rates and less *Pneumococcus* resistance compared with ceftriaxone.[58]

Severe CAP patients with *P. aeruginosa* risk factors, such as structural lung disease (e.g., bronchiectasis), therapy with broad-spectrum antibiotics for more than 7 days in the past month, use of corticosteroids (>10 mg of prednisone daily), malnutrition, and/or HIV infection should receive antipseudomonal therapy. The treatment should include an initial empiric combination of appropriate anti-pseudomonal coverage with antipneumococcal coverage (with a β-lactam anti-pseudomonal therapy, such as imipenem, meropenem, piperacillin/tazobactam, cefepime, ceftazidime) plus an anti-pseudomonal fluoroquinolone (levofloxacin 750 mg/day or ciprofloxacin 400 mg three times a day). For quinolone-allergic patients, aminoglycosides can be substituted, but lack of atypical pathogen coverage mandates addition of a macrolide or doxycycline. Failure to identify a pathogen has not been associated with a worse outcome particularly in the severely ill, but the empiric regimen should cover *S. pneumoniae* and atypical pathogens. In conclusion, the recommendation is empirical combination therapy with two or more antimicrobial agents according to the risk of *Pseudomonas* infection and the consistent atypical coverage mainly for *Legionella* infection.

Despite a strong recommendation,[2] evidence regarding the use of combination empirical therapy is limited to a few randomized control trials,[59–61] and most data are from observational studies of combination therapy versus monotherapy in large populations that include patients with severe CAP admitted to the ICU.[62–64] Because of the limited data and significant heterogeneity between studies, further randomized control trials have been recommended to clarify these questions. Systematic reviews of observational studies suggest that combination therapy of β-lactam agent plus a macrolide for initial empiric therapy reduces mortality in patients with severe CAP.[65] National practice guidelines strongly recommend that locally adapted guidelines should be implemented to improve process-of-care variables and relevant clinical outcomes. Other publications have consistently found a decrease in mortality with the introduction of guideline-concordant antimicrobial therapy or guideline-based protocols.[61,66] Several of the quality indicators—early administration

TABLE 40.5 Antibiotic Therapy for Management of Patients With Severe Community-Acquired Pneumonia

Pathogen Attempted Coverage	Empiric Antibiotic Recommended Alternatives
Streptococcus pneumoniae (including DRSP), *Legionella* spp., *Haemophilus influenzae,* enteric gram-negative bacilli, methicillin-susceptible *Staphylococcus aureus*	Intravenous β-lactams (cefotaxime, ceftriaxone, ceftaroline, ertapenem, ampicillin/sulbactam) *plus* a macrolide (azithromycin or clarithromycin). Intravenous β-lactams (cefotaxime, ceftriaxone, ceftaroline, ertapenem, ampicillin/sulbactam) *plus* a respiratory fluoroquinolone (levofloxacin with the highest dose of 750 mg/day, or moxifloxacin).
Add or Adjust Therapy if Suspected or Risk Factors Present	**Empiric Antibiotic Recommended Alternatives**
MRSA	Add vancomycin or linezolid
Pseudomonas aeruginosa	Intravenous antipseudomonal β-lactam therapy (imipenem, meropenem, piperacillin/tazobactam, cefepime, ceftazidime) *plus* an antipseudomonal fluoroquinolone (levofloxacin 750 mg/day or ciprofloxacin 400 mg three times a day) Intravenous antipseudomonal β-lactam therapy (imipenem, meropenem, piperacillin/tazobactam, cefepime, ceftazidime) *plus* aminoglycosides (amikacin, tobramycin, or gentamicin). *Add* anti-*Legionella* coverage with a respiratory fluoroquinolone, macrolide, or doxycycline.

DRSP, Drug-resistant *S. pneumoniae*; *MRSA,* methicillin-resistant *Staphylococcus aureus.*

of antibiotics, appropriate antibiotic use following the clinical practice guidelines, use of a critical pathway, switch to oral therapy, and early discharge—have all shown improved clinical outcomes in CAP.

In addition to antibiotic therapy, patients with severe CAP with suspected or confirmed influenza virus infection should receive early treatment with oseltamivir or zanamivir in addition to antibiotic treatment, even if the duration of symptoms is longer than 3 days. Outcome is affected by time to initiation of therapy.[67]

Little information exists on the proper duration of therapy in patients with severe CAP. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in responding patients. Generally, *S. pneumoniae* can be treated for 5 to 7 days if the patient is responding rapidly and has received accurate empiric therapy at the correct dose. The presence of extrapulmonary infection (such as meningitis) and the identification of certain pathogens (such as bacteremic *S. aureus*, and *P. aeruginosa*) may require longer durations of therapy. Identification of *L. pneumophila* pneumonia may require at least 14 days of therapy, depending on severity of illness and host defense impairments. However, quinolone therapy may be the best approach to management and durations as short as 5 days may be effective.[68–70] Biomarkers, especially PCT, can assist in shortening duration of therapy for patients with severe CAP and avoid unnecessarily prolonged use of antibiotics and prevent antibiotic-related adverse events.[43] The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones because of the excellent bioavailability between systemic and oral formulations.

Specific Antibiotics

Patients not responding to initial therapy should raise the concern of antimicrobial-resistant pathogens. Dual therapy including a macrolide has been associated with improved outcomes for severe CAP patients with bacteremic pneumococcal pneumonia. Most experts recommend that CA-MRSA be targeted in patients with severe, necrotizing CAP, including those with empyema, after a viral illness, particularly influenza. Severe CAP patients with prior MRSA infection or colonization can receive empiric or direct therapy with vancomycin or linezolid. However, many adverse manifestations in CAP patients with Panton-Valentine leukocidin (PVL)-toxin–secreting *S. aureus* strains are toxin mediated and addition of agents that inhibit the toxin production such as clindamycin and linezolid are associated with lower mortality compared with β-lactams or vancomycin.[71]

Even with severe CAP, most patients become afebrile by day 3 to 5 and most have an objective clinical response by day 3. Nonresponding patients with CAP should be evaluated for alternative diagnoses (inflammatory lung disease, atelectasis, heart failure, malignancy, pulmonary hemorrhage, pulmonary embolus, a nonpneumonic infection); a resistant or unusual pathogen (including tuberculosis and fungal infection); a pneumonia complication (empyema, lung abscess, drug fever, antibiotic-induced colitis, bronchopleural fistula); or a secondary site of infection (central line infection, intraabdominal infection).[72] The evaluation of a nonresponding patient should be individualized but may include CT scanning of the chest, pulmonary angiography, bronchoscopy, and occasionally open lung biopsy.

Adjunctive Therapy

With a comprehensive approach, non-antimicrobial therapies focus on early supportive therapy for patients with evidence of severe CAP.

Respiratory Support

Patients with severe CAP may present with different degrees of hypoxemia and impending respiratory failure requiring respiratory support. The respiratory support can be provided by invasive and noninvasive methods. Avoiding the need for invasive mechanical ventilation is preferred, if possible, to prevent risks such as ventilator-induced lung injury, VAP, neurocognitive sequelae, and increased hospital and ICU length of stay. Noninvasive respiratory support when possible could be delivered by low-flow nasal cannula, simple face mask, Venturi mask, nonrebreather mask, noninvasive positive-pressure ventilation (NIPPV), or high-flow nasal cannula. The type of delivery device used depends on severity of the disease, degree of hypoxemia, and cause of acute respiratory failure. A low-flow nasal cannula delivers dry oxygen at 1 to 6 L/min via small prongs placed on the nares. Other oxygen delivery devices, such as nonrebreather masks, can deliver 5 to 15 L/min of oxygen, and some of these devices can add humidification to the oxygen delivery. For patients with hypercarbia and need for tightly controlled oxygen levels, such as those with COPD, Venturi masks can deliver 24% to 60% oxygen at a flow of 2 to 5 L/min.

NIPPV can be used with supplemental oxygen in addition to the support for the mechanical process of ventilation. Studies have shown that patients with cardiogenic pulmonary edema or acute exacerbation of COPD, rather than CAP, are most likely to benefit with this intervention. However, poor tolerance of NIPPV because of gastric distention, patient discomfort, and inability to communicate, expectorate, or achieve nutrition goals is a limitation. NIPPV should be used with caution in patients with severe CAP, particularly if two of the limitations for NIPPV are present. Delaying the decision to intubate and begin invasive mechanical ventilation has been associated with worse outcomes.[73] Because of problems with NIPPV, a high-flow nasal cannula that delivers blended humidified air and oxygen at a prescribed FIO_2 at high flow rates via a wide-bore nasal cannula is gaining acceptance for the management of patients with impending respiratory failure.[74]

Severe CAP is the most common cause of acute lung injury/ARDS. Therefore patients with severe CAP who require invasive mechanical ventilation should receive a low tidal volume strategy with tidal volume (VT) of 6 mL/kg predicted body weight and positive end-expiratory pressure (PEEP) as recommended for ARDS.[75] For severe CAP patients with refractory hypoxemia despite these ventilatory interventions, other refractory ARDS therapies such as prone positioning, neuromuscular blockade, and initiation of extracorporeal membrane oxygenation (ECMO) should be strongly considered.[76] Prone positioning has shown improved survival in patients with severe ARDS with FIO_2 below 100 to 150.[77] ECMO therapy came into more prominence as salvage therapy for severe H1N1 pneumonia despite associated prolonged duration of ventilatory support, ICU length of stay, and high mortality. The beneficial effect of ECMO in all forms of severe CAP is lacking; however, review of an ECMO registry suggests some of the best outcomes are for patients with pneumonia.[78]

Corticosteroids

Many studies show increased pulmonary and systemic inflammatory cytokine levels in patients with severe CAP. Among ICU patients, higher circulating inflammatory cytokine levels correlate with the presence of bilateral pneumonia, bacteremia, need for mechanical ventilation, and multiple-organ dysfunction syndrome.[79] Balance between proinflammatory and antiinflammatory cytokines is critical in the host response. The fact that inflammatory markers, such as IL-6, IL-8, and IL-10, are elevated in patients with severe CAP

and decrease in the first few days of appropriate antibiotic therapy suggests use of immunomodulators and antiinflammatory medications, such as macrolides or corticosteroids, may be a beneficial adjunct to reduce the proinflammatory cytokines. Meta-analysis suggests a benefit of corticosteroids,[80] particularly in patients with severe CAP,[81] with hyperglycemia as the most important adverse consequence. A prospective randomized controlled trial (RCT) also showed a lower rate of late treatment failure when steroids were used as adjunctive therapy in CAP.[42] Adjunctive corticosteroids in patients with severe H1N1 pneumonia with ARDS and severe acute respiratory distress were associated with an increased mortality,[82,83] suggesting harm from their use in severe viral CAP. Given the currently available data, corticosteroids should not be part of routine therapy of severe CAP.[61] In special situations, however, steroids may have value. Patients with *P. jiroveci* pneumonia clearly benefit from corticosteroid therapy if the initial arterial oxygen tension is less than 70 mm Hg, by attenuating some of the inflammation induced by antibiotic killing of the organisms.[84] In patients with pneumonia and refractory shock, some investigators still consider using corticosteroids to treat relative adrenal insufficiency despite no benefit in a large prospective randomized trial of sepsis.[85,86]

Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

Etiologies

The bacterial etiology of HAP/VAP varies somewhat by the type of ICU and patient population (Table 40.6). Usual CAP pathogens, such as methicillin-sensitive *S. aureus, Escherichia coli*, and even *Pneumococcus,* can cause pneumonia in the ICU with low acuity and limited use of prior antibiotics. As the patient population increases in severity of illness, duration of prior hospitalization, and exposure to antibiotic therapy, the spectrum of etiologies shifts to more drug-resistant pathogens, with MRSA, *P. aeruginosa*, *Acinetobacter* spp., and MDR Enterobacteriaceae most common. Of the Enterobacteriaceae, *Klebsiella* spp., *Enterobacter* spp., and *E. coli* are most common but a wide spectrum of other bacteria in this family can cause pneumonia. This variable spectrum of pathogens has important implications for empirical antibiotic therapy.

Attempts to clinically define groups of patients at low risk for MDR pathogens have been somewhat frustrating. Recent studies of large academic medical centers have found that only 10% or fewer of patients with suspected pneumonia in the ICU did not have risk factors for drug-resistant pathogens.[87] This may reflect improved prevention practices in the ICU that decrease the risk of early-onset pneumonia while having a lesser effect on HAP/VAP owing to MDR pathogens. An alternative possibility is that antibiotic treatment has become so ubiquitous in the ICU that CAP pathogens are never isolated when a patient develops HAP/VAP.

Unfortunately, risk factors for MDR pathogens have little discriminating value. The risks for MRSA and *Pseudomonas*, pathogens that would require distinct empirical antibiotic choices, overlap substantially with that of Enterobacteriaceae treated with a single β-lactam antibiotic. This lack of discrimination has led professional society guideline committees to recommend empirical triple-drug regimens for a large proportion of patients with suspected HAP/VAP.[5,6]

Anaerobes are the one group of pathogens with a very minor role in HAP/VAP. For ventilated patients, the high oxygen tension is adequate anaerobic coverage. This includes patients who may have an episode of small volume aspiration at the time of intubation. β-Lactams with no anaerobic activity, such as cefipime, have equivalent outcomes to those with anaerobic coverage. The one exception may be nonventilated patients with poor oral hygiene and prone to atelectasis; in this setting, a high anaerobic inoculum and low local oxygen tension may allow anaerobes to play a role, although seldom the dominant role.[8]

Other pathogens are markers of prolonged critical illness with persistent immunologic suppression or immunoparalysis of critical illness.[88] These include *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and opportunistic fungi, including *Aspergillus* and *Mucor* spp. Reactivation of latent viruses such as cytomegalovirus (CMV) and herpes viruses also occur in this setting. The benefit of treatment for these viruses is inconclusive, suggesting that they may be simply markers of immunosuppression rather than independent pathogens.[89]

TABLE 40.6 Etiologies of Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

Without MDR Risk[a]	With MDR Risk	Unusual/Prolonged Course
Streptococcus pneumoniae	*Pseudomonas aeruginosa*	*Stenotrophomonas maltophilia*
Staphylococcus aureus: **methicillin-susceptible**	*S. aureus:* methicillin-resistant	*Burkholderia cepacia*
Enterobacteriaceae ***Highly susceptible***	Enterobacteriaceae ESBL Carbapenem-resistant	*Aspergillus* spp. Mucormycocis
Haemophilus **spp.**		CMV, HSV reactivation
Legionella[b]		
Community respiratory viruses		

[a]MDR risk includes prior antibiotic therapy, hospitalization, and/or colonization; immunocompromise.
[b]In hospitals with known nosocomial risks.
CMV, Cytomegalovirus; *ESBL,* extended-spectrum β-lactamases; *HSV,* herpes simplex virus; *MDR,* multidrug resistance.

The role of community respiratory viruses in nosocomial pneumonia is underappreciated, especially in adult ICUs.[90] Pediatric and neonatal ICUs have longer experience and a more aggressive preventative and diagnostic approach. However, the advent of routinely available molecular batteries of respiratory viruses has demonstrated clear-cut nosocomial acquisition, particularly in overtly immunosuppressed patients.

Diagnosis

Clinical/Radiologic Diagnosis

The diagnosis of HAP in nonventilated patients is substantially different than for VAP or for patients with severe HAP requiring intubation and mechanical ventilation. For nonventilated patients with HAP, clinical diagnosis is similar to that for CAP patients. Access to the lower respiratory tract via the endotracheal tube (ETT) allows substantially better diagnostic testing to be performed for intubated patients, the Achilles heel of nonventilated patient diagnosis. However, the effect of critical illness compromising clinical and radiologic diagnosis and the expanded differential diagnosis still results in substantial overlap.

Clinical signs and symptoms are the hallmarks for suspicion of pneumonia, similar to CAP. Some indication of an active infection including fever and leukocytosis is usually mandatory. However, hospitalized patients, particularly the critically ill, may not mount a significant fever because of the severity of their underlying disease. Leukocytosis is very nonspecific and can result from multiple noninfectious causes. Even PCT may be inaccurate for the decision to initiate empirical antibiotics in the critically ill. Physical signs of pneumonia, such as crackles in the egophony, cannot be easily detected in patients who are mechanically ventilated. Increased secretions are hard to quantify in intubated patients and may reflect inadequacies of airway management and macroaspiration rather than a new pneumonia.

Hypoxemia or any change in the oxygen or PEEP requirements of ventilated patients was considered highly sensitive for new-onset VAP. This theory led to a temporary emphasis on ventilator-associated events and complications defined by changes in oxygenation support as an objective quality improvement metric.[91] Subsequent studies demonstrated that ventilator-associated events and complications were neither specific nor sensitive for pneumonia and subject to ventilator manipulation.[92] However, recent attention to decreasing F_{IO_2} as much as possible, based on an associated mortality benefit, may improve the sensitivity of increased oxygen requirement for the diagnosis of VAP.

Radiologic diagnosis in HAP/VAP is also compromised. Critically ill patients often are unable to perform the deep inspiratory maneuver and breath-hold that are critical for good radiographic technique. In addition, the majority of patients with suspected HAP/VAP undergo a portable posteroanterior film without a corresponding lateral radiograph, significantly compromising interpretation. Many patients with suspected pneumonia already have abnormal chest radiographs from the underlying disease causing their ICU admission and changes associated with a new pneumonia may be subtle; comparison with previous chest radiographs is therefore critical. Adjustments in ventilator support can also cause dramatic changes in the degree of alveolar infiltrates, giving the bedside clinician an advantage over trained radiologists who must interpret without the benefit of clinical information.

Alveolar infiltrates are the most common radiographic pattern associated with HAP/VAP. However, the differential diagnosis of alveolar infiltrates in the critically ill patient is large. More specific signs include air bronchograms, especially if not associated with ARDS, and presence of a fissure sign (sharp demarcation of a fissure by an alveolar infiltrate on only one side). Radiographic suspicion of atelectasis based on volume loss on radiographic studies is inaccurate and actually more common in patients with pneumonia.[18]

Although the issue in radiographic diagnosis of HAP/VAP is usually lack of specificity owing to the almost universal presence of an abnormal radiograph, occasionally patients can have other signs and symptoms of pneumonia with a "normal" or unchanged chest radiograph. This may result from purulent tracheobronchitis but is more likely the result of the subtlety of changes or missed infiltrates. The latter are most likely in the lung bases, which are also the most common site for VAP.

CT scans clearly are superior to portable radiographs but cost, radiation exposure, and logistics prevent routine use. Although superior, CT scans are also nonspecific and cannot distinguish between many of the clinical problems in the differential diagnosis, but they clearly can detect occult infiltrates in patients with suspected "normal" chest radiographs. Abdominal CT scans ordered in the search for other sources of the fever or leukocytosis can often reveal alveolar filling densities in the lower lobes. Additional helpful CT scan information is the presence of cavitation, which is highly suggestive of pneumonia caused by specific pathogens—*Pseudomonas*, exotoxin-producing MRSA, and *Aspergillus.* Abdominal CT scans are also extremely accurate in detecting large pleural effusions that may be mistaken for parenchymal lung disease. However, the atelectasis that commonly accompanies larger pleural effusion may still be confused for pneumonia.

Bedside ultrasound may offer an alternative to chest CT scan to discriminate among the different causes of alveolar infiltrates detected on posteroanterior chest radiographs.[93] Ultrasound is clearly very accurate in detecting pleural effusions and can also pick up occult air bronchograms. Further research is needed in this area.

Microbiologic Diagnosis

Given the nonspecificity of clinical/radiographic diagnosis of HAP/VAP, microbiologic diagnosis becomes critically important. Despite decades of research, the microbiologic diagnosis of pneumonia in suspected HAP/VAP patients remains very controversial.

For nonventilated patients, microbiologic diagnosis is limited to blood cultures and rare positive sputum cultures. For institutions with nosocomial *Legionella,* the Binax *Legionella* urinary antigen enzyme immunoassay (Abbott Diagnostics, Santa Clara, CA) may be helpful. Increasing awareness of nosocomial respiratory viral infection has led to increased use of nasopharyngeal PCR assays.[90] However, the overwhelming majority of HAP cases in nonintubated patients have no defined etiology.

Microbiologic diagnosis in patients with HAP that requires intubation is more straightforward. A positive culture result from almost any respiratory sample from the ETT soon after intubation is highly diagnostic. The greatest problem is a negative culture result. In this situation, the result may be negative because pneumonia is not present or because the pathogen is highly sensitive to the empiric antibiotics often started before or soon after intubation. A negative culture result does have value: MDR pathogens such as MRSA, *Pseudomonas*, and *Acinetobacter* are extremely unlikely to disappear after a very short course of antibiotics[94] and empirical coverage can be adjusted appropriately.

The most controversial issue is microbiologic diagnosis in patients with VAP. The major debate is between an invasive approach with

quantitative cultures and use of semiquantitative cultures of tracheal aspirates. Professional society guidelines differ regarding the recommended approach. The IDSA/ATS HAP/VAP guidelines offer a weak recommendation for noninvasive sampling with semiquantitative cultures,[5] whereas the International ERS/ESICM/ESCMID/ALAT (European Respiratory Society/European Society of Intensive Care Medicine/European Society of Clinical Microbiology and Infectious Diseases/Asociación Latinoamericana del Tórax) HAP/VAP guidelines support a weak recommendation for distal quantitative cultures.[6] Discrepancies between the two guidelines may represent differences in the intended use, with concern in the IDSA/ATS guidelines that recommendation for invasive sampling and quantitative cultures could be used by policy makers to require this for even the smallest hospital.[5] The International HAP/VAP ERS/ESICM/ESCMID/ALAT guidelines placed greater emphasis on antibiotic stewardship and minimizing antibiotic therapy.[6]

Both sets of guidelines emphasized the results of two large multicenter clinical trials but vary on the interpretation. A French multicenter trial comparing invasive diagnosis with quantitative cultures to semiquantitative tracheal aspirates mandated that antibiotic therapy was started based only on a positive Gram stain result from the respective specimens (unless the patient was hypotensive).[95] Only 9% of the patients with treatment based on endotracheal aspirates did not receive initial antibiotic therapy compared with 47.5% for invasive culture-based therapy. Invasive culture results were positive in only 44% compared with 86% tracheal aspirate cultures, with significantly more polymicrobial infections and nearly three times more pathogens on culture for tracheal aspirates. All-cause mortality at 14 days after diagnosis, the a priori primary endpoint, was 9.6% less (95% confidence interval [CI] of the difference −17.4 to −1.8, $P = 0.02$) in the invasive group, while severity-adjusted 28-day mortality was also significantly lower. Antibiotic-free days in the next 28 days were significantly lower with invasive diagnosis, including all classes except carbapenems.

In contrast, the Canadian Critical Care Trials Group found no difference in 20-day mortality or use of antibiotics in an RCT of invasive diagnosis versus tracheal aspirates.[96] Two major differences in trial design may explain the discrepancy from the French multicenter trial. First, because of the 2 × 2 factorial design with monotherapy compared to combination therapy,[97] patients at high risk of MDR pathogens were excluded from the diagnostic trial. An equal number of patients were excluded because they were already taking the study antibiotic (imipenem or ciprofloxacin) or had pathogens known to be resistant to the study drugs. The result is that only 6.4% of patients had *Pseudomonas* infection or colonization compared with 20.3% in the French study, and significantly fewer cultures were polymicrobial. In addition, most analyses were carried out combining results of BAL cultures above and below the diagnostic threshold, the main criterion to distinguish between colonization and infection. To compound this issue, antibiotic therapy was not mandated by results of cultures and therefore antibiotics were continued in a high proportion of patients when the attending physician pretest probability of pneumonia being low and a negative culture result for either technique. Unlinking antibiotic treatment from results of cultures obviates the only beneficial effect of a diagnostic technique, severely compromising any conclusions that can be drawn from the study. Clearly, if antibiotic management is not to be based on results of quantitative cultures from distal specimens, no need to do these procedures exists.

Inclusion of both studies in a meta-analysis, along with three other single-center trials, not surprisingly results in no significant difference in clinically important outcomes, the basis of the IDSA/ATS guideline recommendation.[5] However, differences between the two studies may be illustrated by the appropriate use of each strategy. In ICUs with low risk of MDR pathogens and infrequent use of prior antibiotic therapy, the tracheal aspirate culture may be sufficient. Aggressive discontinuation of pneumonia antibiotics in patients with negative endotracheal aspirate culture results will accomplish many stewardship objectives in these units. For ICUs with patients with more complex conditions, higher risk of MDR pathogens, and the resulting need for combination empirical antibiotic therapy, quantitative cultures of distal secretions may be more appropriate, especially for antibiotic stewardship purposes.[6]

Several alternatives exist to address the real issues of availability and cost of bronchoscopic diagnosis of VAP. Two nonbronchoscopic BAL (NBBAL) catheters are commonly available for clinical use. For both, a respiratory therapist can perform the procedure, minimizing cost and allowing routine availability without a bronchoscopist. The first is the BAL CATH (Halyard Health, Inc., Alpharetta, GA), a mushroom-tipped catheter that can be reliably directed to either lung base.[98] Standard BAL quantitative culture procedures, including wedging into subsegmental bronchus, use of large volumes (120–150 mL), discarding the initial aliquot to minimize contamination/colonization, and a 10^4 CFU/mL threshold, can be used with this catheter. In contrast, the CombiCath (Prodimed, Le Plessis Bouchard, France), is a true mini-BAL; the recommended installation volume is only 10 to 20 mL with usual return volumes much less than 10 mL.[99] Because catheters are placed more distally and have less dilution, the usual threshold for positivity is 10^3 CFU/mL. The low return volumes essentially limit testing to Gram stain and culture, without the option for additional specialized tests such as cell count and differential or amylase. No randomized controlled study of antibiotic management based on NBBAL is available. However, comparison to bronchoscopic cultures suggests equivalent sensitivity with slightly worse specificity for NBBAL. The protected specimen brush has been used in many studies of invasive diagnosis of VAP but has fallen into some disfavor because of the additional cost and lower sensitivity compared with bronchoscopic BAL alone.

Quantitative culture of endotracheal aspirates represents an intermediate position between semiquantitative cultures of tracheal aspirates and quantitative cultures BAL specimens. A 1- to 2-log higher threshold for positive cultures ($>10^5$ or $>10^6$ CFU/mL) is required to exclude colonization.[100] Data overall suggest adequate sensitivity at significantly lower sensitivity and distal samples. In addition, the supplemental testing that assists analysis of BAL fluid is inappropriate or inaccurate on tracheal aspirate samples.

One argument against the use of quantitative cultures for each of these specimens is the extra cost and availability compared with semiquantitative cultures of tracheal aspirates. This is a spurious argument because quantitative cultures are performed daily in almost any microbiology laboratory on urine specimens. The quantitative loop technology used for urine cultures can be applied to BAL cultures with minimal differences compared to serial dilutions.

What has also become very apparent from the multiple studies on BAL diagnostic techniques is that quantitative cultures alone are not adequate to distinguish between patients with pneumonia and colonization. Therefore additional tests can be used to increase diagnostic comfort. The first and best validated is the use of a Giemsa stain to look for intracellular bacteria. The presence of intracellular bacteria in as few as 1% of neutrophils correlates with

positive culture results and may help assess borderline cultures.[101] BAL cell count and differential can easily be performed on a hemocytometer. The results and cell counts can be used to assess the adequacy of the lavage sample. Less than 50% neutrophils has a high negative predictive value for bacterial pneumonia and can increase the comfort level for stopping antibiotics in patients with negative or borderline culture results.[102] Occasionally a surprising finding such as a high proportion of eosinophils, indicative of acute eosinophilic pneumonia, or lymphocytes, suggesting either viral disease or hypersensitivity pneumonitis, can be found. An extremely high amylase level in BAL fluid is likely due to aspiration pneumonitis.[103] The advantage of amylase over pepsinogen, which has been used in other studies as an indication of aspiration,[104] is the routine availability of the serum assay and the fact that amylase can detect both oropharyngeal aspiration as well as aspiration of gastric contents, whereas an elevated pepsinogen level is likely only in the latter.

Currently, pathogen identification and antibiotic susceptibility testing of respiratory samples for the diagnosis of HAP/VAP has relied on standard microbiology techniques. However, molecular diagnostics for rapid diagnostics have improved to the point that they are now nearly ready for clinical use. PCR technology to detect the *mec*A gene for MRSA is available in many centers and represents the easiest and most accurate use of PCR technology.[105] Multiplex PCR to identify potential pathogens is limited by the number of slots available in the diagnostic kits. In addition, the high sensitivity of PCR technology will also need threshold determination to avoid over-diagnosing pneumonia in patients with colonization. More problematic is determination of antibiotics susceptibility based on the absence of specific gene mutations leading to antibiotic resistance. The correlation between the presence of a mutation and actual antibiotic susceptibility is not consistent and the clinical relevance of resistance genes detected by PCR is unknown.[106] Despite reservations, PCR and other molecular diagnostic platforms on the horizon offer great hope for more rapid determination of the etiology and antibiotics susceptibility in patients with HAP/VAP.[107]

Differential Diagnosis

Table 40.7 lists important entities in the differential diagnosis of HAP VAP. They can be divided into two groups: (1) those that cause an abnormal radiographic infiltrate with a separate source of fever and/or leukocytosis or (2) entities that themselves cause fever/leukocytosis and a radiographic infiltrate. Common causes of abnormal radiographic infiltrates without fever include congestive heart failure/pulmonary edema, atelectasis, or pleural effusions. In this setting, fever may be due to central line infections, catheter-associated urinary tract infections, or drugs. Other consistent findings in studies of quantitative culture diagnosis of VAP is that multiple other potential causes of fever can be found in patients with negative quantitative cultures.[95,108] Many of these require either a procedure, such as removal of a central venous line, or alternative antibiotics from those standard for HAP/VAP. Aspiration pneumonitis is the most common entity that can cause both radiographic infiltrate and fever/leukocytosis.[8] For most of these alternative etiologies, additional testing in BAL fluid, such as BAL amylase levels, can help redirect investigation to an alternative etiology.

Management

Management of HAP/VAP is predominantly a two-phase antibiotic algorithm with some ancillary support technologies important in certain cases. Antibiotic management is divided into the initial empirical stage and a definitive management phase. The initial empirical antibiotic therapy is very institution specific and may even vary between different ICUs in the same institution. Conversely, once a specific etiology has been established, treatment regimens are fairly standard between institutions, although still not without controversies. Antibiotics commonly used for HAP/VAP are listed in Table 40.8.

Empirical Antibiotic Therapy

The basis of empirical antibiotic therapy is initiation of therapy likely to cover the overwhelming majority of potential bacterial etiologies based on local antibiograms. The threshold for adequate coverage is debatable but is usually greater than 90% of usual isolates.[5,6] Unfortunately, antibiograms available in many hospitals may provide inadequate direction for empirical treatment of HAP/VAP. Almost all antibiograms are based on "reliable" cultures, which are almost exclusively blood cultures. Analysis of only bacteremia may result in a different spectrum of gram-negative bacteria and antibiotic susceptibilities compared with respiratory cultures. For example, *E. coli* bacteremia is dominated by patients with complicated urinary tract and intraabdominal infections and is disproportionately highly sensitive compared with an *E. coli* respiratory sample in a patient with HAP/VAP who has received prior antibiotics. In addition, if multiple cultures with the same pathogen occur in the same patient, only the first is used to construct antibiograms, potentially missing development of resistance during therapy.

β-Lactams are the backbone of treatment for HAP/VAP.[109] Therefore one of the most critical decisions for empirical HAP/VAP treatment is which β-lactam antibiotic to use. Piperacillin/tazobactam dominates the penicillin class of β lactams; cefepime

TABLE 40.7 Differential Diagnosis of Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

No Associated Fever[a]	Associated Fever	
Congestive heart failure	Aspiration pneumonitis	Hypersensitivity pneumonitis
Pulmonary hemorrhage/bleeding	Acute respiratory distress syndrome	Acute eosinophilic pneumonia
Pleural effusion	Transfusion-related	Pulmonary infarction
Atalectasis	Extrapulmonary infection	

[a]Associated fever and leukocytosis from concomitant extrapulmonary infection (e.g., central line, urinary tract, *Clostridium difficile* colitis) or noninfectious (e.g., drug fever, deep venous thrombosis).

TABLE 40.8 Antibiotics Commonly Used for Treatment of Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

Class/Antibiotic	Dose	Low Risk for Multidrug Resistance Only	Multidrug Resistance	Extensively Drug Resistant	Combination Only in Multidrug Resistance
Penicillin					
Piperacillin/tazobactam	4.5 g q6h		X		
Ampicillin/sulbactam	3 g q6h	X		X+	
Cephalosporin					
Ceftriaxone	2 g q24h	X			
Ceftazidime	2 g q8h		X		
Cefepime	2 g q8h		X		
Ceftolazone/tazobactam[a]	3 g q8h			X	
Ceftazidime/avibactam[a]	2.5 g q8h			X	
Carbapenem					
Ertapenem	1 g q24h	X			
Imipenem/cilastatin	0.5 g q6h to 1 g q8h		X		
Meropenem	1 g q6–8h		X		
Meropenem/vaborbactam[a]	2 g/2 g q8h			X	
Aminoglycosides					
Gentamicin	7 mg/kg loading dose, then TDM				X
Tobramycin	7 mg/kg loading dose, then TDM				X
Amikacin	20 mg/kg loading dose, then TDM				X
Plazomicin[a]	15 mg/kg q24h				X
Fluoroquinolones					
Ciprofloxacin	400 mg q8h	X			X
Levofloxacin	750 mg q24h	X			X
Polymixins					
Colistin	5 mg/kg IV loading dose, then 2.5 mg × (1.5 × CrCl + 30) IV q12h				X
Polymixin B	2.5–3.0 mg/kg per day in 2 daily IV doses				X
Tetracyclines					
Tigecycline[b]	100 mg, then 50 mg q12h				X
Minocycline	200 mg q12h				X

[a]Not approved by the U.S. Food and Drug Administration (FDA) specifically for pneumonia.
[b]FDA warning for hospital-acquired pneumonia/ventilator-associated pneumonia, + for *Acinetobacter* only.
CrCl, Creatinine clearance; *IV,* intravenous; *q,* every; *TDM,* Therapeutic drug monitoring.

and ceftazidime are the most common cephalosporins. Narrower-spectrum β-lactams, such as amoxicillin/sulbactam, ceftriaxone, and ertapenem, can only be used empirically in patients who were at low risk for MDR pathogens. In essence, this means patients who have not had prior antibiotic therapy during the current hospitalization; use is therefore often limited to postoperative surgical patients. HAP/VAP guidelines recommend that when a β-lactam antibiotic covers more than 90% of usual isolates, monotherapy with the narrowest-spectrum β-lactam available is appropriate.

The importance of the β-lactam backbone is demonstrated in two clinical scenarios.[109] Patients with reported penicillin allergy fare substantially worse than nonallergic patients with equivalent infections, likely owing to the increased use of aztreonam or other alternatives to β-lactams. The second is the substantially increased mortality associated with carbapenem-resistant Enterobacteriaceae (CRE) infections.[110] Even though resistant by standard laboratory susceptibility testing, a carbapenem combined with an agent like polymyxin B or colistin will result in higher cure rates. Given this adverse effect on outcomes and the very low proportion with true serious β-lactam allergies, many centers perform skin testing for penicillin allergy and/or desensitization in critically ill patients with purported penicillin allergies.[111]

The choice of empirical β-lactam is most dependent on prior antibiotic therapy. Most hospitals have a preferred β-lactam for empirical treatment of suspected resistant gram-negative infections—either a penicillin (piperacillin/tazobactam) or a cephalosporin (cefepime or ceftazidime). Unfortunately, many patients with HAP/VAP have already received prior antibiotics, most likely including this preferred β-lactam. Whether switching to a cephalosporin in patients previously exposed to penicillins, or vice versa, leads to less inappropriate initial empirical antibiotic therapy is very

dependent on local antibiograms. Previously, empirical carbapenem therapy was the safest option. However, the emergence of carbapenem resistance in many species, particularly Enterobacteriaceae, has made this class of antibiotics less reliable as empirical therapy. Clearly the safest option is to not use that class of antibiotic to which the patient has previously been exposed, particularly if that exposure was recent or prolonged.

The majority of ICUs in larger hospitals do not have one β-lactam to which more than 90% of gram-negative isolates are susceptible.[5,6] In this situation, combination therapy is recommended; the most common agents are fluoroquinolones and aminoglycosides. The data supporting this recommendation remain controversial. Meta-analyses cannot demonstrate a significant survival advantage to combination therapy.[112] The largest clinical trial of a combination of a β-lactam and fluoroquinolone compared with a β-lactam alone was from the Canadian Critical Care Trials Group.[97] Unfortunately, as noted earlier, patients at risk for MDR pathogens were specifically excluded from this study. In addition, they used a β-lactam that covered more than 90% of the cultured pathogens. Little potential existed to demonstrate benefit from the addition of the fluoroquinolone with this trial design. Despite this, patients who actually did have an MDR pathogen cultured had better outcome with combination therapy. There are many studies of combination versus monotherapy or U.S. Food and Drug Administration (FDA) registration trials in which a novel agent was compared against a different β-lactam combination regimen. None of these studies allowed entry of patients with immunocompromise or at very high risk of death at the time of diagnosis. In contrast, epidemiologic studies of all patients with a specific pathogen (e.g., *Pseudomonas*) demonstrate better outcomes with combination therapy.[113,114] The strongest argument for combination therapy from an inefficacy standpoint can be made for neutropenic patients and those with septic shock.[115]

However, the main reason for combination therapy is to avoid initially inappropriate antibiotic therapy.[113] Initially inappropriate antibiotic therapy is consistently associated with worse outcome including mortality. These adverse outcomes did not appear to be reversed when correct therapy was subsequently initiated.[116] A dose-dependent effect is seen; longer times to appropriate therapy are associated with progressively higher associated mortality and morbidity. For this reason, professional society guidelines all recommend initial combination therapy for use in the ICU in which less than 90% of gram-negative pathogens are susceptible to a single β-lactam antibiotic.[5,6]

The need for empirical MRSA coverage is also evolving. In many ICUs, the rate of MRSA pneumonia is decreasing, possibly because of better prevention methods. Conversely, increasing toxicity with vancomycin, particularly when combined with common gram-negative agents such as piperacillin/tazobactam, is also being detected.[117] How low of a threshold must be present before empirical anti-MRSA therapy is not needed is unknown. Use of clinical risk factors may allow better estimation of need. Probably the best risk factor is presence of MRSA in nasal swabs of patients admitted to high-risk units and ICUs, as mandated by local law in many states.[118] A recent negative nasal swab has high negative predictive value, especially combined with lack of clinical risk factors such as recent antibiotic exposure, hemodialysis, and need for wound care. Management of suspected MRSA pneumonia is likely the first treatment decision that can be affected by routine availability of new rapid diagnostic tests in tracheal aspirates or BAL. Only a single gene and an easily detected mutation are ideal for PCR technology.

Antimicrobial Treatment of Specific Pathogens

Once results of diagnostic testing are returned, a specific antibiotic treatment regimen can be determined for each pathogen. With the increasing resistance in many species, knowledge of actual minimal inhibitory concentrations (MICs) is desirable rather than a simple designation as sensitive, intermediate, or resistant. MICs that approach breakpoints may require choice of an alternative agent, pharmacodynamic optimization, or continued use of combination therapy. Conversely, pathogens with limited treatment options with an MIC just above the breakpoint may allow use of an agent despite the bacteria being technically resistant.

Pseudomonas aeruginosa

P. aeruginosa HAP/VAP is one of the most difficult infections to treat in the critically ill. *Pseudomonas* has multiple resistance mechanisms affecting every one of the clinically available antibiotics.[119] *Pseudomonas* is also classic for developing antibiotic resistance during therapy.[120,121] *Pseudomonas* HAP/VAP often affects patients with compromised immunity, altering the ability of host defense to contribute to eradication. In addition, *Pseudomonas* has multiple exotoxins that can cause cavitation, bloodstream invasion, and overt septic shock.[122] The initial failure rates above 50% and high recurrence rates seen in many studies are therefore not surprising.[123] Interestingly, only half of supposed recurrences are truly recurrence; the other half are new infections with a different strain of *Pseudomonas*, most likely because *Pseudomonas* is ubiquitous in the hospital environment.[124]

Of all nosocomial pneumonias, *Pseudomonas* HAP/VAP is most consistently treated with combination therapy. Support for this practice comes most clearly from epidemiologic studies.[114] Meta-analyses of the *Pseudomonas* subgroups of randomized controlled trials of HAP/VAP do not show a clear-cut benefit,[112] although clinical response rates in all of these studies were only 50% for both monotherapy and combination therapy.[123] A theoretical benefit of preventing emergence of antibiotic resistance during therapy has never been demonstrated.

Given the lack of a clear-cut benefit for combination intravenous therapy, aerosolized antibiotics have often been used for *Pseudomonas* HAP/VAP.[125] This may be particularly advantageous for patients with cavitary pneumonia in which penetration from the vascular space may be compromised. Despite an encouraging preliminary study,[126] results of an RCT of aerosolized antibiotics showed no overall benefit.[127] However, there was a trend toward benefit in patients with highly resistant pathogens such as *Pseudomonas*.

Acinetobacter species

HAP/VAP caused by *Acinetobacter baumannii* and other species has become extremely difficult to treat. The incidence of *Acinetobacter* as a cause of HAP/VAP varies somewhat dramatically among ICUs, varying from never seen in some ICUs to more common than *Pseudomonas* in others.[128] Intrinsically more resistant than other gram-negative pathogens, the fairly rapid emergence of carbapenem resistance has severely limited treatment options. The sulbactam component of Unasyn has activity against carbapenem-resistant *A. baumannii* (CRAB) and can be used in younger trauma patients and others with intact immune systems.[129]

The high frequency of CRAB in some ICUs has led to resurgence in the use of polymyxins such as polymyxin B and colistin. These older agents are clearly associated with increased nephrotoxicity and of questionable efficacy. Use of tetracyclines, including minocycline[130] and tigecycline, for CRAB pneumonia, despite the

FDA black label warning against use of the latter agent in pneumonia, is also associated with significant failure rates. Currently, use of pharmacokinetic (PK)/pharmacodynamic (PD)-optimized carbapenem with a polymyxin appears to have the best outcomes despite in vitro resistance to the carbapenem.[131] Once again, aerosolization of polymyxins or amikacin is often used in intubated patients, given the limitations of intravenous therapy and a desire to avoid nephrotoxicity.[125] Development of new treatment for CRAB is a Centers for Disease Control and Prevention and FDA high-priority agenda for the antibiotic crisis.

Enterobacteriaceae

The Enterobacteriaceae are a large and heterogeneous group of pathogens that are common causes of HAP/VAP. Some are exquisitely sensitive to narrow-spectrum antibiotic such as ceftriaxone and ampicillin. Others are resistant to all β-lactams, including carbapenem, and many other classes of drugs. The very common *E. coli* can represent the entire spectrum of antibiotic resistance in this family. For the overwhelming majority of Enterobacteriaceae, appropriate antibiotic therapy is predominantly dependent on prior exposure.

The emergence of two specific resistance patterns has led to dramatic changes in the management of HAP/VAP caused by Enterobacteriaceae. The first is the emergence of extended-spectrum β-lactamases (ESBLs). Predominantly driven by prior exposure to cephalosporins, ESBLs are very adequately treated with carbapenems.[132] However, increased antibiotic pressure has led to the second major pattern of antibiotic resistance, the emergence of CRE. The most common mutation causing CREs in the United States is the *Klebsiella*-producing carbapenemase. The variety of specific β-lactamase mutations that cause these resistance patterns has recently been classified into four groups.[133] However, coverage of some members of the group with new antibiotics does not necessarily lead to coverage of the entire group.

Although carbapenems were adequate for ESBL pneumonia, treatment of CRE pneumonia initially consisted of polymyxin-based combination therapy.[110] However, development of new β-lactamase inhibitors appears to be an effective strategy to address CREs, although resistance appears quickly.[134] Ceftazidime/avibactam has been FDA approved for complicated urinary tract and intraabdominal infections but has been used clinically in pneumonia.[134] The recently released meropenem/vaborbactam combination demonstrated superior activity over standard-of-care treatment without the new β-lactamase inhibitors. A variety of other β-lactam and novel β-lactamase inhibitor combinations are in development. However, newer resistance mechanisms, such as New Delhi metallo-β-lactamase, continue to develop in this family of bacteria.

Methicillin-Resistant *Staphylococcus aureus*

Although as noted earlier that MRSA HAP/VAP may be decreasing in overall frequency, it remains an important pathogen. Two main treatment options are available for MRSA pneumonia. As the only potential treatment for MRSA for many years, vancomycin had become the legacy de facto standard of care despite no FDA-approved indication for HAP/VAP. However, vancomycin failure rates consistently in the 40% range were seen in most studies of MRSA HAP/VAP.[135,136] Attempts to improve outcome by increasing trough levels and PK optimization were associated with increased incidence of acute kidney injury and no improvement in clinical outcomes.[137]

Linezolid is the first agent to show superiority to vancomycin. Subgroup analysis of MRSA cases in the two original FDA registration trials of gram-positive pneumonia demonstrated improved outcomes.[135] A head-to-head comparison of adjusted-dose vancomycin and linezolid confirmed this superior clinical response rate.[138] A mortality benefit was found in the subgroup analysis of the registration trials when linezolid salvage therapy was not available for vancomycin failures. This mortality difference was not found in the head-to-head comparison with linezolid available for vancomycin failures. Linezolid has no nephrotoxicity and the clear-cut bone marrow toxicity seen with prolonged use was not observed during the shorter treatments used for HAP/VAP.

Other glycopeptides have been released for treatment of MRSA infections; although possibly superior to vancomycin,[139] they have not been demonstrated to be superior to linezolid for pneumonia and also carry a nephrotoxicity risk. Ceftaroline, a cephalosporin with MRSA activity, has been approved for CAP[140] but experience with HAP/VAP is limited. Other oxazolidonones are also in development for MRSA pneumonia.

Antibiotic Stewardship

Antibiotic stewardship should be a core competency of critical care physicians.[141] Critically ill patients are at the highest risk for death from MDR pathogens while the ICUs are the breeding grounds for MDR pathogens. True antibiotic stewardship is not solely restrictions on antibiotic use and discontinuation of unnecessary antibiotics. Instead, the CDC definition of "the right drug for the right patient at the right dose" implies other important decisions in diagnosis and antibiotic management of HAP/VAP.[142]

Antibiotic Streamlining. Professional society HAP/VAP guidelines recommending initial broad-spectrum combination empirical antibiotic are predicated on subsequent antibiotic streamlining or deescalation once culture or other data reveal the etiology. This streamlining is much easier if an accurate diagnosis is made; hence the international HAP/VAP guideline recommendation for routine use of distal lung samples and quantitative cultures.[6] However, antibiotic streamlining can be safely performed based on negative culture results and less accurate samples.[143] Although intubated patients with a negative lower respiratory tract culture result may still have pneumonia, the negative predictive value for etiology for MDR pathogens such as MRSA, *Pseudomomas*, and *Acinetobacter* is sufficiently high that additional or broader empirical coverage started specifically for these pathogens can be discontinued. The other value of a negative culture result is to direct attention away from pneumonia to other potential sources of fever or pulmonary infiltrates.[95]

Duration of Therapy. The majority of patients with HAP/VAP should be adequately treated with a 7- to 8-day course of antibiotics, especially if initial antibiotic therapy was appropriate. No difference in mortality was seen when patients treated with 8 days of therapy compared with 15-day duration in a large multicenter study.[121] Concern has been raised regarding a higher number of recurrences in the shorter therapy group for patients with a nonfermenter *(Pseudomonas*, *Acinetobacter)* etiology. However, the actual recurrence rate was not different owing to differences in the observation time without antibiotics, and the mortality specifically in the nonfermenter pneumonia population was lower in the 8-day duration group.

The real issue with antibiotic duration is the high incidence of failure of the primary antibiotic regimen in patients with *Pseudomonas* and *Acinetobacter* HAP/VAP.[144] Randomized controlled trials of antibiotic duration do not support the idea that longer duration of therapy prevents this failure. So if a duration of antibiotics

longer than 8 days is considered necessary the safer option may be to alter the antibiotic regimen rather than continuing a regimen that may be failing.

Pharmacokinetic/Pharmacodynamic Optimization. Given the high failure rates for antibiotic treatment of HAP/VAP, an important part of antibiotic stewardship is optimization of the antibiotics used for treatment. Basic PD concepts include understanding the principal determinants of successful treatment. The area under the curve of antibiotic levels in serum, particularly that above the MIC, is the primary PD parameter for antibiotics such as aminoglycosides, quinolones, and linezolid with dose-dependent killing. Administration of larger doses less frequently is the logical extension of these data. For example, dosing every 24 hours is the standard for aminoglycosides. Conversely, time-dependent killing, as measured by time above the MIC, is the critical parameter for β-lactams. This has led to calls for prolonged, even continuous, infusions of β-lactams.

Although optimizing PK/PD seems logical, the clinical support for routine use is still lacking. A major argument against PK/PD optimization is a HAP/VAP clinical trial comparing prolonged (3-hour) infusion doripenem with short infusion of imipenem.[144] Doripenem was the more active drug by distribution of MICs. Despite the PK/PD optimization of doripenem, the Data Safety Monitoring Board stopped the study prematurely because of excess deaths in the doripenem arm. The most likely explanation of this finding is selection for a highly resistant subpopulation with an MIC above that attained by the prolonged infusion, especially in high-inoculum infections such as HAP/VAP. No difference in clinical parameters until discontinuation of the study drug is consistent with suppression but not eradication of a subpopulation. Trial design precluded use of combination therapy, which may address this issue in clinical practice.

Other studies of continuous or prolonged infusion have led to equivocal or conflicting results.[145,146] Given the heterogeneity of infections and patients, this finding is not that surprising. Most likely these equivocal results represent three populations: (1) low-inoculum infections with highly sensitive pathogens in which short infusion is highly effective and a difference with prolonged infusion therefore is difficult to detect; (2) an intermediate- or high-inoculum group with higher MICs but a minimal proportion of highly resistant pathogens in which the benefit of PD optimization can be demonstrated; and (3) a high-inoculum infection with a significant highly resistant subpopulation, in which prolonged infusion is beneficial for the dominant group but selects for the subpopulation. Unfortunately, most HAP/VAP cases fit in the latter two populations where PK/PD optimization is necessary but not sufficient for high rates of clinical cure.

Therapeutic drug monitoring (TDM) is also an important component of PK/PD optimization. However, TDM is only routinely available for a few agents—principally, aminoglycosides and vancomycin. In these settings, the emphasis is more on avoiding toxicity than on improving cure. Attempts to push vancomycin trough levels to improve the cure of MRSA HAP/VAP and even bacteremia were found to increase nephrotoxicity without a benefit in infection outcomes.[137]

Altered pharmacokinetic properties have also been increasingly recognized in the critically ill. Occult acute kidney injury is not surprising given the multitude of renal insults to which critically ill patients are subjected. However, certain patient subpopulations have also been demonstrated to have increased renal clearance with resultant underdosing of antibiotics and other medications.[147] Probably most importantly, both renal and hepatic clearance are dynamic processes in the critically ill and can vary day to day, if not hour to hour.

An additional factor is that clinical TDM measures only serum levels, whereas the clinically relevant level may be in the alveolar space. Antibiotics vary in the amount lung penetration (i.e., the ratio of alveolar to serum levels). Unfortunately, aminoglycosides and vancomycin have poor lung penetration such that even pushing serum levels may not result in higher alveolar levels. As part of new drug development, BAL levels of the new agent are often measured. Unfortunately, often this assessment of alveolar levels is only in healthy volunteers and may not accurately represent the situation in critically ill patients with altered PK. The general approach to this issue is to use higher doses of antibiotics for pneumonia than may be effective in other sites of infection.

Aerosolized Antibiotics. Interest in aerosolized antibiotics is a response to the adverse PK/PD, lung penetration, and toxicity of maximally dosed intravenous antibiotics. A reverse gradient of antibiotic concentration now occurs with the highest levels in the lung and lower levels in serum, potentially avoiding toxicity. In addition, the very high levels attainable in the lung with aerosolization can clearly exceed borderline MICs for MDR pathogens.[127] Once again, clinical proof for this theoretical benefit is not definitive. The largest RCT of supplemental aerosolized antibiotic did not demonstrate a survival benefit overall, although certain MDR pathogens may have benefited.[126] Similar to other antibiotic management issues, the optimal patient population (one highly enriched for MDR pathogens) may not have been studied. A major issue with aerosolized antibiotics is synchronization of delivery with the ventilator such that the majority of the dose is not deposited in the ventilator tubing and ETT.

Assessment of Response

Given the emergence of a variety of resistance patterns, an increase in overall resistance rates, and a shift in MIC distribution to higher levels, failure of initial antibiotic therapy for HAP/VAP is not uncommon.[123] However, the diagnosis of failure of treatment for HAP/VAP is compromised in the critically ill. Despite early closure for excess mortality in the doripenem study,[123] the Clinical Pulmonary Infection Score[148] did not distinguish between the two groups for more than 7 days. The Clinical Pulmonary Infection Score is simply a numerical composite of the parameters most clinicians follow to assess response to therapy—fever, leukocytosis, amount of tracheal secretions, oxygenation, and chest radiographic changes.[149] Simple disappearance of the pathogen on culture, particularly when the respiratory tract is sampled while the patient is still receiving antibiotics, is also not definitive. This difficulty in clinically assessing response to therapy has been long recognized and led the FDA to recommend mortality as the endpoint for equivalency in registration trials of new agents for HAP/VAP.[150]

PCT can assist in identifying patients whose antibiotic therapy is effective and can be discontinued safely. Several RCTs have demonstrated the safety, and even a potential mortality benefit, of discontinuing antibiotics when PCT levels fall to less than 20% of the initial level or below 0.5 ng/dL.[151,152] However, a persistently elevated PCT level does not necessarily correlate with the need for ongoing antibiotic therapy and may simply represent ongoing sterile inflammation.

Adjunctive Treatment

Ventilator Management. Pneumonia is the most common form of acute lung injury, and ventilator management in patients with pneumonia may put them at even greater risk of secondary lung

injury than other etiologies of ARDS.[75] The markedly decreased compliance and airway obstruction in pneumonia are even more likely to shift the distribution of large tidal volumes to noninvolved areas, causing overdistention. These lower tidal volumes and careful attention to plateau pressures may therefore be even more critical in patients intubated for pneumonia. Surprisingly, this is significantly less of an issue in VAP.

Occasionally, severe hypoxemia can result from unilateral pneumonia. In this situation, increasing PEEP or tidal volume may actually exacerbate hypoxemia by alveolar overdistention of the good lung, with a resultant increase in pulmonary vascular resistance and greater shunting of blood to the pneumonic lung. Positional therapy with the good lung down can temporize these until antibiotics and secretion clearance restore hypoxemic vasoconstriction and improve alveolar ventilation. However, simple ventilatory techniques may fail, and pneumonia still remains the most common disease leading to use of venovenous ECMO.[153,154]

Secretion Clearance. Secretion clearance can be a critically important component to the management of pneumonia. The most persistent problem after serious HAP/VAP is an inability to handle secretions, leading to repeated need for endotracheal intubation. Inability to handle secretions is often associated with neuromuscular weakness, leading to ineffective cough and expectoration.

The most effective mucolytic therapy for HAP/VAP is ensuring adequate systemic hydration, followed by use of hypertonic saline solution aerosols. Acetylcysteine (Mucomyst) is no better than saline solution aerosol in patients without airway stents and has been linked to an increase in pneumonia. DNAase is also of no benefit in patients without cystic fibrosis.

An effective cough requires both accessory inspiratory and expiratory muscles. The inspiratory muscles are needed to generate a large tidal volume, whereas the expiratory muscles are required to perform the forced expiratory maneuver needed to mobilize secretions. The third component is the ability to totally occlude the vocal cords or glottis during initial exhalation to generate the large pressure gradient needed to move secretions proximally. All three components are compromised in patients with HAP/VAP, particularly those requiring endotracheal intubation. The catabolic state in pneumonia, underfeeding, and both disuse and use atrophy all affect the skeletal muscle forming the diaphragm and accessory respiratory muscles. When mechanical ventilation duration was long enough to require tracheostomy, effective cough and poor secretion clearance are often the limiting factors of tracheostomy removal once successful weaning from mechanical ventilation occurs.

Prevention of HAP/VAP

Although prevention of CAP is generally outside the responsibility of critical care practitioners, prevention of HAP, especially VAP, is clearly an important consideration for intensivists. Most of the research has been directed at prevention of VAP, although only certain aspects are unique to HAP.

The keys to prevention are to intervene in critical aspects of the pathogenesis and can be organized along these lines. General infection control measures are critically important for prevention of HAP/VAP.[155] Careful attention to universal handwashing, appropriate isolation, and careful decontamination of respiratory therapy equipment are well-established principles.

By far, the most important prevention strategy for VAP is shortening the duration of mechanical ventilation. The risk of VAP increases with each increasing day of mechanical ventilation and begins to increase exponentially after 7 days.[156] Therefore strategies to facilitate early discontinuation of mechanical ventilation are critically important. Daily awakening from sedation and daily spontaneous breathing trials have been demonstrated in RCTs to shorten the duration of ventilation.[157–159] A side benefit of this early discontinuation is decreased VAP rates. The only caveat is that reintubation is a significant risk factor for VAP.[160] Therefore appropriate selection of patients for extubation is critically important.

Prevention of Aspiration

Elevation of Head of Bed

One of the simpler HAP/VAP prevention methods is to keep the head of the bed elevated to decrease the frequency and volume of aspiration.[161,162] The actual degree of elevation and contraindications remain debatable but this has become standard practice in most ICUs. The decrease in early-onset VAP observed over the past few years may be a result of this routine practice. A further extension of this concept is getting the patient out of bed into a chair, even if the patient is still endotracheally intubated.[163] Increased emphasis on mobilization, and even ambulation, of mechanically ventilated patients has multiple beneficial effects, including pneumonia prevention.

Maintenance of Tracheal Tube Cuff Pressure

Aspiration into the proximal trachea is almost impossible to prevent in patients who are endotracheally intubated. The presence of an ETT prevents the vocal cords from fully occluding and compromises laryngeal function. The result is near-universal microaspiration in patients with ETTs. Several manipulations have attempted to minimize the degree of microaspiration. Probably the most effective is maintaining the pressure in the ETT cuff adequately to maintain pressure against the lateral tracheal walls. This pressure is usually in the 20- to 25-cm H_2O range, below that needed to avoid pressure necrosis of the tracheal mucosa, with appropriately sized ETTs. Maintaining continuous control of tracheal cuff pressure resulted in a decrease in VAP incidence from 22 to 9.7 confirmed cases/1000 ventilator days.[164]

Modified Endotracheal Tubes

Several modifications of the standard ETT tube have been attempted to prevent the development of VAP. The most overt modification is the use of continuous aspiration of subglottic secretions (CASS) specialized ETTs. For CASS, a separate catheter incorporated into the dorsal surface of the ETT with an opening just above the ETT cuff is used to aspirate secretions that pool above the cuff. CASS is ineffective unless tracheal tube cuff pressures are maintained high enough to cause secretions to pool.[165] Occlusion of the additional port also occurs frequently. When maintained properly, CASS tubes can significantly lower the risk of pneumonia, particularly in certain populations.[166] However, the dramatic difference in price compared with a standard ETT prevents more routine use.

Another strategy is to modify the composition and shape of the ETT. These tubes attempt to address the problem of microaspiration through folds and standard ETT costs resulting from a diameter intentionally larger than that of the trachea. Thinner, more pliable construction material prevents development of these folds. In addition, a tapering shape may prevent a plunger-like effect of ETT movement that occurs frequently with position changes and patient movement. For either strategy to be effective, cuff pressures once again must be maintained adequately to provide a continuous seal. The benefit of these tubes on preventing VAP is less well established.[167] Although less expensive than CASS tubes, routine use of these tubes can significantly increase cost.

Early Tracheostomy

Considerable debate remains regarding the benefits of early tracheostomy on prevention of VAP.[168,169] The obligate microaspiration resulting from ETT separation of the vocal cords and laryngeal dysfunction can be obviated by tracheostomy. A percutaneous dilatational tracheostomy prevents many of the surgical site infections and other complications seen with the larger incision and tracheal ring resection technique for standard tracheostomy.[168] A tracheostomy is also often associated with less agitation and resultant use of sedative medications and increased caregiver comfort with patient mobility. Despite these theoretical benefits, results of studies of early tracheostomy are somewhat equivocal[169] and significant family resistance to this intervention remains.

Prevention of Oropharyngeal Colonization

A second primary focus of prevention of HAP/VAP is maintaining the normal microbiome of both the oropharynx and the lower respiratory tract. Not surprisingly, antibiotic therapy is the greatest threat to maintenance of the normal microbiome. Multiple studies of diagnostic strategies that result in less antibiotic exposure are associated with decreased mortality, and specifically decreased incidence of new superinfection pneumonia, especially with MDR pathogens.[95,148] Therefore careful attention to antibiotic stewardship is a major component of pneumonia prevention.

Maintenance of a normal lung microbiome in ventilated patients is a new frontier.[1] However, the normal variation in the microbiome throughout the lung is clearly affected by metabolic processes, pH, and oxygen tension. Alteration in the lung microbiome may therefore be an explanation for the finding that lower FIO_2 is associated with lower mortality independent of correction of hypoxemia. Tighter glycemic control, enteral rather than parenteral feedings, and permissive hypercapnia may all exert effects on the lung microbiome, but a differential effect remains to be proven.

Prophylaxis of Gastrointestinal Bleeding

In the past, major emphasis has been placed on the role of stress ulcer prophylaxis in predisposition to pneumonia. The original theory suggested that maintenance of a low gastric pH may prevent pneumonia, therefore favoring sucralfate. Unfortunately, sucralfate was consistently found to create a slightly higher risk of stress mucosal ulceration. More recent data have suggested that, although proton pump inhibitors and histamine-2 blockers may increase the risk of pneumonia, the need for prophylaxis of GI bleeding itself may not be necessary, particularly in patients who are adequately hemodynamically resuscitated and/or receiving enteral nutrition.[166,170,171] The fact that some of the most common etiologies of HAP/VAP—*Pseudomonas*, *Acinetobacter*, and MRSA—are not typically found in the GI tract also suggests prevention of oropharyngeal colonization by maintaining a lower gastric pH is not a significant benefit. Conversely, elevation of the head of the bed may exert its greatest benefit for prevention of pneumonia by minimizing reflux of fluids containing enteric pathogens into the posterior oropharynx.

Treatment of Colonization

An alternative strategy, often used in conjunction with prevention of colonization, is active treatment of colonization. This can be separated into treatment of oropharyngeal colonization only versus entire GI tract decontamination.

Simple oral hygiene, such as routine tooth brushing, has some benefit in prevention of pneumonia. Addition of 2% chlorhexidine oropharyngeal rinsing has incremental benefit and is relatively low risk for selecting for antibiotic-resistant pathogens.[172] The major limitation of these simple measures is cost, both in terms of acquisition costs and the time needed to perform hygiene by the bedside nurses.

Active intervention to treat oropharyngeal colonization is not without risk. The importance of the normal flora is illustrated by the adverse effects of iseganan, an antimicrobial peptide active against almost all bacteria. Oropharyngeal application of iseganan did not significantly decrease VAP rates but was associated with a trend for increased mortality.[173]

Selective Digestive Tract Decontamination

By far the most extensively studied and most aggressive form of topical antibiotic strategy to prevent colonization is selective digestive tract decontamination (SDD). The focus of this strategy is on preventing pneumonia by almost sterilizing the entire GI tract, including the large bowel. Therefore the antibiotics used are directed primarily at gram-negative bacilli (usually polymyxin B and an aminoglycoside) and *Candida* (usually amphotericin B). Most regimens include two components—topical antibiotics in the oropharynx and nonabsorbable antibiotics via a gastric tube. Some regimens also include an initial short course of systemic antibiotics. Despite more than 40 RCTs and several meta-analyses,[174,175] the benefit of SDD remains unclear. However, several patterns have emerged. Selective SDD fairly consistently decreases the incidence of VAP when systemic antibiotics are used for the first 48 to 72 hours.[176] However, an equivalent benefit on prevention of VAP has been found with a short course of prophylactic antibiotics alone.[177] Statistical adjustment was required for the only study to demonstrate a lower mortality in the SDD group, despite lower rates of VAP.[178] A major concern with SDD is the potential to promote antibiotic resistance, especially with the increasing frequency of MDR pathogens. SDD has been studied mainly in ICUs with a low baseline incidence of MDR pathogens, and the result of introduction to units with a high baseline frequency of MDR pathogens is unknown.[179] Recent data on the role of possible gut translocation in causing pneumonia in patients with ARDS suggest another potential high-risk population in which SDD may be beneficial. Despite the extensive clinical database, SDD use remains confined to only certain ICUs or types of patient.

Enteral Nutrition Strategies

Malnutrition is clearly associated with an increased risk of pneumonia and increased mortality in the critically ill.[180] In addition to classic effects on cell-mediated immunity, an effect specific to pneumonia is increased binding of gram-negative bacilli, including *Pseudomonas*, to epithelial cells.[181]

Enteral nutrition is the preferred route for treating and preventing malnutrition in the critically ill. The optimal timing, volume, and site of infusion remain controversial. Continuous enteral nutrition infusions into the stomach increase both gastric pH and gastric volume.[162,182] A randomized trial found that early aggressive feedings increased the risk of VAP compared with low-level enteral nutrition.[183] The lower rate (approximately 20% of the goal feeding rate) was chosen to avoid atrophy of the microvilli of the enteric mucosa, a potential source of nosocomial infection. The increased risk of VAP was attributed to an increased risk of aspiration. However, meta-analysis of early versus delayed enteral nutrition suggests a mortality benefit and probable decreased risk of VAP with early feedings.[184] A balance between potential risks would be early initiation of enteral feeding but avoidance of aggressive

infusions that might cause high gastric residuals and gastric distention.

Several strategies to provide enteral feeding without increasing gastric colonization with pathogenic microorganisms have been tried. An RCT found that bolus feedings did not lower VAP while fewer patients achieved their goal feeding rates.[185] Acidification of enteral feedings not only did not improve VAP rates but also caused adverse consequences from the resultant metabolic acidosis.[186]

Maintaining Normal Alveolar Host Defense

Given that all intubated patients and many nonintubated patients have at least microaspiration and most have lost their normal oropharyngeal flora, the fact that only a minority of patients actually develop HAP/VAP is surprising. The causes for overwhelming of the lower respiratory tract defenses is the least studied or understood component of the pathogenesis of HAP/VAP. A major reason may be that causes are multiple, heterogeneous, and patient dependent, rather than the stereotypical steps of colonization and aspiration.

Patients in whom VAP develops have a form of acquired immunosuppression.[88] The frequent occurrence of other nosocomial infections, including multiple separate episodes of VAP,[121] in patients with HAP/VAP supports this concept. Many of the causes of compromised lower respiratory tract defenses are due to the underlying disease or critical illness precipitating ICU admission and need for mechanical ventilation. Some of the more common interventions leading to compromised alveolar host defenses are listed in Table 40.9.

TABLE 40.9 Common Causes of Alveolar Host Defense Compromise in Critically Ill Patients

Prior infections	Concomitant viral infection (e.g., HSV, CMV)
Blood transfusions	Hyperglycemia
Chemotherapy	Protein calorie malnutrition
Immunosuppressants	Acetylcysteine (Mucomyst)
Corticosteroids	Norepinephrine
Proton-pump inhibitors/histamine-2 blockers	

CMV, Cytomegalovirus; *HSV,* herpes simplex virus.

Key Points

- The discovery of a normal lung microbiome has forced reconsideration of the prior definition of pneumonia as invasion of microorganisms into a sterile alveolar space.
- CAP and influenza are the leading causes of death from infectious diseases in the United States and around the world.
- Despite extensive conventional diagnostic testing, the etiology of CAP remains unknown in the majority of cases, including those requiring ICU admission.
- Specific objective decision tools used in conjunction with clinician experience and clinical judgment can identify CAP patients with an increased likelihood of need for ICU care.
- Severe CAP should be routinely treated with a β-lactam–based combination therapy with coverage of atypical bacterial pathogens and consideration of coverage for less common pathogens such as CA-MRSA and *Pseudomonas.*
- Despite decades of research, microbiologic diagnosis in patients with suspected HAP/VAP remains controversial, but quantitative cultures of distal specimens are more likely to improve antibiotic stewardship.
- Unless known local antibiotic susceptibility patterns demonstrate more than 90% susceptibility to a single agent, β-lactam–based combination empirical therapy is recommended for HAP/VAP in the ICU.
- Discontinuation in culture-negative cases of suspected HAP/VAP and optimized PK/PD, shortened duration of therapy, and consideration of aerosolized therapy for MDR pathogens are important antibiotic stewardship practices in the ICU.
- Prevention of HAP/VAP requires a multidimensional approach to decrease microaspiration, preserve normal flora, and avoid compromising alveolar host defenses.

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Review Questions

1. A patient is diagnosed with *Pseudomonas* ventilator-associated pneumonia (VAP) and starts antibiotic therapy with piperacillin/tazobactam and amikacin. Combination therapy with amikacin was discontinued after 48 hours when piperacillin/tazobactam susceptibility was confirmed. On day 7 of therapy, the patient is afebrile and normotensive. The patient requires suctioning every 3 to 4 hours but secretions are nonpurulent. Arterial saturation is 93% on fraction of inspired oxygen (FIO_2) of 0.30. The white blood cell count has increased from 9500 cells/mm^3 yesterday to 11,300 cells/mm^3. Procalcitonin has decreased from 3.5 ng/dL at the beginning of therapy to 0.65 ng/dL. What would you do at this point?

- **a.** Continue piperacillin/tazobactam for an additional 7 days
- **b.** Switch to meropenem 1 g infused over 3 hours every 8 hours for an additional 7 days
- **c.** Restart amikacin with a loading dose of 20 mg/kg and follow drug levels for redosing
- **d.** Discontinue piperacillin/tazobactam and monitor closely
- **e.** Continue piperacillin/tazobactam and add aerosolized polymyxin B

Answer: d. The patient appears to have successful therapy manifested by a low FIO_2, is afebrile, and has a procalcitonin level less than 20% of the initial value. The white blood cell count and amount of secretions are notoriously inaccurate in assessing response to therapy. More than 60% of patients with *Pseudomonas* pneumonia are adequately treated with a 7- to 8-day course of antibiotics, particularly when initial therapy is appropriate.[121]

2. Ten days after initiation of intubation and mechanical ventilation a patient develops fever to 101.7°F at midnight. Nursing reports increased purulent secretions. Cefepime and linezolid are started empirically after submission of an endotracheal aspirate for culture. Morning laboratory studies reveal leukocytosis, and a chest radiograph demonstrates a new left lower lobe alveolar filling density with air bronchograms. Amikacin is also started at that time. After 72 hours, the endotracheal aspirate culture remains negative. Which of the following would be the most appropriate management strategy?

- **a.** Continue current triple-antibiotic regimen for 7-day course
- **b.** Discontinue all antibiotics
- **c.** Discontinue linezolid and amikacin and complete 7-day course of cefepime
- **d.** Discontinue linezolid but complete 10-day course of cefepime and amikacin
- **e.** Check a procalcitonin level and discontinue all antibiotics if less than 0.50 ng/dL

Answer: c. Culture-negative suspected VAP represents a difficult decision. However, data are fairly clear that samples obtained before or shortly after initiation of antibiotics are adequate to exclude methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant pathogens, such as *Pseudomonas* and *Acinetobacter.* Therefore choices a. and d. are clearly incorrect. A single procalcitonin level 3 days into the course of treatment is difficult to interpret; it may actually represent persistent elevation and therefore discontinuing antibiotics based on this single value has some risk. The clinical scenario in addition to a positive radiograph indicates a greater than 90% probability of the patient having pneumonia. A negative endotracheal aspirate culture may represent disappearance of easy to treat pathogens or sampling of the right lower lobe rather than left lower lobe. Therefore continuing a single antibiotic is reasonable. A bronchoalveolar lavage (BAL) sample from the left lower lobe with less than 50% neutrophils could justify discontinuing all antibiotics.

3. A previously completely healthy, athletic 40-year-old presents with fever, cough, and dyspnea for 24 hours. His cough is occasionally productive of bright red blood. The patient has no periodontal disease. A chest radiograph reveals a right midlung dense infiltrate with a small cavity, patchy infiltrate in the left lower lobe, and a pleural effusion. Initial antibiotic regimen should be which of the following?

- **a.** Metronidazole in addition to ceftriaxone and azithromycin to cover for anaerobes
- **b.** Linezolid in addition to ceftriaxone and azithromycin for suspected community-acquired MRSA (CA-MRSA) pneumonia
- **c.** Clindamycin monotherapy for anaerobic pleuropneumonia
- **d.** Piperacillin/tazobactam and ciprofloxacin for possible *Pseudomonas* pneumonia
- **e.** Isoniazid (INH), rifampin, pyrazinamide, and ethambutol for tuberculosis

Answer. b. The presentation is classic for toxigenic *S. aureus* community-acquired pneumonia, both methicillin-susceptible and methicillin-resistant. Athletic locker room exposure increases the risk of MRSA and therefore clindamycin may not be adequate, although it also suppresses exotoxin production like linezolid. The patient has no risk factors for anaerobic pneumonia, *Pseudomonas* pneumonia, or tuberculosis.

4. A 64-year-old concert pianist presents to the emergency department for fever, very productive cough, and shortness of breath. On examination, she is slightly confused according to her daughter. She is normothermic and normotensive with a heart rate of 110 beats/min. Respiratory rate is 32 breaths/min with mild use of accessory inspiratory muscles. She has crackles with some egophony in the left lower lobe. She appears mildly dehydrated. Her chest radiograph demonstrates a left lower lobe pneumonia with air bronchogram. Arterial saturation is 89% on room air but improves to 96% on 2 L via simple nasal cannula. The white blood cell count is 12,000 cells/mm^3, platelets 110,000/mm^3. Electrolytes are normal with a blood urea nitrogen of 19 mg/dL. What would be your management plan?

- **a.** Start intravenous hydration and admit to the medical intensive care unit (ICU)
- **b.** Initiate noninvasive ventilation
- **c.** Perform an arterial or venous blood gas to assess pH and partial pressure of carbon dioxide (PCO_2)
- **d.** Start intravenous hydration and admit to a medical floor
- **e.** Start intravenous hydration and monitor in the emergency department for 2 hours before assessing transfer to the floor

Answer: a. This patient presents a not uncommon management dilemma, and the correct answer may vary somewhat on the health care system and available resources. She has borderline severity for admission to the ICU but she is at high risk. Confusion is a particularly worrisome symptom in a previously highly functional adult and would warrant ICU or step-down unit admission in highly resourced hospitals. She would only receive 2 CURB-65 points and only has 2 IDSA/ATS minor criteria (confusion, respiratory rate). A low pH or abnormal PCO_2 may warrant either ICU admission or prolonged initial emergency department management before transferred to a floor. The latter is associated with lower risk of emergent ICU transfer from the floor and lower mortality.[50]

41

Weaning from Mechanical Ventilation

MARTIN J. TOBIN

CHAPTER OUTLINE

Pathophysiology of Weaning Failure
- Control of Breathing
- Respiratory Mechanics
- Patient Effort
- Respiratory Muscles
- Cardiovascular Performance
- Gas Exchange

Weaning-Predictor Testing
- Pitfalls in Use of Weaning-Predictor Tests
- Respiratory Frequency/Tidal Volume Ratio

Weaning Trials
- Multiple T-Tube Trials
- Intermittent Mandatory Ventilation
- Pressure Support
- Once-Daily T-Tube Trials
- Comparison of Weaning Methods
- Weaning by Protocol Versus Usual Care
- Extubation

Conclusion

Mechanical ventilation is often lifesaving but it is associated with numerous complications.[1,2] Accordingly, it is imperative to disconnect patients from the ventilator at the earliest feasible time. Deciding the right time to initiate this disconnection process, usually referred to as *weaning,* is one of the greatest challenges in critical care medicine.[3] If a physician is too conservative and postpones the initiation of weaning, the patient is placed at an increased risk of life-threatening, ventilator-associated complications. Conversely, if weaning is begun prematurely, the patient may experience cardiopulmonary or psychological decompensation of sufficient severity to set back the patient's clinical course.[4]

This chapter reviews the pathophysiology of weaning failure, weaning-predictor testing, different weaning techniques, and extubation.

Pathophysiology of Weaning Failure

After patients have been disconnected from the ventilator, up to 25% experience respiratory distress severe enough to necessitate the reinstitution of mechanical ventilation.[5,6] The pathophysiologic mechanisms of weaning failure can be divided into those occurring at the level of the respiratory control system, mechanics of the lung and chest wall, the respiratory muscles, the cardiovascular system, and gas-exchange properties of the lung.[7]

Control of Breathing

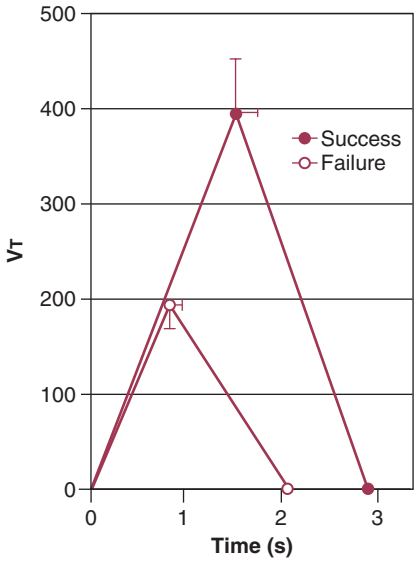
Many patients in whom weaning fails develop hypercapnia. Accordingly, it had been thought that these patients experience an acute decrease in minute ventilation consequent to a decrease in respiratory center output.[3] Measurements of respiratory motor output, using mean inspiratory flow or airway occlusion pressure ($P_{0.1}$), have consistently revealed an increase, not a decrease, in respiratory drive in patients with weaning failure.[4,8,9]

Weaning-failure patients, however, exhibit marked abnormalities in respiratory timing, specifically marked shortening of inspiratory time (T_I), which is coupled with shortening of expiratory time (T_E). The decrease in both T_I and T_E means that respiratory frequency (f) is markedly elevated. The shortening of T_I combined with a normal mean inspiratory flow (V_T/T_I) results in a marked decrease of tidal volume (V_T).[8] This combination (elevated f and decreased V_T) is referred to as rapid shallow breathing—now recognized as the physiologic hallmark of weaning failure (Fig. 41.1).[5]

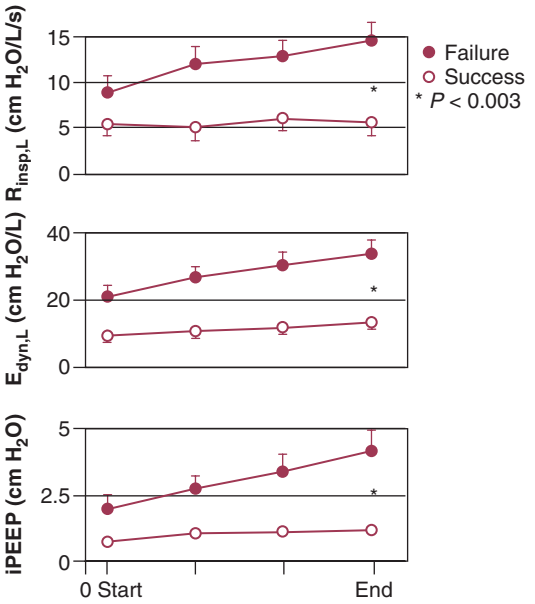
Respiratory Mechanics

The most detailed study of respiratory mechanics during weaning trials was carried out by Jubran and Tobin.[10,11] Immediately before commencement of a trial of spontaneous breathing, patients who went on to tolerate or fail the trial showed little or no difference in detailed measurements of passive respiratory mechanics.[11] Resistance, elastance, and intrinsic positive end-expiratory pressure (iPEEP) were equivalent in the two groups.

Over the course of the trial, all of these variables became more abnormal in the weaning-failure patients than in weaning-success patients (Fig. 41.2).[10] Respiratory resistance increased progressively, reaching about seven times the normal value at the end of the trial. Pulmonary elastance increased, reaching five times the normal value. iPEEP more than doubled over the course of the trial. A similar pattern has been observed by other investigators.[12] The observation that respiratory mechanics were equivalent in patients with weaning success and weaning failure immediately before a weaning trial but deteriorated immediately in the weaning-failure patients as soon as they began to breathe spontaneously indicates that some mechanism associated with the act of spontaneous breathing causes the worsening of respiratory mechanics that leads to weaning failure.



• **Fig. 41.1** The mean respiratory cycle during spontaneous breathing in 7 weaning-failure patients and 10 weaning-success patients. The early termination of inspiratory time in the weaning-failure patients leads to a decrease in tidal volume *(VT).* The decrease in inspiratory time, coupled with a decrease in expiratory time, results in a faster respiratory frequency. Bars represent 1 standard error. (Redrawn from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis.* 1986;134:1111–1118.)



• **Fig. 41.2** Inspiratory resistance of the lung *(Rinsp,L),* dynamic lung elastance *(Edyn,L),* and intrinsic positive end-expiratory pressure *(iPEEP)* in 17 weaning-failure patients and 14 weaning-success patients. Data displayed were obtained during the second and last minutes of a T-tube trial, and at one-third and two-thirds of the trial duration. Between the onset and end of the trial, the failure group developed increases in Rinsp,L ($P < 0.009$), Edyn,L ($P < 0.0001$), and iPEEP ($P < 0.0001$) and the success group developed increases in Edyn,L ($P < 0.006$) and iPEEP ($P < 0.02$). Over the course of the trial, the failure group had higher values of Rinsp,L ($P < 0.003$), Edyn,L ($P < 0.006$), and iPEEP ($P < 0.009$) than the success group. (Redrawn from Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1997;155:906–915.)

Patient Effort

To compensate for the marked worsening of respiratory mechanics, patients need to make a greater inspiratory effort. It had been thought that weaning-failure patients make weaker inspiratory efforts than do weaning-success patients.[7] On the contrary, direct measurements of work of breathing and pressure-time product[13,14] show that weaning-failure patients consistently make a greater inspiratory effort than do weaning-success patients (Fig. 41.3).[10,15]

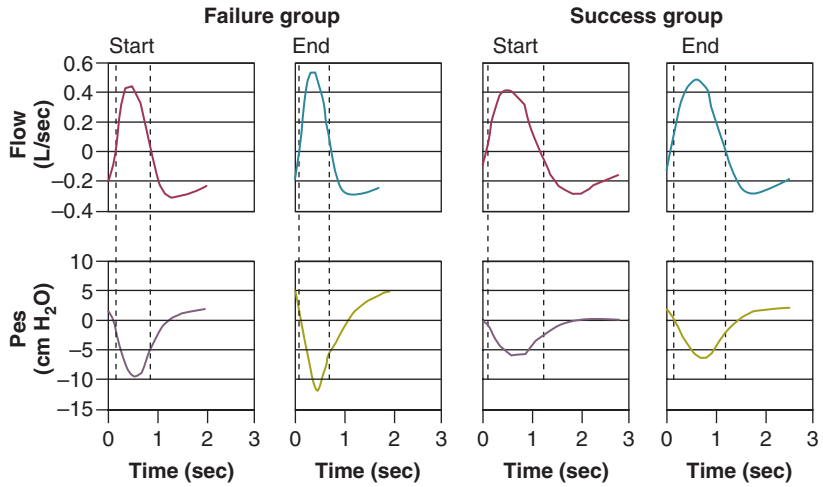
Respiratory Muscles

Numerous research groups have shown that maximal inspiratory pressure (PImax), a measure of respiratory muscle strength, does not discriminate between patients with weaning success and weaning failure.[7] These findings led to the belief that respiratory muscle weakness is not an important determinant of weaning outcome. PImax, however, can misrepresent respiratory muscle strength because the values are heavily influenced by patient motivation and cooperation.[13] A more objective measure of diaphragmatic strength is obtained by stimulation of the phrenic nerves and recording the resulting transdiaphragmatic pressure (Pdi). In weaning-failure patients twitch Pdi values are below 10 cm H_2O, whereas values of 35 to 39 cm H_2O are observed in healthy subjects.[16] These data suggest that weaning-failure patients may have considerable muscle weakness.

Stimulation of the phrenic nerves and recording of the resulting Pdi also provide the most direct measure of diaphragmatic fatigue.[13] Laghi and coworkers[17] used this technique in 11 weaning-failure and 8 weaning-success patients before and after a T-tube trial. No patient in either group exhibited a fall in twitch pressure. This result was surprising. Related analyses disclosed why. Weaning-failure patients became progressively distressed during the trial, leading clinicians to reinstate ventilator support before patients had breathed long enough to develop fatigue (Fig. 41.4).[17,18] In other words, monitoring clinical signs of distress provides sufficient warning to avoid respiratory muscle fatigue.

Cardiovascular Performance

During a weaning trial, patients can experience substantial increases in right and left ventricular afterload.[19,20] These afterload increases most likely result from associated increases in negative swings of intrathoracic pressure. At the completion of a weaning trial, the level of oxygen consumption is equivalent in weaning-success and weaning-failure patients. How the cardiovascular system meets the oxygen demand differs in the two groups of patients. In weaning-success patients, oxygen demand is met through an increase in oxygen delivery, mediated by the expected increase in cardiac output on discontinuation of positive-pressure ventilation.[20] In weaning-failure patients, oxygen demand is met through an increase in oxygen extraction; these patients have a relative decrease in oxygen delivery.[20] The greater oxygen extraction causes a substantial decrease in mixed venous oxygen saturation, contributing to the arterial hypoxemia that occurs in some patients.[20]



• **Fig. 41.3** Ensemble average plots of flow and esophageal pressure *(Pes)* at the start and end of a T-tube trial in 17 weaning-failure patients and 14 weaning-success patients. At the start of the trial, the inspiratory excursion in Pes was greater in the failure patients, and it increased further by the end of the trial. To generate these plots, flow and Pes tracings were divided into 25 equal time intervals over a single respiratory cycle for each of the 5 breaths for each patient in the 2 groups. For a given patient, the five breaths from the start of the trial were then superimposed and aligned with respect to time, and the average at each time point was calculated. The group mean tracings were then generated by ensemble averaging of the individual mean from each patient. The same procedure was performed for breaths at the end of the trial. (Redrawn from Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1997;155:906–915.)

Gas Exchange

Studies using the multiple inert-gas technique have revealed that the ventilation-perfusion maldistribution and acute hypercapnia observed in weaning-failure patients is produced primarily by shallow breathing (low V_T).[7] About half of weaning-failure patients experience an increase in the arterial partial pressure of carbon dioxide ($PaCO_2$) of 10 mm Hg or more over the course of a spontaneous breathing trial.[10] The hypercapnia is not usually a consequence of a decrease in minute ventilation. Instead, it results from rapid, shallow breathing, which causes an increase in dead-space ventilation.

Weaning-Predictor Testing

In randomized controlled trials (RCTs) of different weaning techniques, most patients who had received mechanical ventilation for a week or longer were able to tolerate ventilator discontinuation on the first day that weaning-predictor tests were measured.[5,6] Many of these patients probably would have tolerated extubation a day or so earlier. Much of this delay in ventilator weaning results from clinicians' overconfidence in their intuition that a patient is not ready for a weaning trial.[4] Another source of error is the failure of clinicians to pay close attention to pretest probability—they fail to recognize the importance of Bayesian principles in clinical decision making. When caring for a ventilator-supported patient, physicians should be mindful of these cognitive processes and use compensatory tactics, specifically the use of screening tests, to spot a patient's readiness for weaning. By alerting an unsuspecting physician to a patient's readiness to tolerate unassisted ventilation—hours or days before he or she would otherwise order a spontaneous breathing trial—weaning-predictor tests circumvent the cognitive errors inherent in clinical decision making.[4]

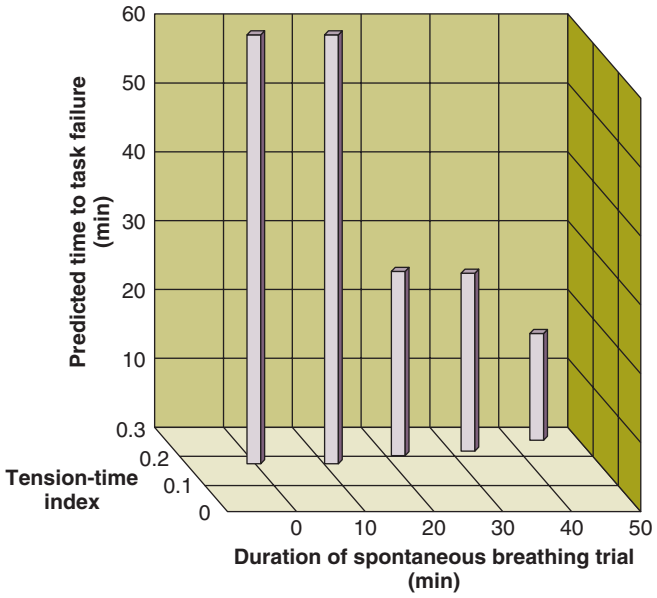
Pitfalls in Use of Weaning-Predictor Tests

Physicians commonly view diagnostic testing in monolithic terms: a test is a test is a test. In reality, diagnostic testing has to satisfy two very different tasks; one is screening, the other is confirmation.[21] The characteristics of these test types differ, and a single diagnostic test rarely fulfills both functions.[21]

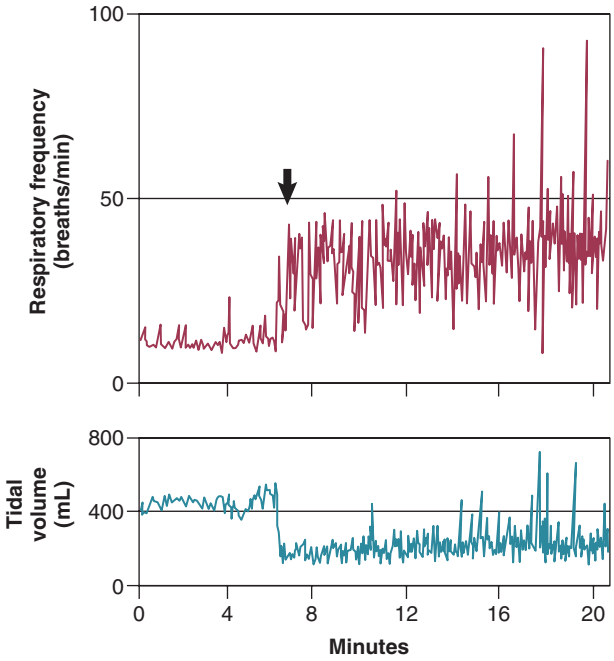
The fundamental job of a weaning-predictor test is screening.[4] Because the goal is to not miss anybody with the condition under consideration, a good screening test has a low rate of false-negative results; to achieve this goal, a higher false-positive rate is acceptable. Thus an ideal screening test has a high sensitivity.[4,21]

Weaning involves the use of three diagnostic tests in sequence: measurement of predictors, a weaning trial, and a trial of extubation.[4] The sequential nature of the testing gives rise to particular problems in studies undertaken to investigate the reliability of a predictor test. One is spectrum bias. This occurs when a new study population contains fewer (or more) sick patients than the population in which a diagnostic test was originally developed.[21,22] A second is test-referral bias. This occurs when the results of a test under evaluation are used to select patients for a reference-standard test, such as use of a weaning-predictor test to select patients for a reference-standard test (passing a weaning trial that leads to extubation).[21,22]

A third factor that affects studies of the reliability of a predictor test is base-rate fallacy.[22,23] Consider a diagnostic test for a disease that has a false-positive rate of 5% and false-negative rate of 0%, and the incidence of the disorder (under consideration) is 1 per 1000 persons. A randomly selected person undergoes diagnostic testing. The result comes back positive. What is the chance this person has the disease? More than 80% of physicians answer 95%. The correct answer is 1.96%.[23] Physicians who answer 95% are failing to take into account the pretest probability of the disorder. Thus they fall into the trap of base-rate fallacy.



• **Fig. 41.4** Interrelationship among the duration of a spontaneous breathing trial, tension-time index of the diaphragm, and predicted time to task failure in nine patients who failed a trial of weaning from mechanical ventilation. The patients breathed spontaneously for an average of 44 minutes before a physician terminated the trial. At the start of the trial, the tension-time index was 0.17, and the formula of Bellemare and Grassino[18] predicted that patients could sustain spontaneous breathing for another 59 minutes before developing task failure. As the trial progressed, the tension-time index increased and the predicted time to development of task failure decreased. At the end of the trial, the tension-time index reached 0.26. That patients were predicted to sustain spontaneous breathing for another 13 minutes before developing task failure clarifies why patients did not develop a decrease in diaphragmatic twitch pressure. In other words, physicians interrupted the trial on the basis of clinical manifestations of respiratory distress before patients had sufficient time to develop contractile fatigue. (Redrawn from Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10–48.)



• **Fig. 41.5** A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The *arrow* indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator. (Redrawn from Tobin MJ, Perez W, Guenther SM, et al. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. *Am Rev Respir Dis.* 1986;134:1111–1118.)

Pretest probability is a physician's estimate of the likelihood of a particular condition (weaning outcome) before a diagnostic test is undertaken.[4] Posttest probability (typically expressed as positive or negative predictive value) is the new likelihood after the test results are obtained. A good diagnostic test achieves a marked increase (or decrease) in the posttest probability (over pretest probability). For every test in every medical subspecialty, the magnitude of change between pretest probability and posttest probability is determined by Bayes' theorem.[22] Three factors (alone) determine the magnitude of the pretest to posttest change: sensitivity, specificity, and pretest probability. Sensitivity and specificity are commonly assumed to remain constant for a test. In truth, test-referral bias, a common occurrence in studies of weaning tests, leads to major changes in sensitivity and specificity.[21] Likewise, major changes in pretest probability arise as a consequence of spectrum bias.[21] All of these factors need to be carefully considered when reading a study that evaluates the reliability of a weaning-predictor test.

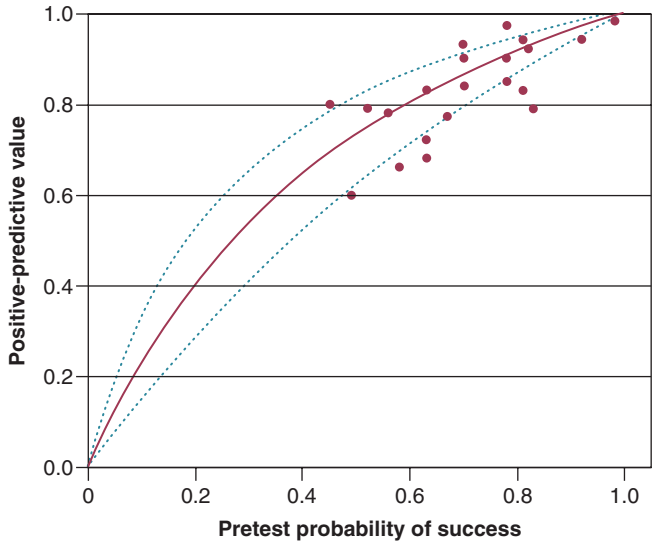
Respiratory Frequency/Tidal Volume Ratio

The ratio of respiratory frequency to tidal volume (f/VT) is measured during 1 minute of spontaneous breathing (Fig. 41.5).[24] Measurements of f/VT in the presence of pressure support or continuous positive airway pressure (CPAP) will result in inaccurate predictions of weaning outcome.[4] The higher the f/VT ratio, the more severe the rapid, shallow breathing and the greater the likelihood of unsuccessful weaning. An f/VT ratio of 100 best discriminates between successful and unsuccessful attempts at weaning.[24]

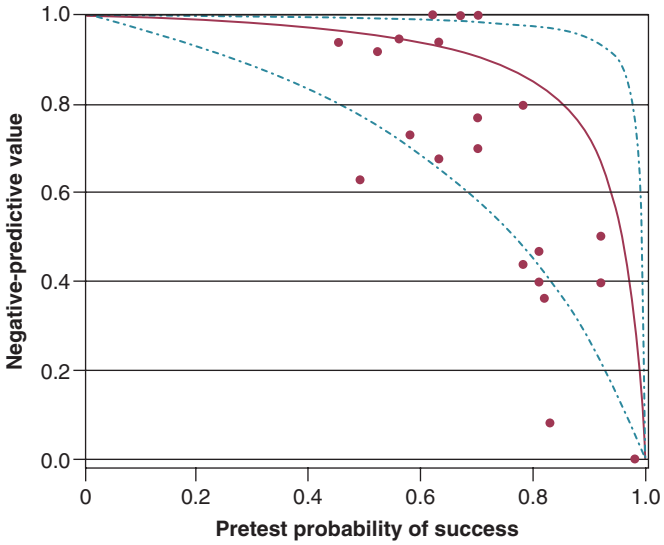
The initial evaluation of f/V_T was reported in 1991.[24] Since then, this test has been evaluated in more than 25 studies. Reported sensitivity ranges from 0.35 to 1.[22] Specificity ranges from 0 to 0.89.[22] At first glance, this wide scatter suggests that f/VT is an unreliable predictor of weaning outcome. This was also the viewpoint of an Evidence-Based Medicine Task Force that undertook a meta-analysis of the studies.[25,26] The Task Force, however, failed to take into account test-referral bias and spectrum bias.[4] As a consequence, the Task Force committed at least 15 major errors—any one of which was sufficient to scupper their conclusions.[27,28] In contrast, when data from the studies (included in the meta-analysis) were compared against the test characteristics in the original 1991 report, taking into account Bayesian pretest probability, the weighted Pearson correlation coefficient was 0.86 ($P < 0.0001$) for positive predictive value and 0.82 ($P < 0.0001$) for negative predictive value (Figs. 41.6 and 41.7).[22]

The primary job of a weaning-predictor test is screening, which requires a high sensitivity.[4,21] The average sensitivity in all of the studies on f/VT was 0.89, and 85% of the studies reveal sensitivities higher than 0.90.[22] This sensitivity compares well with commonly used diagnostic tests.[4]

The whole purpose of diagnostic screening is to perform a simple test at a time when a physician's pretest probability is low (<50%).[4] A screening test should be cheap, easy to perform, pose



• **Fig. 41.6** Positive predictive value (posttest probability of successful outcome) for f/VT plotted against pretest probability of successful outcome. The curve is based on the sensitivity and specificity originally reported by Yang and Tobin[24] and Bayes' formula for 0.01-unit increments in pretest probability between 0.00 and 1.00.[22] The lines represent the upper and lower 95% confidence intervals for the predicted relationship of the positive predictive values against pretest probability. The observed positive predictive value in a study is plotted against the pretest probability of weaning success (prevalence of successful outcome). (Redrawn from Tobin MJ, Jubran A. Variable performance of weaning-predictor tests: role of Bayes' theorem and spectrum and test-referral bias. *Intensive Care Med*. 2006;32:2002–2012.)



• **Fig. 41.7** Negative predictive value (posttest probability of unsuccessful outcome) for f/VT. The curve, its 95% confidence intervals, and placement of a study on the plot are described in the legend of Fig. 41.6. The observed negative predictive value in a study is plotted against the pretest probability of weaning success (prevalence of successful outcome). (Redrawn from Tobin MJ, Jubran A. Variable performance of weaning-predictor tests: role of Bayes' theorem and spectrum and test-referral bias. *Intensive Care Med.* 2006;32:2002–2012.)

minimal risk to patients, and provide a quick answer. A spontaneous breathing trial that involves 30 to 120 minutes of monitored performance is the antithesis of a screening test. Yet the Evidence-Based Medicine Task Force recommends that clinicians should start weaning with a spontaneous breathing trial (a confirmatory test) and use the initial few minutes of the trial as a screening test.[25] This is analogous to saying that when you suspect diabetes, start with a glucose tolerance test and then, as the test gets under way, ask the patient for a urine sample to perform a dipstick measurement.[29]

Weaning Trials

Weaning-predictor tests are not done to forecast a failed weaning trial, but to alert a physician that a patient might tolerate a weaning trial sooner than the physician otherwise thinks and move that weaning trial earlier in time and shorten the overall of duration mechanical ventilation. When a screening test result is positive, the clinician proceeds to a confirmatory test.[21] The goal of a positive result on a confirmatory test is to rule in a condition[19]: the likelihood of a patient tolerating a trial of extubation is high. An ideal confirmatory test has a low rate of false-positive results (i.e., a high specificity).[21] Unfortunately, the specificity of a spontaneous breathing trial is not known. Indeed, its specificity will never be known because its determination would require an unethical experiment: extubating all patients in whom a weaning trial fails and counting how many require reintubation.[4]

Multiple T-Tube Trials

Of the four methods available for conducting a weaning trial, the use of repeated T-tube trials, several times a day, is the oldest method.[3] The patient receives an enriched supply of oxygen through a T-tube circuit. Initially 5 to 10 minutes in duration, T-tube trials are extended and repeated several times a day until the patient can sustain spontaneous ventilation for several hours. This approach has become unpopular because it requires considerable time on the part of intensive care staff.

Intermittent Mandatory Ventilation

For many years, intermittent mandatory ventilation (IMV) was the most popular method of weaning.[3] With IMV, the mandatory rate from the ventilator is reduced in steps of 1 to 3 breaths/min, and an arterial blood gas value is obtained about 30 minutes after each rate change.[30] Unfortunately, titrating the number of breaths from the ventilator in accordance with the results of arterial blood gases can produce a false sense of security. As few as 2 to 3 positive-pressure breaths/min can achieve acceptable blood gas values, but these values provide no information regarding the patient's work of breathing (which may be excessive).[4] At IMV rates of 14 breaths/min or fewer, patient inspiratory efforts are increased to a level likely to cause respiratory muscle fatigue.[31,32] Moreover, this occurs not only with the intervening spontaneous breaths but also with ventilator-assisted breaths. Consequently, use of IMV may actually contribute to the development of respiratory muscle fatigue or prevent its recovery.[7]

Pressure Support

When pressure support is used for weaning, the level of pressure is reduced gradually (decrements of 3–6 cm H_2O) and titrated on

the basis of the patient's respiratory frequency.[33] When a patient breathes without distress at a "minimal level of pressure support," he or she is extubated. The problem with this line of thinking is that pressure support of 5 cm H_2O produces an average decrease in work of breathing of approximately 40% (much more in some patients)[34]; it is difficult to understand how physicians judge this effect to be "minimal."

Once-Daily T-Tube Trials

The fourth method of weaning is to perform a single daily T-tube trial, lasting for 30 to 120 minutes. If this trial is successful, the patient is extubated. If the trial is unsuccessful, the patient is given at least 24 hours of respiratory muscle rest with full ventilator support before another trial is performed.[4]

Comparison of Weaning Methods

Until the early 1990s, it was widely believed that all weaning methods were equally effective, and the physician's judgment was regarded as the critical determinant.[3] The results of RCTs have revealed that the period of weaning is as much as three times as long with IMV as with trials of spontaneous breathing.[5,6] In a study involving patients with respiratory difficulties on weaning, trials of spontaneous breathing halved the weaning time compared with pressure support[6]; in another study, the weaning time was similar with the two methods.[5] Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day but much simpler.[6]

The most difficult patients to wean are those requiring prolonged ventilation in a long-term acute care hospital. In a randomized trial, Jubran et al.[35] found that intermittent unassisted breathing (using a tracheostomy collar) resulted in 1.43 times faster removal of the ventilator than did pressure support.

Weaning by Protocol Versus Usual Care

Six groups of investigators have undertaken RCTs comparing the use of protocols versus usual care in weaning management. Three groups[36–38] found that protocolized weaning was without benefit. Of the other three studies, two studies[39,40] were marred by major problems of internal validity. The third study[41] revealed no benefit in one of its two intensive care units (ICUs). In summary, only half of one study of six revealed valid support for protocolized weaning, with the remainder providing no evidence of benefit.

Tanios and colleagues[42] undertook an RCT to determine whether the inclusion of f/VT in a weaning protocol influenced weaning time. In the f/VT-protocol group, patients could proceed to a weaning trial (CPAP and pressure support) if—and only if—they had an f/VT of less than 106. In the second study arm, clinicians did not follow the protocolized approach to weaning. The duration of weaning was longer in the f/VT-protocol group than in the nonprotocol group.

The study has two major problems. First, the investigators assume that physicians managing patients in the control group did not calculate f/VT. Physicians, however, are highly aware that respiratory frequency and tidal volume are key variables in deciding whether a patient will tolerate weaning and extubation.[3] Once this knowledge has crept into a physician's brain, it cannot be surgically extirpated at the point of commencing an RCT. To ensure that physicians did not use breathing pattern in the decision making, Tanios and colleagues[42] would have had to have taken steps to hide or occlude the display of frequency and tidal volume on the bedside monitor and ventilator screen.

Second, f/VT was one component in a weaning protocol. It is important to make a distinction between the use of a protocol in conducting a research study and its use in everyday clinical practice. In the research protocol of Tanios and colleagues,[42] patients who had an f/VT of 105 or less progressed to a weaning trial, whereas patients with an f/VT of 106 or higher resumed ventilator support. When conducting research, this is exactly how a protocol must be specified and followed. No flexibility is permitted. A competent clinician, however, would think it daft to slavishly comply with a protocol that decided an entire day of ventilator management on a one-unit difference in a single measurement of f/VT.[43] Rather, intelligent physicians customize knowledge to the particulars of each patient and are expected to outperform the inflexible application of a protocol—as has been shown in numerous studies of weaning protocols.

Extubation

Decisions about weaning and decisions about extubation are commonly combined.[44] When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. Before removing the endotracheal tube, however, the clinician must also judge whether or not the patient will be able to maintain a patent upper airway after extubation.

Of patients who are expected to tolerate extubation without difficulty, approximately 10% to 20% fail and require reintubation.[5,6] The mortality rate among patients who require reintubation is more than six times as high as the mortality rate among patients who can tolerate extubation.[35] The reason for the higher mortality rate is unknown. It might be related to the development of new problems after extubation or to complications associated with reinsertion of a new tube. A more likely explanation is that the need for reintubation reflects greater severity of the underlying illness.[42]

Many physicians find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cm H_2O and PEEP 5 cm H_2O based on the belief that such "minimal ventilator settings" are simply overcoming the resistance engendered by an endotracheal tube.[45] This claim ignores the inflammation and edema that develop in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance. Straus and associates[46] demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus applying any level of pressure support causes physicians to underestimate the respiratory resistance a patient will encounter after extubation. The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cm H_2O decreases inspiratory work by 31% to 38% and 10 cm H_2O decreases work by 46% to 60%.[34,47] Independently, the addition of 5 cm H_2O of PEEP can decrease the work of breathing by as much as 40% in ventilated patients.[4] In the case of a patient who might experience cardiorespiratory difficulties after extubation, it is incumbent on a physician to ensure that the patient is able to breathe comfortably for about 30 minutes in the complete absence of pressure support or PEEP before removal of the endotracheal tube.[45]

Conclusion

To minimize the likelihood of either delayed weaning or premature extubation, a two-step diagnostic strategy is recommended: measurement of weaning predictors followed by a weaning trial. Because each step constitutes a diagnostic test, clinicians must be mindful of the scientific principles of diagnostic testing when interpreting the information generated by each step. The critical step is for the physician to contemplate the possibility that a patient *just might* be able to tolerate weaning. Such diagnostic triggering is assisted through the use of a screening test, which is the rationale for measurement of weaning-predictor tests. Importantly, one should not postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial. Many complex facets of pulmonary pathophysiology impinge on weaning management. Thus weaning requires individualized care at a high level of sophistication.

Key Points

- Most patients with an unsuccessful trial of weaning from mechanical ventilation do not succeed because of a markedly increased respiratory load, which, in turn, is secondary to severe worsening of respiratory mechanics over the course of the weaning trial.
- Less common reasons for weaning failure include weakened respiratory muscles or impaired cardiovascular performance; primary abnormalities of the respiratory centers or intrapulmonary shunt are uncommon mechanisms of weaning failure.
- Several studies suggest that most patients weaned successfully could have tolerated the weaning attempts had they been initiated a day or more earlier. Such data emphasize the need for the early use of screening tests.
- The primary goal of a screening test is to not miss anybody with the condition under consideration; thus the test should have a high sensitivity. The ratio of respiratory frequency to tidal volume (f/VT) has been evaluated in more than 25 studies; its average sensitivity is 0.89.
- Weaning involves the undertaking of three diagnostic tests in sequence. The sequential nature of the testing predisposes to the occurrence of test-referral bias and spectrum bias.
- Of the techniques used for a weaning trial, IMV has been repeatedly shown to be inferior to the use of T-tube trials or pressure support.
- Six randomized trials have evaluated the usefulness of protocols in the management of weaning. Three studies observed no benefit with the use of protocols. Two of the remaining three studies had major methodologic problems, leaving only one study supporting the use of protocols.

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Review Questions

1. A 62-year-old man with a history of chronic obstructive pulmonary disease (COPD) was admitted to the intensive care unit (ICU) for multilobar pneumonia and COPD exacerbation. He required intubation and mechanical ventilation and was given intravenous broad-spectrum antibiotics and steroids. By day 3, he had improved and was undergoing mechanical ventilation with assist control mode, with tidal volume 400 mL; respiratory rate (RR) 12 breaths/min; positive end-expiratory pressure (PEEP) 5 cm H_2O; fraction of inspired oxygen (FIO_2) 0.40; and oxygen saturation by pulse oximetry (SpO_2) 96%. A weaning trial (spontaneous breathing with T-piece trial) was started but the patient became diaphoretic with an RR of 40 breaths/min, a tidal volume of 250 mL, and an SpO_2 of 88%. Which of the following is the most likely cause of weaning failure?

- **a.** Increased respiratory load and worsening of respiratory mechanics
- **b.** Weaker inspiratory effort resulting in tachypnea
- **c.** A decrease in respiratory drive
- **d.** Hypercapnia owing to a reduction in minute ventilation

Answer 1: a. Patients experiencing weaning failure typically have worsening of respiratory mechanics to include substantial increases in resistance, intrinsic PEEP, and pulmonary elastance. Direct measurements of work of breathing show that weaning-failure patients consistently make greater, not weaker, inspiratory efforts than do weaning-success patients. Similar, respiratory drive is typically increased. Hypercapnia can occur during weaning failure but is typically due to increased dead-space ventilation secondary to shallow breathing or intrinsic PEEP, as opposed to a reduction in minute ventilation. A spontaneous breathing trial also can place substantial work on the myocardium as venous return is increased, left ventricular afterload increased, and if hypoxia, hypercapnia, or intrinsic PEEP occur, and increased right ventricular afterload as well. Given this, clinicians should always also think of cardiac performance as a possible contributor to weaning failure.

2. With respect to weaning methods:

- **a.** All weaning methods are equally effective.
- **b.** Effective weaning involves the gradual withdrawal of support and RR delivered by intermittent mandatory ventilation.
- **c.** A ½-hour trial of spontaneous breathing is as effective as a 2-hour trial.
- **d.** Weaning trials should be performed several times per day, as opposed to one, as evidence supports earlier liberation from the mechanical ventilator.

Answer 2: c. All weaning methods are definitely not equally effective. Weaning with intermittent mandatory ventilation has consistently been proved to be an inferior method. Breathing trials performed once per day are equally as effective as multiple trials per day. The clinician should not automatically condemn a patient to weaning failure for the day after failing a breathing trial. Rather, reasons for failure should be sought and corrected, and another breathing trial should be conducted, knowing the literature supports this.

3. Which one of the following is the least likely cause for reintubation?

- **a.** Inability to tolerate respiratory load
- **b.** Upper airway obstruction
- **c.** Excessive secretions
- **d.** Steroid myopathy

Answer 3: d. Patients who require reintubation have higher severity of illness scores, are older, and have a longer duration of mechanical ventilation than successfully extubated patients. It is not clear whether reintubation per se contributes to mortality rate or is simply a marker of disease severity. Reintubated patients have a much higher mortality rate than successfully extubated patients. Steroid myopathy is an uncommon cause for reintubation. Excessive secretions (16%–28% of reintubations) and inability to tolerate an additional respiratory load (28%–37% of reintubations) are the most common causes of reintubation. Upper airway obstruction is reported to be the reason in 15% of reintubations.

4. Which of the following is true regarding weaning predictor tests and weaning trials?

- **a.** Compared with clinical intuition, weaning predictor tests do not identify a cohort of patients ready to wean from the ventilator.
- **b.** A rapid shallow breathing index (RSBI) or the ratio of respiratory frequency to tidal volume (f/VT) of 100 best discriminates between successful and unsuccessful attempts at weaning.
- **c.** The application of pressure support or continuous positive airway pressure (CPAP) at low levels has no influence in respiratory mechanics or the accuracy of the predictive ability of f/VT.
- **d.** Weaning trials performed as part of a protocol have consistently shown benefit by decreasing mechanical ventilator days.

Answer 4: b. Data have shown that many patients receiving mechanical ventilation tolerate mechanical ventilation discontinuation on the first day they are extubated. This suggests that a big barrier to extubation is lack of clinician recognition of readiness to wean. The RSBI has been studied in a myriad of investigations. Although imperfect, compared with other predictors of readiness to wean (e.g., negative inspiratory pressure, minute ventilation), it has consistently been shown to be the most reliable marker. In the original studies, RSBI was measured in the complete absence of ventilator assistance. The application of low levels of support can markedly reduce work of breathing and overcome resistance. As such, they will alter the values of weaning predictors as compared with no support via a T-piece. Although commonplace, protocolized weaning has not been shown to improve outcome above and beyond usual care. Reasons for failure should be sought and corrected, and the patient should be observed by the treating clinician during a weaning trial; liberation from the ventilator should be customized to the individual patient.

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Acute Pulmonary Embolism

KENNETH V. LEEPER, JR.[†] AND MICHAEL STERLING

CHAPTER OUTLINE

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Duplex Compression Ultrasonography
Ventilation-Perfusion Nuclear Scans
Multidetector Computed Tomography Scan of the Chest
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Risk Stratification
Clinical and Hemodynamic Parameters
Electrocardiogram
Cardiac Biomarkers
Brain Natriuretic Peptide
Cardiac Troponin
D-Dimer
Echocardiography
Computed Tomography Pulmonary Angiography
The Management of Acute Pulmonary Embolism
Pharmacologic Management
Submassive Pulmonary Embolism With Hemodynamic Stability and Right Ventricular Dysfunction
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Right-Sided Heart Thrombi
Chronic Thromboembolic Pulmonary Hypertension
Prophylaxis
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Pulmonary Embolism Response Team

Pulmonary venous thromboembolism (VTE) and deep venous thrombosis (DVT) are different manifestations of the same disease. Despite adequate VTE prophylaxis in the intensive care unit (ICU) the presence of a VTE event is a constant threat to critically ill patients. Although the critical care clinician may encounter the embolization of air, fat, infected clots, amniotic fluid, tumor, and inorganic substances, by far VTE will be the most common pulmonary embolic condition encountered. Critical care clinicians will encounter life-threatening pulmonary embolism (PE) ranging from hemodynamically stable patients with varying degrees of right ventricular dysfunction (RVD) to acute massive PE, defined as hemodynamic shock from acute PE, which represents the most serious manifestation along the spectrum of venous thromboembolic disease.[1–3] According to population-based studies, the annual incidence of VTE in the United States has ranged from 200,000 to a recent estimate of 900,000 cases in which approximately 300,000 people die every year from acute PE.[4,5] More recently (in 2006), 467,000 patients were hospitalized with DVT and 247,000 patients were admitted with acute PE.[6] VTE is associated with significant health care costs. Based on 2004 provider payments, the economic burden of VTE costs ranges between $5.8 billion and $7.8 billion.[7]

The mortality rate can exceed 58% in patients with acute PE presenting with shock, and most of these deaths occur within 1 hour of presentation.[1,2] Acute PE is the third most common cause of death among hospitalized patients, and with an aging population the number of people with VTE is expected to increase. For these reasons, the U.S. Surgeon General issued a "Call to Action" in 2008, identifying VTE as a major public health problem.[8]

The development of DVT occurs largely in the lower extremities and can result in the sequelae of PE, postthrombotic syndrome, and chronic thrombotic pulmonary hypertension.[9] Venous thrombosis is associated with significant morbidity and mortality rates but can be prevented in most patients.[2,3]

In this chapter we review the epidemiology, risk factors, diagnosis, risk assessment, and management of acute PE. In our discussion we review VTE in special adult populations, VTE prophylaxis in the ICU, and long-term prognosis.

Prevalence of Venous Thromboembolism in Intensive Care Unit Patients

ICU patients represent a heterogeneous population. In prospective screening studies for DVT, in the absence of thromboprophylaxis,

[†]Deceased.

the incidence of DVT in a medical-surgical ICU ranges from approximately 13% to 33%.[10–12] In an autopsy review of 6 studies of 436 critically ill patients the incidence of PE ranged from 7% to 27% (mean 13%); PE contributed or directly caused death in 0% to 12% (mean 3%) of the patients. It is important to note that in a majority of the patients there was no antemortem suspicion of fatal PE.[13]

Contemporary prevalence of patients with VTE who are admitted to or VTE that occurs in the ICU setting can be obtained from large VTE clinical trials. Approximately 10% of patients entered into the PIOPED-I (Prospective Investigation of Pulmonary Embolism Diagnosis) study for possible PE were hospitalized in a medical or surgical critical care unit.[14] In the recent international multicenter EINSTEIN PE trial,[15] which randomly assigned 4823 symptomatic patients with PE to rivaroxaban or enoxaparin and a vitamin K antagonist, 600 patients (12.4%) required ICU admission. Finally, in the PROTECT trial (Prophylaxis for Thromboembolism in Critical Care Trial)[16] among 3764 critically ill patients enrolled in which a majority were supported by mechanical ventilation and 40% were receiving vasopressor therapy, dalteparin and unfractionated heparin (UFH) were the agents used for VTE prophylaxis. The primary endpoint was proximal DVT presence. Using compression ultrasonography (CUS), 3.5% of the patients had proximal DVT on admission. The incidence of proximal DVT was 5.1% in the dalteparin group and 5.4% in the UFH group. The proportion of patients with pulmonary emboli was significantly lower with dalteparin (24 patients, 1.3%) than with UFH (43 patients, 2.3%).[16]

There is controversy over routine DVT screening in the ICU. As mentioned earlier, most ICU patients with DVT are asymptomatic and the clinical signs for DVT are nonspecific. CUS is time-consuming and not cost-effective. Efforts must be made to ensure adherence to current DVT prophylaxis guidelines. In ICU patients in whom these guidelines cannot be fully implemented (intracranial, spinal, or leg injuries, or patients at increased bleeding risk) then routine CUS screening may be appropriate.[17–21]

Risk Factors

In the nineteenth century Virchow described stasis, vascular wall abnormalities, and hypercoagulability as general risk factors for the development of DVT.[22]

As illustrated in Table 42.1, patients admitted to the ICU possess multiple preexisting VTE risks factors on admission to the ICU, yet in the International Cooperative Pulmonary Embolism Registry (ICOPER) 20% of the patients had idiopathic or unprovoked PE.[3]

The interaction between patient-related and setting-related risk factors appears to be responsible for the development of the VTE.[23–25] Patient-related risk factors are usually acquired and are long-standing. Examples of patient-related risk factors are age, history of prior VTE, malignancy, neurologic and medical illnesses that result in immobility, cardiopulmonary disorders, collagen vascular disease, and vasculitis. In addition, patient-related factors may include genetic and acquired thrombophilia and hormone replacement therapy and oral contraceptive therapy. Setting-related risk factors are usually temporary. Examples of setting-related risk factors include hospitalizations, nursing home placement, and admission to the ICU.

Virchow has described several risk factors unique to the ICU setting that predispose patients to VTE events. In a prospective observational study of 93 medical-surgical ICU patients, the investigators identified several ICU-related factors associated with increased risk of VTE, including mechanical ventilation, immobility, femoral venous catheters, sedatives and paralytic drugs, and failure to prescribe VTE prophylaxis. Prolonged immobility in the ICU setting is the result of mechanical ventilation, sedative administration, and paralytic agents. These four factors (mechanical ventilation, immobility, sedation, and paralysis) may converge to greatly increase the risk of VTE.[26] Sedation and paralysis also predispose to other ICU complications, including increased duration of mechanical ventilation, and critical illness polyneuropathy.[27,28]

See the online supplement for additional discussion on Risk Factors.

Deep Venous Thrombosis

It is estimated that as many as 95% of clinically significant pulmonary emboli originate from the deep veins of the lower extremity. The proximal deep veins of the leg are the most common sites of origin of clots that embolize to the pulmonary circulation. A general consensus suggests that clinically significant proximal DVTs and risk for PEs originate by proximal extension of calf DVT.[47,48] Venous thrombi are created in the setting of low flow and low shear stress. These thrombi consist of fibrin strands, red blood cells, and platelets. The thrombi form in the valve pockets of calf veins and extend to the proximal veins.[48] After the thrombosis is formed there is raised venous capillary pressure, which increases the transcapillary filtration and the pressure rate, resulting in edema. In approximately 50% of patients, venous outflow obstruction decreases within 3 months by lysis and recanalization.[49] Patients who have early edema are most likely to have residual thrombosis. Clots that continue to propagate have a greater risk to break apart and lead to embolization. This generally occurs more frequently in the first few days

TABLE 42.1 Selected Risk Factors for Venous Thromboembolism

Genetic Risk Factors	Acquired Risk Factors	Triggering Risk Factors	ICU-Acquired Risk Factors
Antithrombin III deficiency	Age	Surgery	Sepsis
Protein S and C deficiency	Previous VTE	Pregnancy	Vasopressor use
Prothrombin gene mutation	Obesity	Estrogens	Central venous line
	Malignancy	Immobility	Platelet transfusions
	Antiphospholipid syndrome		Pharmacologic paralysis
	Collagen vascular disease		Use of recombinant factor VIIa

ICU, Intensive care unit; *VTE,* venous thromboembolism.

VTE events increase with age. In one population-based study, there was a nonlinear, exponential increase in VTE events with age and a significant increase noted after the age of 60 years.[29] In the elderly, rates of PE are rising faster than the rates of DVT; thus a VTE event in an elderly person is more likely to be a PE, with its associated increased mortality.[3,30]

Anderson and Spencer[31] reviewed multiple risk factors associated with a diagnosis of VTE and found that the risk factors were not equal in their impact on VTE occurrence. The strongest risk factors were hip and leg fractures, major general surgery, hip or knee replacement, major trauma, and spinal cord injury. Moderate risk factors included arthroscopic knee surgery, central venous lines, chemotherapy, congestive heart failure, hormonal replacement or oral contraceptives, cancer, pregnancy, thrombophilia, and prior VTE.[31] Heit and associates[32] found that the hospital setting, nursing home, or other chronic facility confinement was an independent risk factor for VTE. This is most likely due to increasing degrees of immobility.

Several acquired and inherited hypercoagulable states have been shown to increase the risk of VTE and are collectively known as thrombophilia. Major acquired hypercoagulable conditions include malignancy, myeloproliferative disorders, and antiphospholipid syndrome (APS).[33] DVT, the most common manifestation of the APS, occurs in 29% to 55% of patients with the syndrome, and about half of these patients have pulmonary emboli.[34–36]

The occurrence of a VTE event in a young adult should alert the clinician to the potential of an underlying inheritable thrombophilic condition. Nearly half the patients with a VTE event before the age of 45 years have an associated inherited disorder.[33] Factor V Leiden mutation causing resistance to activated protein C is the most common inherited risk factor. Factor V Leiden mutation is present in up to 5% of the normal population and is the most common cause of familial thromboembolism.[33] Factor V Leiden mutation appears to be more associated with the development of DVT rather than PE.[37] Primary or acquired deficiencies in protein C, protein S, and antithrombin III are other risk factors and their thrombotic expression is variable.[33]

Several primary disorders are associated with a high risk for fatal VTE. Patients frequently present with massive PE, and ICU admission is required. From the RIETE (Computerized Registry of Patients with Venous Thromboembolism) study, risk factors of immobilization secondary to neurologic disease, cancer, and cardiopulmonary disorders had two- to threefold increased risk for fatal PE.[38] In hospitalized cancer patients, VTE is the second leading cause of death.[39] The risk of VTE in cancer patients undergoing surgery is three to five times greater than that in surgical patients without cancer. Moreover, cancer patients with symptomatic DVT exhibit a high risk of recurrent VTE.[40] Heart failure is a frequent admission diagnosis in the coronary care unit. In patients with severe heart failure (ejection fractions <30%) PE is a major cause of morbidity and mortality.[41,42] Among 198 patients with severe heart failure in the coronary care unit, 9.1% developed PE during their hospitalization, despite a majority receiving thromboprophylaxis.[41] In an autopsy series of cardiac patients nearly a quarter had PE and the diagnosis was unsuspected in 82% of the patients.[43] Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a common reason for admission to the general hospital ward service and the ICU. Increased work of breathing leads to immobility, which is a risk factor of DVT. In a prospective cohort of 196 patients with COPD exacerbation, all patients had ultrasonography of the lower extremities performed. Among the 196 patients, 21 (10.7%) had DVT and the majority of patients were asymptomatic.[44] Moreover, hospitalized patients with unexplained exacerbations of COPD, when routinely evaluated, show demonstrated PE in 25% to 29%.[45,46]

after clot formation. Clots that do not continue to propagate resolve by either fibrinolysis or organization. These processes generally occur within 7 days of clot formation.[49,50]

In general, only 25% of patients with suspected DVT actually have it.[47] The detection of DVT in critically ill patients is hampered by the patient's inability to report symptoms and the unreliability of physical signs of DVT. CUS is noninvasive and highly sensitive and specific for the diagnosis of proximal lower extremity DVT.[51] Full compressibility of either the femoral or popliteal veins excludes proximal DVT[51] when compared to the gold standard demography; CUS has a sensitivity of 97% to 100% and a specificity of 98% to 99% for the detection of proximal thrombosis. Ultrasonography is less accurate in the diagnosis of distal calf vein thrombosis.[51,52] Whether high-risk critically ill patients should be systematically screened for DVT using CUS, given the high incidence of DVT and limitation of clinical examination, is unresolved.[13,17]

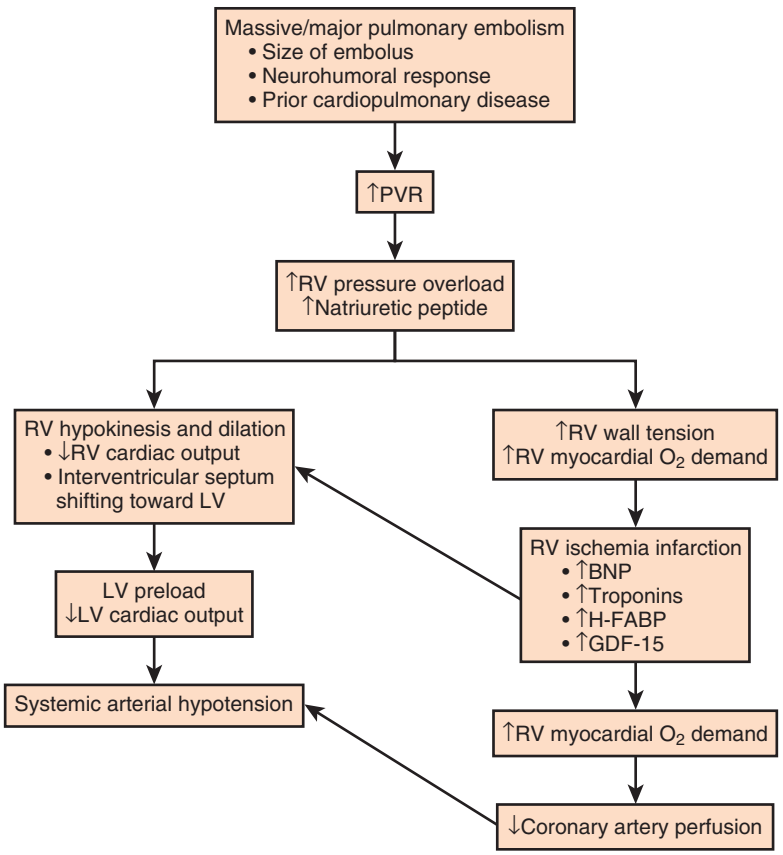
Upper extremity deep venous thrombosis (UEDVT) accounts for approximately 4% of the venous thromboembolic events.[53] Primary UEDVT makes up one-third of all UEDVTs. Primary UEDVTs appear to be associated with inherited thrombophilic conditions, and the risk markedly increased to 14-fold when oral contraceptives were used.[54] Catheter UEDVTs are associated with the placement of a central venous catheter, and these patients are more likely to be inpatients than outpatients, as demonstrated by a large registry.[55] In addition, patients with cancer have an increased occurrence of UEDVT when a central venous catheter is placed in these areas.[55] Catheter-related UEDVT may have a higher pulmonary embolic potential than primary UEDVT.[52]

Pathophysiology

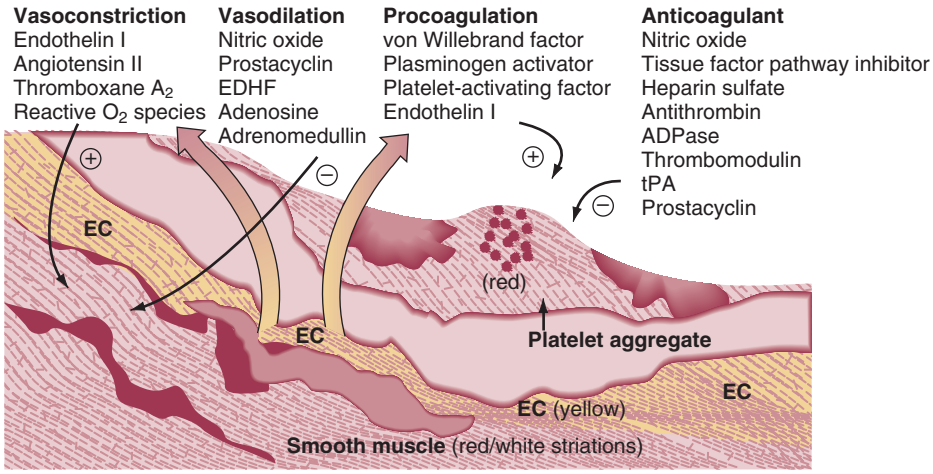
Nearly two-thirds of patients who die from pulmonary thromboembolism die within 1 hour of presentation, but anatomically massive pulmonary emboli (>50% obstruction of the pulmonary circulation) are responsible for only half of the deaths. The term *major pulmonary thromboembolism* has been used to describe any pulmonary thromboembolus that results in a hemodynamically significant event.[1] In patients with pulmonary thromboembolism, hemodynamic presentation is an important predictor of survival. The Urokinase Pulmonary Embolism Trial (UPET) demonstrated that the presence of hemodynamic decompensation was associated with a sevenfold increase in mortality rate.[56] ICOPER confirmed these results by demonstrating a fourfold increase in mortality rate for those patients with hemodynamic instability.[3] Because of the associations between outcome from pulmonary thromboembolism and shock or hypotension, aggressive intervention in patients thought to have pulmonary thromboembolism has given rise to the term *golden hour,* during which timely diagnosis and treatment are paramount.[1]

Hemodynamic Consequences

The principal pathophysiologic effects of pulmonary thromboembolism result from the acute impaction of material into pulmonary circulation and the resulting vascular obstruction and humoral mediator release as depicted in Fig. 42.1.[57] In nonthrombotic obstruction of the pulmonary vasculature, obliteration of 60% to



• **Fig. 42.1** The pathophysiology of acute massive/major pulmonary embolism. *BNP,* Brain natriuretic peptide; *GDF-5,* growth differentiation factor-15; *H-FABP,* heart-type fatty acid–binding protein; *LV,* left ventricle; *O_2,* oxygen; *PVR,* pulmonary vascular resistance; *RV,* right ventricular.



• **Fig. 42.2** Platelet-derived vasoactive factors influencing pulmonary vascular resistance. *ADPase,* Adenosine diphosphatase; *EC,* extracellular; *EDHF,* endothelium-derived hyperpolarizing factor; *O_2,* oxygen; *tPA,* tissue plasminogen activator.

70% of the vascular tree is required to cause an elevation of the pulmonary artery (PA) pressure. In contrast, only 30% of the vascular tree must be obstructed in pulmonary thromboembolism for elevation of the PA pressure to be achieved.[58,59] Therefore factors other than simple mechanical obstruction of the pulmonary vascular system play a role in the elevation of the pressures in the pulmonary vasculature during pulmonary thromboembolism.

The production of platelet-derived vasoconstrictors may play a role in augmenting the increase in pulmonary vascular resistance (PVR) (Fig. 42.2).[57,58,60] Thromboxane A_2 (TxA_2) is a potent vasoconstrictor and is the end product of arachidonic acid metabolism. TxA_2 is produced by endothelial cells, and even in greater quantities by platelets in response to platelet aggregation. It has been demonstrated that there is increased production of TxA_2 in the early phase of PE, which contributes to the PVR elevation and may be attenuated by cyclooxygenase inhibition in animal models.[57] Serotonin (5-hydroxytryptamine) is one of the most potent pulmonary vasoconstrictors. Infusion of serotonin in an animal model can actually simulate the signs and symptoms of PE. Like TxA_2, platelets are the primary source of serotonin production in PE. Serotonin antagonism can reduce PVR.[57,60]

As shown in Fig. 42.1, the degree of mechanical obstruction, the interplay of neurohumoral mediators, and the patient's underlying cardiopulmonary status will dictate the degree of RVD. A rapid rise in the PA resistance produces a significant rise in right ventricular (RV) afterload, thereby causing RV dilatation. The dilation of the right ventricle results in shifting of the interventricular septum into the left ventricle, decreasing left ventricular (LV) preload.[61–63] Moreover, RV dilation potentially promotes an increase in constrictive forces by the pericardium, leading to reduced LV compliance. Decreasing LV preload and compliance subsequently lead to lowering of the cardiac output and systemic hypotension with a resultant decrease in aortic perfusion pressure and decreasing right coronary perfusion pressure.[64,65] A compromised and burdened right ventricle is a direct result of oxygen demand outstripping oxygen supply, creating an ischemic environment for the right ventricle. The functional status of the cardiopulmonary system is very important in the initial hemodynamic presentation and is a major determinant of short- and long-term outcome.[66] In patients without cardiopulmonary disease the anatomic and humoral obstruction must be 75% or greater to cause a mean PA pressure of 40 mm Hg or higher, which is not sustainable; even the previously healthy heart may fail, leading to cardiovascular collapse.[66] Right atrial pressure (RAP) elevation occurs when the mean PA pressure is 30 mm Hg or higher and obstruction exceeds 35% to 40%.[67] Many patients who have a pulmonary embolic event have underlying cardiopulmonary disease. In these patients, cardiopulmonary deterioration (CPD) may occur with a lesser degree of vascular obstruction.[66] This concept is illustrated by the UKEP (Urokinase-Embolie Pulmonaire) Trial in which an initial presentation of shock with acute PE was seen in 56% of patients who had prior cardiopulmonary disease compared with 2% without cardiopulmonary disease. Obstruction of greater than 50% was uncommon.[68]

Respiratory Consequences

Hypoxemia is the most common gas exchange abnormality in patients. However, the Pao_2 and alveolar-arterial (A-a) gradient have been reported to be normal in approximately 30% of patients with PE.[69] Fig. 42.2 summarizes the gas exchange abnormalities as a result of the pulmonary embolic event. Ventilation-perfusion mismatch and low mixed venous oxygen levels are the prevalent causes of hypoxemia.[70,71] As PA pressures increase, right-to-left flow across a patent foramen ovale may occur. Endothelial damage may result from hypoxic exposure and further lead to pulmonary vasoconstriction. Hypoxemia may even promote a prothrombotic and antifibrinolytic effect.[57]

In acute PE an increase in alveolar dead space impairs carbon dioxide (CO_2) elimination; however, the increase in minute ventilation results in hypocapnia. In patients with massive PE there can be a paradoxical elevation of the $PaCO_2$ as a result of a marked increase in dead-space ventilation.[72] In patients with PE because of an increase in alveolar dead space there is a reduction in alveolar CO_2 content, which can be detected by capnography by a reduction in the capnographic waveform area. In one study, patients with PE significantly demonstrated a reduction in the capnographic waveform area compared with patients without PE.[73] There is widening of the partial pressure of end-tidal carbon dioxide ($PETCO_2$)-$PaCO_2$ gradient. Bedside $PETCO_2$ coupled with a Wells score has been shown to have a high negative predictive value.[74]

Clinical Presentation

The signs and symptoms of acute PE are at best nonspecific. The presence of syncope, current DVT, hemoptysis, leg swelling, active cancer, surgery, leg pain, and shock each marginally increases the probability of PE. Further, the absence of dyspnea or tachycardia marginally reduces the probability of PE.[75]

Approximately 50% of patients with acute PE present to the emergency department. In the Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR Registry), among 1880 documented PE patients from 22 U.S. emergency departments, the most common presenting signs and symptoms were dyspnea at rest (50%), pleuritic chest pain (39%), dyspnea with exertion (24%), and syncope, which occurred in 5% as the initial presentation of acute PE. Only 58 patients (3%) had systolic blood pressures of 90 mm Hg or lower on presentation.[76]

Clinical prediction rules have been used in the emergency department setting to determine the pretest probability of acute PE.[77] The most widely known prediction model has been the Wells score and it can allow for a dichotomous classification.[78,79] Other prediction scores have been used, such as the Geneva and the modified Geneva.[77,78] All prediction scores appear to have similar accuracy but are influenced by the local prevalence of PE. The clinical prediction scores are enhanced in identifying the patient with low probability of PE coupled with low D-dimer value.[79]

Clinical Presentation on Admission to the Intensive Care Unit

In patients admitted to the ICU with PE the clinical manifestations may be more demonstrative, as shown in Table 42.2. In the Urokinase Pulmonary Embolism Trial (UPET), the clinical features of massive PE were evaluated. Sudden unexplained onset of dyspnea was the most common symptom and was present in 80% of the patients. A majority of the patients had a well-defined risk factor. Tachypnea and tachycardia were present in 88% and 63% of the patients, respectively. Accentuated second heart sound was noted in 67%, and S_3 or S_4 gallop was present in 47%. Clinical shock was noted in 9%.[80] Syncope can occur. Retrosternal nonpleuritic chest pain may mimic the pain experienced with a myocardial infarction and represent demand ischemia of the right ventricle. The differential diagnosis of pulseless electrical activity (PEA) is massive PE and should be expected when there is a known major risk factor.

The signs and symptoms of submassive PE depend on the degree of RVD. Dyspnea may be progressive over the past 4 to 6 days. Chest pain can be either pleuritic or nonpleuritic in nature. If pulmonary infarction occurs as the result of distal embolization, then hemoptysis may occur. From the PIOPED-II database, 92% of patients with main or lobar pulmonary emboli had dyspnea or tachycardia in contrast to segmental emboli dyspnea and tachycardia, where 65% had these findings.[81,82]

Patients with massive PE and shock manifest systemic hypotension, poor perfusion of the extremities, tachycardia, and tachypnea. In addition, patients appear weak, pale, diaphoretic, oliguric, and develop altered mental status. The patient may be hypoxemic and require high-flow oxygen or urgent intubation and mechanical ventilation. Varying degrees of RVD may be observed. The presence of jugular venous distention, with and without inspiratory collapse, RV heave, summation gallop, accentuated P_2, and presence of tricuspid regurgitation represent the impact the embolus has had on pulmonary vasculature and RV function. If a central line is placed via the subclavian or jugular route, the central venous oxygen saturation ($Scvo_2$) is usually less than 65%.

TABLE 42.2 Clinical Signs and Symptoms of Acute Pulmonary Embolism Potentially Requiring Intensive Care Unit Management

Clinical Variable	Frequency (%) Submassive PE	Frequency (%) Massive PE
Symptoms		
Dyspnea	78	86
Pleuritic CP	85	67
Apprehension	50	70
Altered Mental Status*	5	
Diaphoresis	20	44
Syncope	4	17
Signs		
Tachycardia	42	66
Tachypnea	81	87
Fever	51	50
Deep venous thrombosis	47	39
Cyanosis	3	24
Other Signs		
Jugular venous distention		80
Shock		10
Cardiac arrest (PEA)		28

*Adapted from Stein PD, Willis PW 3rd, DeMets DL. History and physical examination in acute pulmonary embolism in patients without pre-existing cardiac or pulmonary disease. *Am J Cardiol.* 1981;47;218–223.
PE, Pulmonary embolism; *PEA,* pulseless electrical activity.

Recognition of Pulmonary Embolism During Intensive Care Unit Admission

When a patient is admitted to the ICU for a non–PE-related clinical diagnosis, the abrupt and unexplained occurrence of some combination of chest pain, dyspnea, tachypnea, hypotension, and hypoxemia should raise the suspicion of PE. Unexplained fever with and without mild leukocytosis could represent a possible VTE event.[83] Hemoptysis can occur as a result of small distal pulmonary emboli causing alveolar hemorrhage. If PE occurs while the critically ill patient or postoperative patient is using mechanical ventilation, the clinical suspicion and conformation can be difficult. An increase in minute ventilation, dead space, or an increase in supplemental oxygen may be clues to an embolic event. If the patient has end-tidal CO_2 ($PETCO_2$) monitoring, an increase in the $PaCO_2$-$PETCO_2$ gradient may occur.[73]

Diagnostic Testing for Pulmonary Embolism

Arterial Blood Gas Measurement

Hypoxemia and an increased alveolar-arterial gradient are usually seen in PE but can be normal in about 14% and are most likely the result of small embolic events.[84,85] The initial acid-base disturbance is a respiratory alkalosis, which may evolve to a metabolic

(lactic) acidosis as hypotension and shock ensue. A linear relationship between PE severity and Pa_{O_2} in patients without prior cardiopulmonary disease has been described. In the UPET and PIOPED trials 12% and 19% of patients, respectively, had Pa_{O_2} 80 mm Hg or greater.[86] Hypocarbia is usually present with acute PE because of hyperventilation, but hypercapnia can occur with large PEs producing increased dead space.[87,72]

Chest Radiography

The chest radiograph is abnormal in most cases of PE; however, radiographic findings possess inadequate sensitivity to rule out PE. Common radiographic abnormalities include atelectasis, pleural effusion, parenchymal opacities, and elevation of a hemidiaphragm. Radiographic findings of pulmonary infarction often show a wedge-shaped, pleural-based triangular opacity with an apex pointing toward the hilus (Hampton hump). Focal oligemia or decreased vascularity has been known as the Westermark sign. These findings are suggestive of PE but are infrequently prospectively observed.[88,89] Radiographic findings of RVD may include a prominent central PA (knuckle sign) and cardiomegaly. In one large prospective cohort of patients with PE a normal chest radiograph was found in 24% of the patients.[89] A normal-appearing chest radiograph in a patient with severe dyspnea and hypoxemia is suggestive of a pulmonary embolic event.

Electrocardiography

In 1935 McGinn and White first described the association between acute PE and specific electrocardiogram (ECG) changes when they noted the $S_1Q_3T_3$ pattern in seven patients with acute cor pulmonale.[90] A normal ECG can occur with PE in a frequency ranging from 9% to 30%. The most common ECG abnormalities in the setting of PE are tachycardia and nonspecific ST-T wave abnormalities. The classic findings of right-sided heart strain and acute cor pulmonale are tall, peaked P waves in lead II (P pulmonale); right-axis deviation; right bundle branch block; and an $S_1Q_3T_3$ pattern. Only 20% of patients with proven PE have any of these classic ECG abnormalities.[91–93] T-wave inversion in the precordial leads representing subepicardial ischemia may be seen. The presence of this ECG finding is associated with increased degree of vascular obstruction and elevation of the PA pressure.[94] The new onset of atrial fibrillation has been thought to be associated with a pulmonary embolic event. In a recent study the occurrence of atrial fibrillation did not in general increase the probability of PE.[95] However, if chest pain were the only symptom, the presence of atrial fibrillation increases the probability of PE (odds ratio [OR] 2.42, 95% confidence interval [CI] 0.97–6.07).

D-Dimer Assay

The serum D-dimer is a degradation product produced by plasmin-mediated proteases of cross-linked fibrin. D-Dimer is measured by a variety of assays. These assays are categorized as quantitative, semiquantitative, qualitative rapid enzyme-linked immunosorbent assays; quantitative and semiquantitative latex; and whole-blood assays. The quantitative rapid enzyme-linked immunosorbent assays are the best assays to use in terms of sensitivity and likelihood ratio.[96] When clinical prediction scores indicate that the patient has a low or moderate pretest probability of PE, D-dimer testing is useful to further define the likelihood of PE. Negative results on a high-sensitivity D-dimer test in a patient with a low pretest probability of PE (Wells rule) are associated with a low likelihood of VTE and reliably exclude PE.[97] In a large prospective, randomized trial in patients with a low probability of PE who had negative D-dimer results, not performing additional diagnostic testing was not associated with an increased frequency of symptomatic VTE during the subsequent 6 months.[98]

D-Dimer testing loses its ability to predict the likelihood of PE in older patients and in the presence of cancer, pregnancy, and various inflammatory or infectious disorders. If the pretest probability for PE is high, D-Dimer testing should not be performed and objective testing should be done.[96]

Combining D-dimer results with measurement of the exhaled P_{ETCO_2} to the partial pressure of oxygen (P_{O_2}) (P_{ETCO_2}/P_{O_2}) can be useful for diagnosis of PE. Kline and colleagues demonstrated in moderate-risk patients a positive D-dimer result (>499 ng/mL) and a P_{ETCO_2}/P_{O_2} ratio less than 0.28 significantly increased the probability of finding segmental or larger PE on computed tomography (CT) multidetector-row pulmonary angiography.[99] In contrast, a P_{ETCO_2}/P_{O_2} ratio greater than 0.45 predicted the absence of segmental or larger PE.

Duplex Compression Ultrasonography

Currently, DVT is largely diagnosed by duplex CUS. When using CUS, the ultrasonographic transducer pressed against veins shows they are easily compressed, but the muscular arteries are extremely resistant to compression. Where DVT is present, the veins do not collapse completely when pressure is applied using the ultrasonographic probe.[100–102]

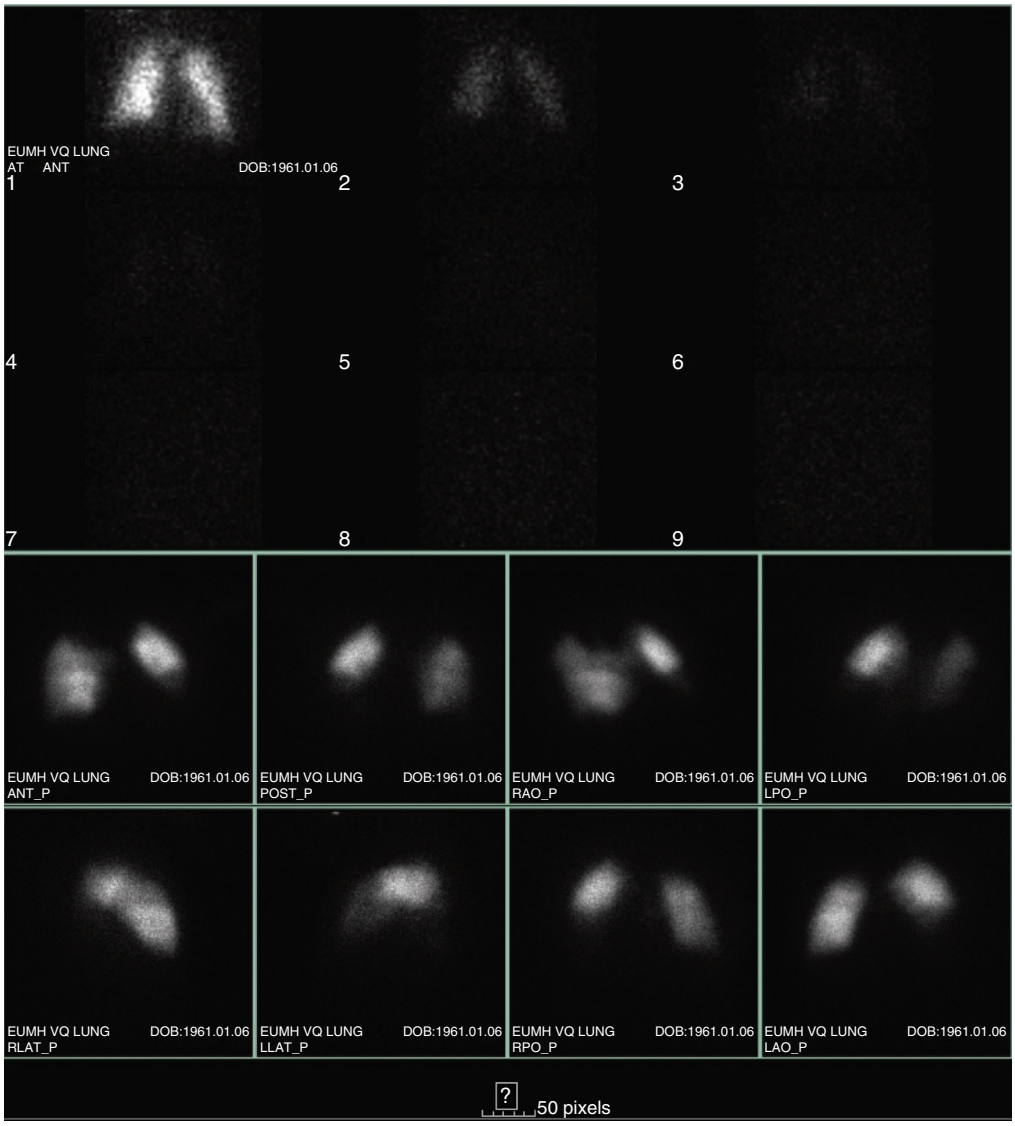
Before an ultrasonographic scan can be considered negative, the entire deep venous system must be examined using centimeter-by-centimeter compression testing of every vessel. The risk of a DVT event after a single whole leg CUS in 3 months is 0.57% (95% CI 0.25–0.89).[103]

CUS is associated with a sensitivity of 97% for proximal DVT, 72% for distal DVT, and a specificity of 94%.[104] In a meta-analysis of the role of CUS in DVT, CUS alone had a sensitivity of 93.8% (92.0%–95.3%) for proximal DVT, 56.8% (49.0%–66.4%) for distal DVT, and specificity of 97.8% (97.0%–98.4%).[105]

Ventilation-Perfusion Nuclear Scans

The ventilation-perfusion ($\dot{V}/\dot{Q}$) scan has a limited role in the diagnosis of acute PE in the ICU, although its diagnostic accuracy is no different from that in non–critically ill populations.[106] Because of the advancing technology of CT scanning, the lung scan is used in critical care units in special circumstances such as renal insufficiency or in the patient who is not intubated and capable of transport from the ICU to the nuclear medicine suite for a full view scan. If the institution has a portable lung scanner, this can be used in the ICU but the number of images is reduced compared with the standard $\dot{V}/\dot{Q}$ scan.

A high-probability scan, as shown in Fig. 42.3, is sufficient diagnostic evidence of PE to begin anticoagulation therapy, and a normal $\dot{V}/\dot{Q}$ scan is considered sufficient evidence to exclude PE. However, the frequency of low- or intermediate-probability scans (indeterminate scans) can be as high as 50% to 70%, with a 10% to 50% probability of PE. Therefore it is impossible to initiate anticoagulation therapy based on this indeterminate lung scan probability. In the first PIOPED study, only 40% of patients with PE had a high-probability $\dot{V}/\dot{Q}$ scan result, whereas another 40% of patients with PE had an indeterminate result and 14%



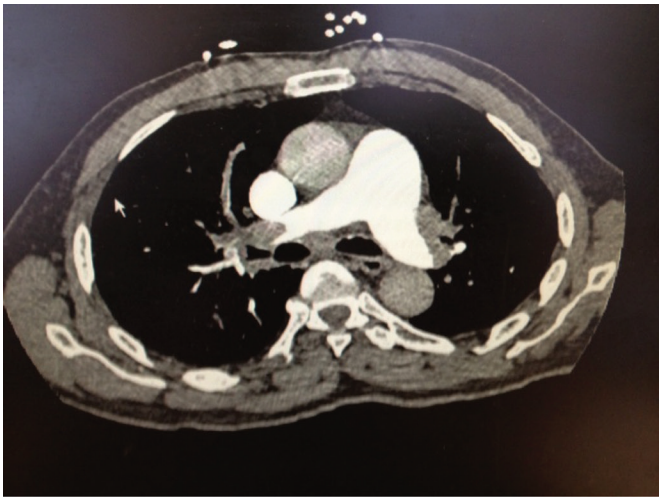
• **Fig. 42.3** High-probability ventilation-perfusion lung scan in a patient with submassive pulmonary embolism and right ventricular strain. Large left lung perfusion defects with a right upper lobe apical perfusion defect are present. Ventilation is normal.

had a low-probability result. A high-probability $\dot{V}/\dot{Q}$ scan result had a positive predictive value of 88% in patients without prior history of PE. The combination of a high clinical probability with the high-probability lung scan resulted in a 96% positive predictive value. The negative predictive value of a low-probability scan result was 88% and improved to 96% when combined with a low clinical probability. Thus a low-probability scan result with a low clinical probability score rules out PE as definitively as a normal scan result. Finally, 39% of the patients had intermediate scan results and 32% of these patients had angiographically proven PE.[14,107]

Preexisting cardiopulmonary disease diminishes the clinical utility of $\dot{V}/\dot{Q}$ scans by increasing the prevalence of nondiagnostic scans. Nondiagnostic scans are more likely to occur in patients with preexisting cardiopulmonary disease. Lung scans are not useful to either establish or rule out the diagnosis of PE in more than 80% of cases. A similar disadvantage of $\dot{V}/\dot{Q}$ lung scans is noted in critically ill patients with prior cardiopulmonary disease. Nevertheless, $\dot{V}/\dot{Q}$ lung scans can be performed in the critically ill, even if patients are receiving mechanical ventilation, and chest radiographic abnormalities can be used as a surrogate of ventilation defects. Despite the limited ventilation component under positive-pressure respiration, the perfusion component is not significantly affected by mechanical ventilation. $\dot{V}/\dot{Q}$ scans remain a useful tool in patients with contraindications to pulmonary angiography or CT angiography.[108,109]

Multidetector Computed Tomography Scan of the Chest

The PIOPED II study firmly established the role of CT pulmonary angiography (CTPA) and largely replaced ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scintigraphy as the main imaging modality in suspected PE.[110] The technology is continually evolving and its use is widespread. As illustrated in Fig. 42.4, CTPA provides direct visualization of emboli throughout the pulmonary arterial vasculature. The advantage of CTPA over pulmonary angiography and lung scan



• **Fig. 42.4** Extensive bilateral lobar pulmonary emboli.

is the discovery of an alternative diagnosis when PE is not found on CTPA. In one study, an alternative diagnosis was established in 57% of patients who did not have a PE.[111] Currently, CTPA is the gold standard for PE diagnosis. A meta-analysis of 23 studies with 4657 patients with a negative CTPA who did not receive anticoagulation showed a 3-month rate of subsequent VTE of 1.4% (95% CI 1.1–1.8) and a 3-month rate of fatal PE of 0.51% (95% CI 0.33–0.76), which compares favorably with the results noted after a normal gold standard invasive contrast pulmonary angiogram.[112] The increased use of CTPA raises concerns about the increased incidence of cancer attributable to radiation.[113] For this reason, combined use of CTPA and CT leg venography should not be performed because the latter adds little to diagnostic utility. In the PIOPED II trial, no patient with PE or DVT would have been undiagnosed if imaging of the pelvic and proximal leg veins had been omitted.[107,110]

Magnetic Resonance Imaging

In the PIOPED II study, as many as 25% of patients had a contraindication to CT angiography of the chest. Preexisting renal failure and pregnancy were the primary conditions that prevented this modality from being used as the primary test for the evaluation of PE.[110] Thus gadolinium-enhanced magnetic resonance pulmonary angiography (MRA) could potentially be used to diagnose PE because it is devoid of radiation. The accuracy of this technique combined with magnetic resonance venography (MRV) has been studied in the prospective, multicenter PIOPED III accuracy study. The proportion of technically inadequate images ranged from 11% to 52% across the seven participating centers. Technically adequate MRA had a sensitivity of 78% and a specificity of 99%, whereas technically adequate MRA and MRV had a sensitivity of 92% and a specificity of 96%. However, 194 (52%) of 370 patients had technically inadequate results, which substantially restricts its clinical use.[114]

Risk Stratification

Death from an embolic event almost always results from hemodynamic deterioration owing to an abrupt rise in PVR overwhelming the contractile power of the right ventricle. The highest-risk individuals present with progressive hemodynamic and respiratory deterioration that characterizes the clinical presentation of major or massive PE and is seen in approximately 5% of patients with PE.[2] Patients who present with relative hemodynamic stability but exhibit varying degrees of RVD can be categorized as having submassive PE. It is important while discussing treatment strategies to identify this group of patients. Risk stratification schemes in normotensive patients center on RV function assessment after an embolic event and identify patients who may be at risk for progressive hemodynamic deterioration. Approximately 50% of patients who are normotensive have varying degrees of RVD and 10% will die. The European Society of Cardiology recommends a classification of PE into high-risk and non–high-risk groups. The high-risk groups represent the massive or major PE presentations. The non-UEDVT high-risk group is further subdivided into intermediate risk in which the mortality rate ranges between 3% and 15% and a low-risk group in which the mortality rate is less than 3%. Initial therapeutic interventions are greatly influenced by risk stratification that includes clinical scoring systems, laboratory data, and imaging.[115–117]

The presence of RVD is a predictor of the increased risk of embolic-related adverse events and mortality rates compared with patients without RVD.[2] Patients who present with circulatory shock usually have severe RVD and have mortality rates up to 65%.[1,2,115] In PE patients with normal hemodynamics and evidence of RVD the mortality rates can range from 8% to 14%. Several registry studies have observed that the frequency of RVD in normotensive patients is approximately 40%.[116,117] In PE patients with initial normal hemodynamics and no RVD the mortality rate is low (0%–3%).

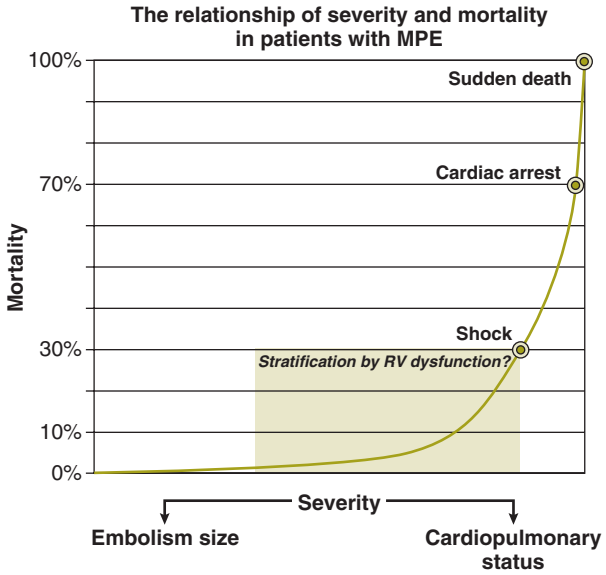
Clinical and Hemodynamic Parameters

The initial hemodynamic presentation of PE is the most powerful predictor of outcome, as illustrated in Fig. 42.5. Arterial hypotension at the time of PE presentation is an early predictor of death. In the 2392 patients from the ICOPER study, the 90-day mortality rates were 52.4% in patients with systolic arterial blood pressures below 90 mm Hg, and 14.7% in those patients who had preserved arterial blood pressures. In addition, comorbid conditions increase the risk of adverse clinical events, even in the presence of anatomically small PE. In the ICOPER findings, age over 70 years, congestive heart failure, cancer, and chronic lung disease were identified as independent predictors of 3-month mortality risk, with approximately twofold increase in the risk of death.[2] In one study, altered mental status at presentation was associated with a sevenfold increase in risk of adverse outcome. Altered mental status most likely reflected decreased cardiac perfusion or hypoxia. In the same study the initial presentation of shock was associated with a threefold increase in risk of 30-day adverse outcome (death, secondary shock, or recurrent PE).[117]

Patients can be clinically risk stratified by the use of a clinical scoring system known as the Pulmonary Embolism Severity Index (PESI), which also has a simplified version.[118,119] This prognostic model was developed by Aujesky and colleagues (Table 42.3) using a large database of hospitalized PE patients from which they derived and validated a prediction rule that identified acute PE patients with low to high risk for fatal PE and adverse events. Using 11 variables of predictors, 5 distribution categories emerged looking at inpatient fatality, 30-day all-cause mortality rate, and the adverse outcomes of nonfatal cardiogenic shock or cardiopulmonary arrest. Class I to class III all-cause mortality rates ranged between 0% and 3.1%, although class IV to class V all-cause mortality rates

were between 10% and 24%. This score has an excellent negative predictive value and readily identifies low-risk patients but suffers in the attempt to predict patients at high risk for adverse events.[119] A more simplified PESI score has been developed and has a high negative prediction value.[120]

In patients with symptomatic acute PE, the presence of DVT may have prognostic significance. In a prospective study by Jiménez and coworkers, among 707 patients diagnosed with acute PE, 51.2% had concomitant DVT and 10.9% had PE-specific fatality at a 3-month follow-up. Patients with PE with the presence of DVT at the time of diagnosis had an adjusted hazard ratio (HR) of 2.05% (95% CI 1.24–3.38) and PE-specific fatality-adjusted HR of 4.25% (95% CI 1.61–11.25). These findings were validated by a large international registry trial (RIETE) that again demonstrated a significant prediction of all-cause mortality rate and PE-specific mortality rate when concomitant DVT was present during the acute embolic event. These results suggest that patients with symptomatic acute PE have an increase in all-cause mortality rate, PE-related death, and recurrent VTE over a 3-month period if at the time of the PE a diagnosis of proximal DVT is also present.[121]



• **Fig. 42.5** Pulmonary embolism mortality rate based on initial hemodynamic presentation. *MPE,* massive pulmonary embolism; *RV,* right ventricular.

Electrocardiogram

Several studies have demonstrated that ECG signs of RV strain correlate with the presence of RVD.[122,123] A study by Punukollu and associates showed that T-wave inversion in leads V_1 to V_3 had a specificity of 88% and diagnostic accuracy of 81% for RVD in acute PE.[124] Daniel and colleagues developed an ECG scoring system based on typical features of acute PE such as presence of right bundle branch block, T-wave inversions, and additional features of right-sided heart strain that predicted severe pulmonary hypertension (systolic PA pressure >50 mm Hg) with a specificity of 97.7% if the patient's "ECG score" is 10 or greater.[125] The ECG may also be a tool for risk stratification of normotensive acute PE patients. In a study by Vanni and coworkers among 306 patients with documented PE, 130 (34%) patients demonstrated ECG findings of right-sided heart strain. In this study ECG findings of right-sided heart strain were defined as incomplete or complete right bundle branch block, $S_1Q_3T_3$, or inverted T waves in the precordial leads

TABLE 42.3 Pulmonary Embolism Severity Index

SCORING	
Predictor	**Points Assigned**
Age	Age, in years
Male gender	+10
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Pulse >110 beats/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate >30 breaths/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial Sao_2 <90%	+20

RISK CLASSIFICATION				
Class and Distribution	**Score Range**	**Inpatient Mortality Rate (%)**	**30-Day Mortality Rate (%)**	**Nonfatal Cardiogenic Shock or Cardiopulmonary Arrest**
Class I (19.4%)	<65	0.8	1.1	0.4
Class II (21.5%)	65–85	1.8	3.1	1.3
Class III (21.7%)	85–105	4.2	6.5	2.1
Class IV (16.4%)	106–125	5.9	10.4	1.9
Class V (21.0%)	<125	15.8	24.5	4.6

Sao_2, Arterial oxygen saturation.
Adapted from Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med.* 2005;172:1041–1046.

V_1, V_2, and V_3. For this study only one of these ECG patterns had to be present. The investigators demonstrated that the presence of RV strain on the initial ECG was associated with clinical deterioration and death (HR 2.58) in normotensive PE patients.[122]

Cardiac Biomarkers

Biomarkers are important components in the risk stratification of patients with PE. Tests for biomarkers are widely available and there is usually a quick turnaround from the clinical laboratory. Caution must be taken on the interpretation of these biomarkers. It is important for the critical care clinician to understand the clinical issues that affect the interpretation of the biomarkers and understand the negative and positive predictive values.[115] Elevations of brain natriuretic peptide (BNP), troponin, and D-dimer, occur in many patients with PE and correlate with the magnitude of RVD.

See the online supplement for discussion of Brain Natriuretic Peptide, Cardiac Tropinin, and D-Dimer.

Echocardiography

The echocardiogram has become the main imaging modality to assess RV structure and function. In addition, PA pressures can be estimated. Most hospitals in the United States have portable echocardiographic technology allowing for serial assessment of the impact of treatment on RVD. In hemodynamically stable patients with PE, 20% to 40% will have some echocardiographic finding of RVD.[116,117] Box 42.1 illustrates the echocardiographic finding of acute PE. Toosi and colleagues performed a quantitative risk assessment of various echocardiographic measurements of RVD in acute PE. For inpatient mortality rate the positive predictive values range between 11% and 20% and the negative predictive values are between 97% and 100%.[147] The major drawback with the role of the echocardiographic definition of RVD of acute PE is that it lacks standardization. There is no clear agreement on which of the echocardiographic findings predicts adverse outcomes and fatality in normotensive submassive PE. However, an echocardiographic finding of a right ventricle/left ventricle ratio greater than 0.9 was found to be an independent risk factor of in-hospital death (OR 2.7% CI 1.7–6.0) in a large registry trial.[148]

In the ICOPER study that included 1035 PE patients with systolic arterial pressure 90 mm Hg or higher, an echocardiogram was performed within 24 hours of PE diagnosis. The incidence of RVD was 39% (405 patients). The 30-day survival rates were lower in patients with RV hypokinesis (84%) compared with those without RV hypokinesis (91%), HR 1.94 (CI 1.41–3.16; $P \leq 0.001$). The negative predictive value of 30-day mortality rate of echocardiographic confirmation of RVD was 91%. The positive predictive value was 16%.[2]

In the assessment of RVD, if cardiac biomarkers are elevated, how well does this correlate with RVD on transthoracic echocardiography? A study by Logeart and coworkers found that a BNP level less than 100 pg/mL had a negative predictive value of 100% and TnI of less than 0.10 ng/mL had a negative predictive value of 67% for the presence of RVD on echocardiography. Combining a BNP greater than 100 pg/mL and TnI greater than 0.10 ng/mL had a positive predictive value of 80% for the presence of RVD by echocardiography.[149]

The echocardiogram can visualize free-floating right-sided heart thrombi. In the ICOPER study patients with this finding had a mortality rate of 21% compared with 11% in those without right-sided heart thrombi.[150] The detection of a patent foramen ovale or atrial septal defect by echocardiography may be a warning finding for the development of paradoxical embolization, which is associated with a risk of stroke and increased mortality rate.[151]

For the evaluation of circulatory shock transesophageal echocardiography (TEE) is a useful diagnostic modality. In patients with massive PE who cannot undergo CTPA, when TEE is performed, it has a 60% to 80% sensitivity and a 95% to 100% specificity to diagnose acute PE. TEE has a 9% to 95% sensitivity and a 100% specificity in main PA PE.[152] In patients with unexplained cardiac arrest or PEA, TEE has been shown to identify acute massive PE. In a small study of 25 patients with PEA, TEE demonstrated eight (36%) patients with massive PE.[153]

Echocardiography is an important diagnostic and prognostic tool in the management of patients with PE. Echocardiography also influences the therapeutic strategy based on cardiac hemodynamics and RV function. It is simple, quick, noninvasive, accurate, convenient, and safe, while providing critical information on the physiologic effects of PE on cardiac hemodynamics as well as RV size and function.

• BOX 42.1 Echocardiographic Features of Acute Pulmonary Embolism

Global reduction of RV function
RV dilation
RV hypokinesis
McConnell sign (free wall hypokinesis sparing of the apex)
Interventricular septal flattening
"D-shaped" LV resulting from paradoxical septal motion
RV/LV thrombus
Dilated inferior vena cava without inspiratory collapse
Pulmonary hypertension
Tricupid regurgitation with a jet velocity >2.6 m/s
Patent foramen ovale—result of increased pulmonary artery pressures

LV, *Left ventricle;* RV, *right ventricle.*

Computed Tomography Pulmonary Angiography

CT scan findings of right-sided heart dysfunction are illustrated in Figs. 42.6A and B. The detection of RV enlargement by spiral chest CT has recently been evaluated in the risk stratification of patients with acute PE. Using measurements from a reconstructed CT four-chamber view, RV enlargement, defined as a ratio of RV to LV dimension of greater than 0.9, was a significant independent predictor of mortality occurring within 30 days.[153] In a recent multicenter study of 460 consecutive patients with multidetector CT–confirmed PE a majority of the study cohort were hemodynamically stable and 50% had RVD at the time of diagnosis. Again, an RV/LV ratio of 0.9 or greater provided good correlation with RVD demonstrated by echocardiography. In addition, RVD found on multidetector CT was an independent risk factor for death and clinical deterioration. The investigators propose that multidetector CT scan potentially can be the single procedure, not only for diagnosis of PE but also for risk stratification. However, this assumption will require more validation studies.[112]

In hemodynamically stable patients with acute PE, assessing the RV/LV ratio may be important in not only risk stratification but also the location of the emboli. In a recent multicenter study

Brain Natriuretic Peptide

The heart will release natriuretic peptides as result of ventricular volume overload. Ventricular stretch results in cellular production of proBNP. This peptide is subsequently cleaved to the biologically active BNP and the inactive N-terminal fragment (NT-proBNP).[126] Both BNP and NT-proBNP can be measured clinically and have been validated as diagnostic and prognostic markers of ventricular stretch in multiple conditions, including congestive heart failure, pulmonary hypertension, and acute PE.[127] Elevated concentrations of BNP distinguish patients with PE at higher risk for a complicated in-hospital course and death from those with low BNP levels. Both BNP and NT-proBNP have been extensively investigated as prognostic markers in acute PE. In an early study, ten Wolde and colleagues[127] demonstrated in a prospective cohort of normotensive acute PE patients that those who died within 90 days had a significantly increased BNP level at the time of diagnosis compared with those patients who did not die in follow-up (245 pg/mL vs. 30 pg/mL, respectively). In addition, using a cutoff point of 75 pg/mL, these investigators reported that BNP had a positive predictive value of PE-related fatality of 17%, whereas the negative predictive value for death was 99%.[127] As will be seen for most of the prognostic markers for acute PE, the investigators noted that BNP was able to identify those at low risk of adverse outcomes but is a poor discriminator in identifying those who were likely to die from their PE.

Normal levels of BNP or NT-proBNP have a high negative predictive value for short-term fatality and overall short-term complicated clinical outcome in patients with acute PE. This is illustrated by the study by Kucher and colleagues,[128] who investigated the prognostic capabilities of NT-proBNP in a prospective cohort of patients with acute PE. In those who experienced an adverse event (defined as a combined endpoint of in-hospital death or need for escalation of care, including cardiopulmonary resuscitation, mechanical ventilation, vasopressor, or thrombolysis), NT-proBNP was significantly higher compared with those who did not experience an adverse event (median of 4250 pg/mL vs. 121 pg/mL, respectively). An NT-proBNP cutoff point of 500 pg/mL yielded a negative predictive value for adverse outcome of 97% with a corresponding positive predictive value of adverse outcome of 45%.[128] In a meta-analysis of 13 studies by Klok and associates, they indeed demonstrated that both increased BNP and proBNP were risk factors for short-term fatality, adverse clinical events, and a marker for RVD. However, the investigators caution against using this biomarker alone to justify more aggressive medical therapy, such as thrombolytic therapy.[129]

Cardiac Troponin

Serum troponins are widely available for the evaluation of diverse forms of myocardial injury. The assays are rapid and are well suited as a risk stratification tool. A number of studies and meta-analyses have evaluated the prognostic value of cardiac troponin I (TnI) or T (TnT) (determined by conventional assays) in acute PE.[130–132] Overall, the elevation of cardiac troponin levels was associated with an adverse early outcome including fatality.

In hemodynamically (normotensive) stable patients with PE the incidence of elevated troponins can be as high as 40%.[133] As with the management of acute myocardial infarction, in a patient with acute PE, troponin levels must be obtained serially. The first troponin level in patients with PE may be normal, and subsequently levels will increase. This was illustrated in the study by Ferrari and colleagues who investigated the time course of TnT elevation in patients with acute PE. In a prospective cohort, they found that whereas 50% of normotensive patients with acute PE were found to have an elevated TnT, 5% of these patients had an initial normal TnT that became abnormal at the 6-hour analysis; moreover, 25% of those with an elevated TnT (0.01 ng/mL) died during the hospitalization compared with no deaths in patients who had a TnT value less than 0.01 ng/mL.[134]

In a recent meta-analysis, Becattini and colleagues[132] analyzed the prognostic usefulness of cardiac troponins in acute PE. In this meta-analysis of 20 studies, the investigators reported that 20% of patients with elevated troponins died compared with 3.7% of patients with normal troponin levels. A high level of either TnT or TnI was associated with a fivefold increased risk of in- hospital or 30-day death. The investigators noted that a multitude of different troponin assays and selected cutoff points were used in the included reports, although results were generally consistent across studies. Most studies included in the meta-analysis defined an elevated troponin level as any value above the upper limit of normal for the individual troponin assay.[132]

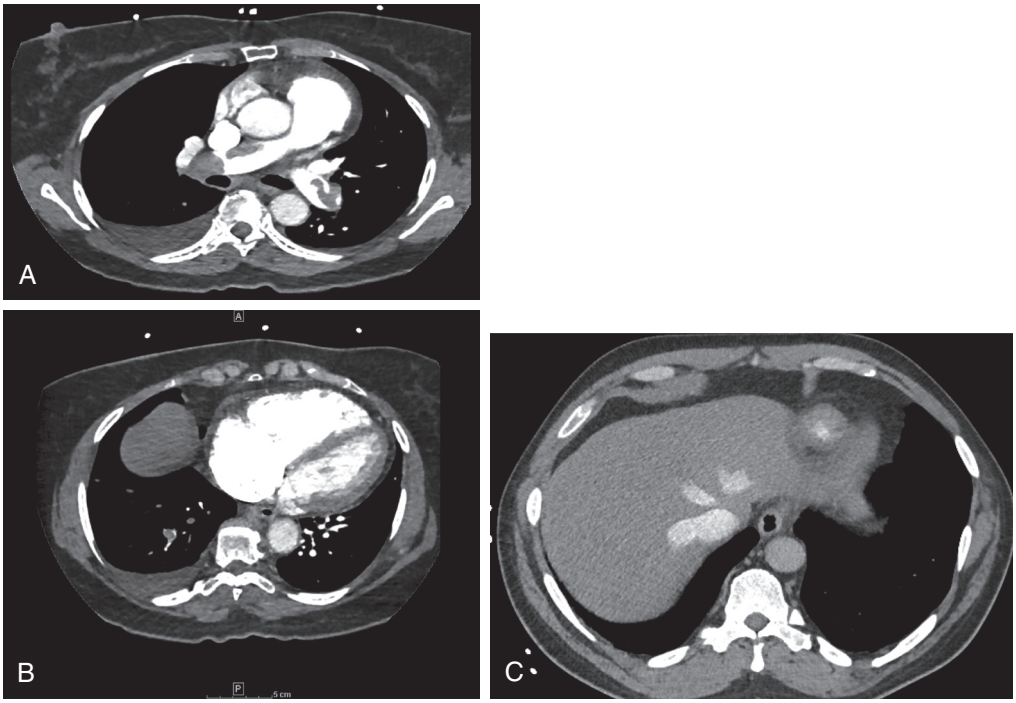
Combining biomarkers with imaging may enhance the prognostication of normotensive patients with acute PE. In one study, the presence of an elevated troponin, echocardiographic evidence of RVD, and the presence of a proximal DVT were associated with an increased 30-day mortality rate.[135]

New generations of highly sensitive troponin assays in patients with acute myocardial infarction have demonstrated excellent diagnostic performance and the potential to improve early risk stratification PE.[136]

Other cardiac biomarkers are released in the systemic circulation when the myocardium is injured. Heart-type fatty acid–binding protein (H-FABP) is a cytosolic protein that is within cardiac myocytes that is released faster than cardiac troponins during injury. Studies have demonstrated that H-FABP has a good negative predictive value for adverse outcomes and, in one study, a 28% positive predictive value in patients with acute PE.[137,138] Growth differentiation factor (GDF)-15 is a distant member of the transforming growth factor-β family. Under normal conditions, myocardium does not produce GDF-15, but its cardiac expression sharply increases after pressure overload and ischemia. The prognostic value of GDF-15 was investigated in a study including 123 patients with acute PE.[23] On multivariate analysis, cardiogenic shock on admission, cardiac TnI, and GDF-15 were independently associated with an adverse outcome at 30-day follow-up.[139] Further studies are needed to confirm these preliminary results.

D-Dimer

The predictive value of D-dimers in the setting of a low pretest probability has been addressed earlier in this chapter. D-Dimer has also been studied as a biomarker for the risk stratification of acute PE.[140–145] As with BNP and troponin, a high negative predictive value has been noted in several studies.[140,141] Elevations of D-dimer in the setting of PE are associated with both 15-day and 3-month mortality.[143,144] Higher levels of D-dimer have also been associated with a more central embolus location, which has been identified as both a mortality and adverse event risk factor.[143,145,146] Although cutoff values vary with each study, D-dimer levels of 3000 ng/mL or their equivalent or more in the setting of PE should be considered significant.



• **Fig. 42.6** A, Computed tomography (CT) scan findings of major pulmonary emboli with right ventricular dysfunction (RVD). B, CT scan findings of RVD (right ventricle/left ventricle ratio >0.09). C, Hepatic reflux of contrast indicated significant RVD.

of 516 hemodynamically stable PE patients, central localization of emboli was found to be an independent mortality risk factor, although distal localization was inversely associated with adverse events. Thus anatomic findings by CT scan may be important in assessing risk in hemodynamically stable patients with pulmonary embolus.[146] Table 42.4 summarizes the various risk modalities used in risk stratification of acute PE.

The Management of Acute Pulmonary Embolism

Pharmacologic Management

The anticoagulation treatment for DVT and acute PE is essentially the same. Anticoagulation therapy does not dissolve the clot but prevents extension. Anticoagulation therapy indirectly decreases clot burden by allowing the natural fibrinolytic system to dissolve thrombus. When PE is suspected, if there is no contraindication, anticoagulation therapy should be started immediately while diagnostic studies are being performed.[154]

Unfractionated and Low–Molecular-Weight Heparin

Heparins act by binding to the natural anticoagulant antithrombin, thereby accelerating the inactivation of thrombin by antithrombin and several other activated coagulation factors This mechanism of action will prevent extension of the thrombus. UFH is usually administered as an initial bolus, followed by a continuous intravenous infusion. Because of a large individual difference in the binding of heparins to plasma proteins, the doses should be adjusted to the results of the activated partial thromboplastin time (aPTT) or the anti–factor Xa (anti-Xa) activity.[155]

TABLE 42.4 Risk Stratification Determination in Acute Pulmonary Embolism

Risk Stratification Test	RV Dysfunction Potentially Present
Compression ultrasonography	Presence of proximal DVT
Natriuretic peptide	BNP >90 pg/mL NT-proBNP >500 pg/mL
Cardiac troponins	TnT >0.1 ng/mL TnI >0.4 ng/mL
Transthoracic echocardiography	Apical four-chamber view: RV/LV ratio >0.9 Qualitative RV systolic dysfunction
Chest computed tomography pulmonary angiogram	Reconstructed four-chamber view: RV/LV ratio >0.9
Electrocardiogram	New complete or incomplete RBBB Anteroseptal ST-segment elevation or depression Anteroseptal T-wave inversion

BNP, Brain natriuretic peptide; *DVT,* deep venous thrombosis; *LV,* left ventricle; *NT-proBNP,* N-terminal fragment proBNP; *RBBB,* right bundle branch block; *RV,* right ventricle; *TnI,* troponin I; *TnT,* troponin T.

The effectiveness of heparin therapy depends largely on achieving a critical therapeutic level of heparin within the first 24 hours of treatment. Nomogram dosing of heparin has been shown to achieve this goal.[156] The critical therapeutic level of heparin is 1.5 times the baseline control value or the upper limit of normal range of

the aPTT. This level of anticoagulation is expected to correspond to a heparin blood level of 0.2 to 0.4 U/mL by the protamine sulfate titration assay and 0.3 to 0.6 by the anti-Xa assay.[157] If intravenous UFH is chosen, an initial bolus of 80 U/kg or 5000 U followed by an infusion of 18 U/kg per hour or 1300 U/h should be given, with the goal of rapidly achieving and maintaining the aPTT at levels that correspond to therapeutic heparin levels. Fixed-dose and monitored regimens of subcutaneous UFH are available and are acceptable alternatives.[154,156]

Low–molecular-weight heparins (LMWHs) have many advantages over UFH. These agents have a greater bioavailability, can be administered by subcutaneous injections once or twice a day, and have a longer duration of anticoagulant effect. There is a lower risk of osteoporosis and immune-mediated thrombocytopenia.[158] A fixed dose of LMWH can be used and laboratory monitoring is not necessary except in clinical circumstances such as morbid obesity, low weight (<40 kg), pregnancy, and renal insufficiency.[159] Comparison trials between LMWH and UFH have demonstrated that LMWH is at least as effective and as safe as UFH, and there are no significant differences in recurrent thromboembolic events, major bleeding, or mortality risk between the two types of heparin.[160] Caution must be used when administering LMWH in patients with renal insufficiency. LMWH is primarily cleared by the kidneys. Therefore monitoring anti-Xa activity should be performed in patients with impaired renal function. If the creatinine clearance is less than 30 mL/min, UFH should be used.[161]

LMWH has a significantly lower incidence of heparin-induced thrombocytopenia (HIT), yet HIT can still occur with exposure to LMWH. Thus LMWH is not an anticoagulant substitute for the patient with HIT requiring VTE prophylaxis or thrombosis treatment.[162]

LMWH can be administered safely in an outpatient setting. This has led to the development of programs in which clinically stable patients with PE are treated at home, at substantial cost savings.[163] An international, open-label, randomized trial compared outpatient and inpatient treatment (both using the LMWH enoxaparin as initial therapy) of low-risk patients with acute PE and concluded that outpatient treatment was not inferior to inpatient treatment.[164]

Fondaparinux

Fondaparinux is a synthetic polysaccharide derived from the antithrombin binding region of heparin. Fondaparinux catalyzes factor Xa inactivation by antithrombin without inhibiting thrombin, and studies have shown that it is effective in the initial treatment and prophylaxis of the VTE. Fondaparinux has been shown to be just as effective and safe as UFH and enoxaparin.[165] Fondaparinux dosing is based on various weight ranges. For patients weighing less than 50 kg, 5 mg once daily is recommended. Patients weighing 50 to 100 kg are given 7.5 mg, and those weighing more than 100 kg receive 10 mg daily. HIT is rare with the use of fondaparinux because of this lack of interaction with platelet factor 4 (PF4).[154]

Warfarin Therapy

The anticoagulant effect of warfarin (Coumadin) is mediated by the inhibition of vitamin K–dependent factors, which are II, VII, IX, and X. Vitamin K antagonists (VKAs) include substances with a short (acenocoumarol), intermediate (warfarin, fluindione), or long (phenprocoumon) half-life. For this reason, and because of genetically induced metabolic variability, the variable vitamin K content of food, a narrow therapeutic index, and interactions with other drugs, the effect on coagulation must be closely monitored. The peak effect does not occur until 36 to 72 hours after drug administration and the dosage is difficult to titrate. Administration of heparins or fondaparinux should overlap during at least 5 days with that of VKAs. After 5 days the parenteral drug can be stopped when the anticoagulant concentration induced by the VKA has achieved international normalized ratio (INR) between 2.0 and 3.0.[154,166]

The current American College of Chest Physicians (ACCP) guidelines for warfarin therapy suggest that the target INR is 2.5 even in high-risk patients (e.g., antiphospholipid syndrome). Because of its lack of validation, the ACCP does recommend pharmacogenetic testing. Warfarin should be started on day 1 or 2 that heparin is started. Usually warfarin 10 mg is administered and INR is adjusted to target INR. There is an increased risk of bleeding when antiplatelet drugs (acetylsalicylic acid, clopidogrel) are administered along with warfarin. In patients with acute coronary syndrome, mechanical valves, or recent coronary artery bypass or coronary stents, there is a likely benefit from the combination. Nonsteroidal antiinflammatory drugs (NSAIDs) also increase the risk of bleeding when taken with warfarin and should be avoided.[166]

New Oral Anticoagulants

A new generation of anticoagulants is emerging with promising advantages over current therapy. These drugs have their effect on specific steps of the coagulation cascade. These agents are taken orally and do not require hematologic monitoring. The direct thrombin inhibitor dabigatran and factor Xa inhibitors rivaroxaban, apixaban, and edoxaban are now approved in the United States to treat DVT or PE. Rivaroxaban has been shown to be as effective as warfarin.[15,167] A major drawback to the factor Xa inhibitors is that there are no specific reversal agents currently available.[168] Idarucizumab, a humanized monoclonal antibody fragment, is now available in the United States as a reversal agent for dabigatran. Andexanet alfa, an anti-Xa decoy agent, is currently under review by the U.S. Food and Drug Administration (FDA).[169]

Duration of Anticoagulation Therapy

A patient with a first thromboembolic event occurring in the setting of reversible risk factors, such as immobilization, surgery, or trauma, should receive warfarin therapy for at least 3 months. No difference in the rate of recurrence was observed in either of two studies comparing 3 versus 6 months of anticoagulant therapy in patients with unprovoked first events.[69,70] The current recommendation is anticoagulation for at least 3 months in these patients; the need for extending the duration of anticoagulation should be reevaluated at that time.[170]

The current ACCP guidelines recommend that all patients with unprovoked PE should undergo a risk-benefit evaluation to determine if long-term therapy is needed (grade 1C).[170] Long-term treatment is recommended for these patients who do not have risk factors for bleeding and in whom accurate anticoagulant monitoring is possible (grade 1A). Patients who have PE and preexisting irreversible risk factors, such as deficiency of antithrombin III, protein S and C, factor V Leiden mutation, or the presence of antiphospholipid antibodies, should undergo long-term anticoagulation.

Heparin-Induced Thrombocytopenia

Thrombocytopenia is common in the ICU setting but rarely is it caused by HIT. Because heparin is a common drug used in the ICU setting, this entity frequently is included in the differential diagnosis of the thrombocytopenia. The downstream consequences

of overdiagnosis can be problematic, especially if it produces breaches in treating patients with VTE or protecting them from VTE.

HIT is a transient prothrombotic disorder initiated by heparin. The main features of HIT are (1) thrombocytopenia resulting from immunoglobulin G–mediated platelet activation and (2) in vivo thrombin generation and increased risk of venous and arterial thrombosis.[171] HIT may manifest clinically as an extension of the thrombus or formation of new arterial thrombosis. HIT should be suspected whenever the patient's platelet count falls to less than 100,000/μL or less than 50% of the baseline value, generally after 5 to 15 days of heparin therapy. However, if a patient has been previously exposed to heparin, falling platelet counts and the clinicopathologic syndrome of HIT can be seen earlier. The pretest probability for HIT can be determined by the application of the "4 Ts": (1) *t*hrombocytopenia, (2) *t*iming, (3) *t*hrombosis, and (4) no o*t*her explanation of thrombocytopenia. At low scores the probability of the presence of platelet-activating HIT antibodies is low; at high scores there is a moderate probability of the presence of the antibodies.[171,172]

The diagnosis of HIT is based on assays that detect the presence of platelet-activating antibodies. The PF4-dependent enzyme immunoassay (EIA) test may lead to overdiagnosis of HIT. However, a negative EIA result essentially rules out HIT. The serotonin release assay is more specific for HIT than the PF4-dependent EIA. EIA is measured in optical density units, and the strength of this measurement is a strong predictor of a positive serotonin release assay result and confirmed HIT. In a patient with thrombocytopenia in whom the optical density units of EIA were less than 1.5 units the thrombocytopenia was not caused by HIT.[171,172]

The treatment of patients in whom HIT develops is to stop all heparin products, including catheter flushes and heparin-coated catheters, and to initiate an alternative, nonheparin anticoagulant, even when thrombosis is not clinically apparent. Preferred agents include direct thrombin inhibitors, such as lepirudin or argatroban. Warfarin therapy should be started while the patient receives an alternative, nonheparin anticoagulant and only when the platelet count has recovered to at least 100,000/μL (preferably to 150,000/μL).[154]

Thrombolytic Therapy

The goal of thrombolytic therapy, by accelerating the conversion of plasminogen to plasmin, is to promote clot lysis and unload the right ventricle by decreasing pulmonary vascular obstruction. Thrombolysis has demonstrated a more rapid resolution of pulmonary vascular obstruction with improvement of RV hemodynamics within 2 hours after initiation of infusion. However, it remains controversial as to whether unloading of the right ventricle with thrombolytic therapy is associated with improved mortality. In the larger original thrombolysis trials, streptokinase and urokinase were compared with heparin alone at infusion rates of 24 and 12 hours, respectively. These studies demonstrated rapid reperfusion of the pulmonary vasculature, reduction in pulmonary resistance, and no difference in mortality rate when compared to heparin.[173,174]

Currently three thrombolytics have FDA approval in the United States for acute PE: streptokinase, urokinase, and alteplase. Streptokinase and urokinase are nonselective agents activating both circulating and clot-bound plasminogen. Both agents have significant limitations; streptokinase is antigenic and may cause hypotension. Alteplase (tissue plasminogen activator [tPA]) is fibrin specific and is the thrombolytic of choice for the management of PE.[175,176]

The current ACCP key recommendations for the use of thrombolytic therapy in acute PE are noted here[170,177]:

1. In patients with acute PE associated with hypotension (e.g., systolic blood pressure <90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (grade 2B).
2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (grade 1B).
3. In selected patients with acute PE whose conditions deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (grade 2C quality evidence).
4. When a thrombolytic agent is used, we suggest short infusion times (e.g., a 2-hour infusion) (grade 2C—weak recommendation [suggestion]/low-quality or very-low-quality evidence).
5. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein. Central administration is not deemed necessary (grade 2C—weak recommendation [suggestion]/low-quality or very-low-quality evidence). The incidence of major hemorrhage from systemic thrombolytic administration can be as high as 20%, including a 3% to 5% risk of hemorrhagic intracranial complications.

Currently, the thrombolytic that is recommended is tPA at a dose of 100 mg given intravenously over 2 hours. Once the tPA infusion is started, the UFH infusion is stopped. After the 2-hour infusion the heparin is restarted, without a loading dose, when the aPTT is less than 80 seconds after the tPA infusion is complete.

Contraindications to systemic thrombolytic therapy in acute PE include an intracranial neoplasm, recent (i.e., <2 months) intracranial surgery or trauma, active or recent internal bleeding during the prior 6 months, history of a hemorrhagic stroke, bleeding diathesis, severe uncontrolled hypertension (i.e., systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg), nonhemorrhagic stroke within the prior 2 months, surgery within the previous 10 days, and thrombocytopenia (i.e., <100,000 platelets/mL). Thrombolytic therapy may cause moderate bleeding in menstruating women, but it has not been associated with major hemorrhage. Therefore menstruation is not a contraindication to thrombolytic therapy.[178]

Submassive Pulmonary Embolism With Hemodynamic Stability and Right Ventricular Dysfunction

In patients with acute PE who are normotensive but demonstrate some degree of RVD, the treatment is somewhat controversial and may depend on the degree of RVD present to initiate aggressive steps to protect RV function. There is a spectrum of RVD and RV injury. If RVD is manifested by only RV wall dilation and not injury, then the outcome may be different when injury begins to occur. The normotensive patients with evidence of RV injury will require expedited protection of RV function.

Role of Thrombolytic Therapy in Normotensive Submassive Pulmonary Embolism With Right Ventricular Dysfunction

Patients with known or suspected PE must be treated initially with UFH infusion. It appears that RVD in normotensive PE patients is associated with an increased risk of short-term adverse events

and death than in patients without RVD. A number of studies have suggested that thrombolytic therapy should be considered in these patients. In the Management Strategy and Prognosis of Pulmonary Embolism Registry, of 719 acute PE patients with normal systemic arterial blood pressure and echocardiographic evidence of RVD, 550 were treated with heparin alone and 169 patients received thrombolytic therapy. The subgroup analysis demonstrated that patients undergoing thrombolysis had a significantly lower in-house mortality rate at 4.1% in contrast to anticoagulation alone at 10.5%. PE recurrence was observed in 7.7% in the thrombolysis group and in 18.7% in patients receiving anticoagulation alone.[2] Although this study demonstrated differences in terms of mortality rates and PE recurrence between the two groups, it must be emphasized that this was a registry trial and not a randomized clinical investigation Therefore it was subject to unavoidable selection bias.

An important study that attempted to determine whether normotensive patients with PE-induced RVD should receive thrombolytic therapy produced some very interesting conclusions. In a prospective trial (MAPPET-3 [Management Strategies and Prognosis of Pulmonary Embolism-3 Trial]) of 256 patients with PE, the investigators randomly assigned patients to receive heparin plus either recombinant tPA (rtPA) or placebo. This study used a combined endpoint of in-hospital death or clinical deterioration (escalation of therapy needed). Clinical deterioration was defined as a requirement for either a catecholamine infusion to treat hypotension or shock, secondary or "rescue" thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency catheter or surgical embolectomy. Initially the study results seem to support the use of thrombolytic therapy. Patients treated with anticoagulation alone were more likely to die or require treatment escalation than those who received rtPA (24.6% vs. 11.0%; $P = 0.006$), and importantly, there was no difference in the incidence of major bleeding or intracranial hemorrhage between the two treatment groups. The difference between the two groups was due to a more frequent need for secondary emergency thrombolysis in the heparin group, although the overall mortality rate was not affected by thrombolysis.[179] One of the major problems with this study was the lack of a consistent definition of RVD. In this study various modalities were used to define RVD and included echocardiography, right-sided heart catheterization, and even ECG signs of RV strain. Nevertheless, this study has been the catalyst for a large multinational European trial currently under way to attempt to resolve the controversy surrounding the role of thrombolytic therapy in patients with PE who are normotensive but have RVD.

Based on the current ACCP guidelines, normotensive PE patients who have RVD (from clinical, biomarker, and echocardiographic findings) and no contraindications to thrombolysis, systemic thrombolysis should be considered (grade 2C recommendation).

Role of Catheter-Directed Therapy in Normotensive Submassive Pulmonary Embolism With Right Ventricular Dysfunction

Catheter-directed therapy (CDT) has the potential to locally reduce clot burden in the PA by mechanically disrupting the clot or locally infusing low-dose thrombolytics or both. In hemodynamically stable patients with RVD who have right and left pulmonary PE or main PA clot, CDT may be considered. However, CDT provides an additional option in the treatment of patients with life-threatening PE and a possible alternative to surgical embolectomy and systemic thrombolysis, especially in patients who are poor surgical candidates and have relative contraindications to systemic thrombolysis. Bleeding risk appears to be lower in CDT administered thrombolysis compared with systemic thrombolysis.[180]

There are no large prospective randomized CDT trials for making evidence-based recommendations. In a meta-analysis of 594 patients with acute massive PE treated with CDT, clinical success was achieved in 86.5%, with success defined as the stabilization of hemodynamics, resolution of hypoxia, and survival to hospital discharge.[181] In the same study, 96% of patients received CDT as the first adjunct to heparin with no previous systemic tPA infusion, and 33% of cases were initiated with mechanical treatment alone without local thrombolytic infusion. When injected locally, the required dose of tPA is likely to be lower compared with a full-dose systemic tPA infusion, and there is less risk for bleeding. Indeed, the rate of major complications from modern CDT has proved to be only 2.4%.

In a recent propensity score–matched cohort study from the National Readmission Database comparing systemic lytics to CDT, CDT demonstrated lower in-house mortality and there was also a lower composite secondary outcome of in-hospital mortality, gastrointestinal bleeding, and intracranial hemorrhage. Interestingly, there was a higher cost of hospitalization in the CDT group even after adjusting for shock and cardiac arrest.[182]

The three types of catheter-based interventions are (1) aspiration thrombectomy, (2) thrombus fragmentation, and (3) rheolytic thrombectomy. Each of these techniques has similar success rates in systematic reviews.[180]

The goal of all these techniques is rapid central clot debulking to relieve life-threatening heart strain and immediately improve pulmonary perfusion. Catheter intervention is important not only for creating an immediate flow channel through the obstruction, but also for exposing a greater surface area of thrombus to the effects of locally infused thrombolytic drug. In patients with overt shock, thrombus fragmentation is usually the first priority of therapy with the goal to expedite reduction in clot burden.

The infusion of tPA can be accomplished unilaterally or bilaterally at a total dose rate of 1.0 to 2.0 mg/h depending on the degree of clot burden. In patients who may be at greater risk for bleeding or may require prolonged infusions greater than 24 hours, fibrinogen levels should be monitored. When the fibrinogen level is decreased below 150 to 200 mg/dL the infusion should be reduced or discontinued.[180] The ACCP currently recommends that CDT be considered in selected highly compromised patients with PE who are unable to receive thrombolytic therapy because of bleeding risk. Although there is a growing body of evidence in favor of CDT, the decision to consider CDT therapy should be multidisciplinary and based on the patient's risk of systemic thrombolysis, his or her status as a surgical candidate, and a case-by-case assessment based on risk stratification findings.

Role of Inferior Vena Cava Filters in Patients With Submassive Pulmonary Embolism With Right Ventricular Dysfunction

The goal of the inferior vena cava (IVC) filter intervention is to prevent further potentially lethal embolic episodes from impact on an already compromised right ventricle. The current IVC filters in use are retrievable and usually placed by interventional radiology. There has been a marked increase in the use of IVC filters for treatment and prevention of the venous thromboembolic disease. Stein and colleagues showed that the use of IVC filters in the United States has increased from 2000 in 1979 to 92,000 in 2006.[183]

IVC filters are usually placed in patients with acute PE or DVT who develop active bleeding during anticoagulation and have an

existing contraindication to anticoagulation. IVC filters should also be considered in the following situations: (1) recurrent thromboembolism despite adequate anticoagulation, (2) the presence of a large free-floating caval thrombus, (3) chronic recurrent PE with pulmonary hypertension, and (4) patients who have had surgical embolectomy or pulmonary endarterectomy.[184]

The Greenfield filter was introduced in 1973, and subsequently many types of permanent IVC filters have been developed; these filters are usually placed under fluoroscopic guidance.[185] Retrievable IVC filters offer an attractive alternative to the standard permanent filters. These retrievable filters are inserted in patients who may have transient contraindications to anticoagulation or patients who have increased bleeding risks (e.g., trauma patients and neurosurgical patients) or in whom the RV hemodynamics normalize. These filters should be removed within 3 months after implantation; unfortunately, these filters are not removed in real-world practice.[184]

The 1998 PREPIC study and its 8-year follow-up suggested that IVC filters reduce the risk of PE while increasing the risk of recurrent DVT, and do not reduce the all-cause mortality rate.[186] Four hundred patients with proximal DVT were randomly assigned to receive IVC filter or no IVC filter and all had received enoxaparin or UFH as a bridge to warfarin therapy, which was continued for at least 3 months. The primary endpoints were recurrent DVT, PE, major bleeding, and death. The patients were followed up at day 12, at 2 years, and then annually up to 8 years after randomization. At day 12, there were fewer PEs in the group that received filters (OR 0.22, 95% CI 0.05–0.90). However, at year 2, there was no significant difference in PE development in the filter group compared with the no-filter group (OR 0.50, 95% CI 0.19–1.33). Additionally, at year 2, the filter group was more likely to develop recurrent DVT (OR 1.87, 95% CI 1.10–3.20). At year 8, there was a significant reduction in the number of PEs in the filter group versus the no-filter group (6.2% vs. 15.1%, $P = 0.008$). However, at 8-year follow-up, IVC filter use was associated with increased DVT (35.7% vs. 27.5%, $P = 0.042$). There was no difference in mortality rate between the two groups. In summary, the use of IVC filters was associated with decreased incidence of PE at 8 years, offset by higher rates of recurrent DVT and no overall mortality benefit.[186,187] Importantly, the indications for IVC filter use in this study differ from the current ACCP guidelines; all patients were given concomitant anticoagulation for at least 3 months, which might not be possible in patients for whom the ACCP recommends IVC filters.

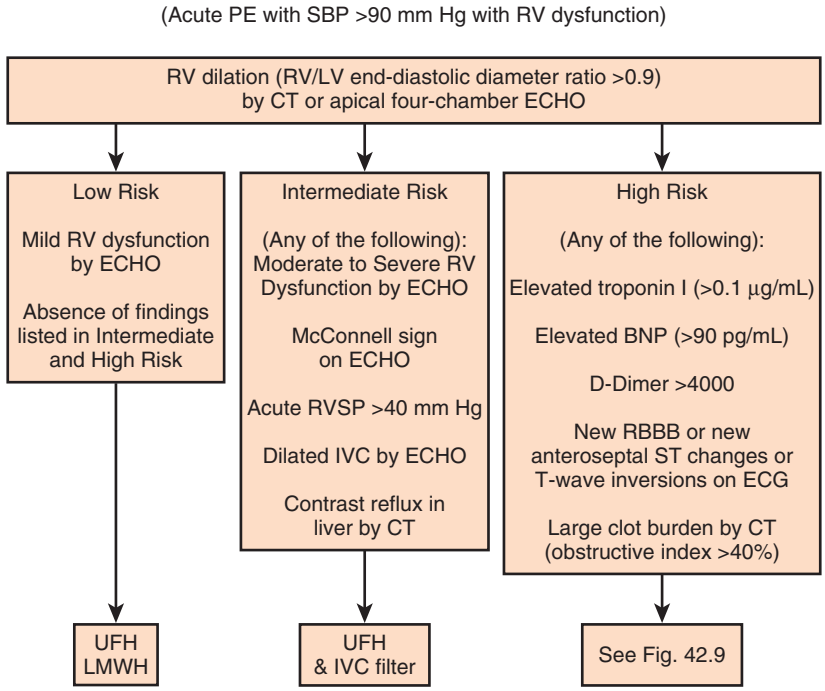
In patients with submassive PE and RVD who are normotensive the role of the retrievable IVC filter to prevent further embolization is controversial. In a small retrospective study adjunctive placement of an IVC filter, especially in patients with RV strain, resulted in no deaths. In patients who did not receive a filter the in-house mortality rate was 10.2%.[188] Prospective studies are needed to further explore the role of retrievable IVC filters in this patient population.

Fig. 42.7 illustrates the therapeutic options available for the management of submassive PE in normotensive patients with RVD. In summary, the goals of these interventions are to reduce clot burden and to prevent further embolic impact on a compromised right ventricle.

Massive Pulmonary Embolism

Respiratory Support

Although mechanical ventilation is often required in massive PE, the hemodynamic effects of mechanical ventilation may further aggravate the vicious circle of RVD and ischemia by augmenting



• **Fig. 42.7** Submassive pulmonary embolus algorithm. *BNP,* Brain natriuretic peptide; *CT,* computed tomography; *ECG,* electrocardiogram; *ECHO,* echocardiogram; *IVC,* inferior vena cava; *LMWH,* low–molecular-weight heparin; *PE,* pulmonary embolism; *RBBB,* right bundle branch block; *RV,* right ventricle; *RV/LV,* right ventricle/left ventricle; *RVSP,* right ventricular systolic pressure; *SBP,* systolic blood pressure; *UFH,* unfractionated heparin.

RV afterload and further decreasing LV preload. Limiting the vasodilating hemodynamic effects of sedation and anesthesia needed for intubation is important. Intubating a patient with massive PE should not be prophylactic, and the risk versus benefit must be weighed carefully for each patient.[189]

Hemodynamic Support in Massive Pulmonary Embolism

Volume Resuscitation

Fluid should be administered in massive PE with caution. Fluid resuscitation may increase RV afterload precipitating RV failure as well as augment septal ballooning into the left ventricle, further decreasing cardiac output and worsening systemic hypotension. It is therefore recommended that small boluses of fluid (250- to 500-mL aliquots) be used initially to evaluate affect.[190,191]

Vasoactive Drugs

There are no randomized controlled studies among different vasoactive agents in massive PE. Norepinephrine (NE), which has both α-adrenergic and β-adrenergic effects, is superior to phenylephrine in a canine model of PE in terms of improving both cardiac output and myocardial perfusion.[192] NE has been shown to increase cardiac contractility and RV perfusion pressure, thus increasing coronary blood flow. Therefore NE has become the most frequently used vasoactive agent for hemodynamic support of massive PE.[192,193] Dopamine, which possesses both β-adrenergic and, at sufficiently high doses, β-adrenergic agonist effects, appears to offer similar benefit. However, its use may be limited by the development of tachycardia.[194]

Inotropic Agents

Dobutamine, in combination with NE in the hypotensive patient, should be considered first-line therapy when treating cardiogenic shock secondary to a massive PE. In 10 patients with massive PE, dobutamine was able to increase cardiac index while reducing right atrial pressure, systemic vascular resistance, and PVR.[195] Although phosphodiesterase inhibitors have been used to support the circulation in cardiogenic shock secondary to massive PE, these agents should be used with caution given the lack of literature support. Their significant vasodilating capabilities could potentially worsen hypoxemia owing to their ameliorating effect on hypoxic vasoconstriction and potentially worsen systemic hypotension.[196]

Pulmonary Vasodilators

RVD contributes to many of the signs and symptoms noted in acute submassive PE. The goal of pulmonary vasodilator therapy is to provide afterload reduction to the RV and thereby ameliorate some or all of this dysfunction. Unfortunately, to date there have been no large randomized controlled studies of either IV or inhaled epoprostenol, or inhaled nitric oxide in acute PE. Although these agents have some theoretical advantages in their ability to unload the RV, they also have some potential disadvantages in altering $\dot{V}/\dot{Q}$ and worsening hypoxemia, as well as contributing to systemic hypotension; therefore as of this writing, they cannot be recommended as routine therapy.[197,198]

Systemic Thrombolysis in Massive Pulmonary Embolism

If there are no contraindications, thrombolytic therapy is the treatment of choice for massive PE resulting in severe hemodynamic and respiratory compromise. This recommendation is sanctioned by the current ACCP guidelines.[170] Several studies have demonstrated the superiority of thrombolytic therapy in improving RV function (24–48 hours) compared with heparin alone. The studies have not demonstrated an improvement in mortality rate with thrombolysis.[173,174,199–201] One reason is that the studies were not large enough for mortality rate to be an outcome measurement. A meta-analysis by Wan and colleagues demonstrated that patients with massive PE had a reduction in mortality rate and PE recurrence and adverse events compared with heparin alone (19.0% to 9.4%; OR 0.45, 95% CI 0.22–0.92).[202] If thrombolytic therapy is given within 48 hours of the pulmonary embolic event there may be greater clinical improvement. However, thrombolysis may continue to be beneficial even in patients who have symptoms up to 2 weeks after their initial PE symptoms.[203]

The thrombolytic agent usually given is tPA in a 2-hour infusion via peripheral venous line. UFH should not be given at the time with thrombolytic therapy. UFH should be restarted after the thrombolytic infusion is completed and when the aPTT is less than twice the normal value.

Massive PE can lead to cardiac arrest and the initial rhythm may include PEA and asystole. When cardiac arrest occurs, the mortality rate is in the range of 66% to 95%. Thrombolytic therapy given in boluses of 50 mg has been shown in case reports to be lifesaving.[204]

Inferior Vena Cava Filters in Massive Pulmonary Embolism

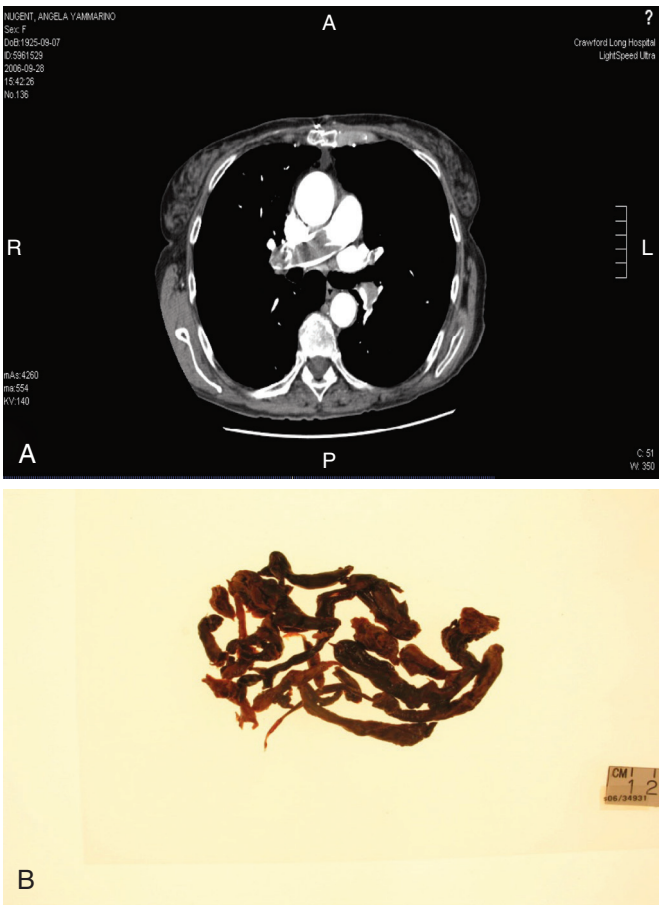
An observational study from an international registry that suggests that IVC filter placement in patients with massive PE (i.e., with hypotension) was associated with a reduction in a combined endpoint of mortality rate and recurrent PE. This study cohort was small; however, it appears to be reasonable that IVC filters should be placed in patients with poor cardiopulmonary reserve.[205]

Unstable PE patients who are treated with standard anticoagulation therapy may benefit further with prophylactic placement of IVC filters. In a recent study by Stein and associates,[206] the mortality rate in 38,000 unstable patients treated with standard anticoagulant therapy alone was 51% compared with 33% in 12,850 who had vena cava filters in addition to anticoagulants. This represents a 35% decrease in the case fatality rate when vena cava filters are combined with standard anticoagulant therapy.

Pulmonary Embolectomy in Massive Pulmonary Embolism

The indications for pulmonary embolectomy are patients with documented massive PE confirmed if possible by angiography (CTPA or pulmonary angiography) with persistent hemodynamic instability despite aggressive medical therapy, including consideration of the local or systemic thrombolysis. Patients with refractory shock in which massive PE is strongly suspected should be transferred to a center where emergent surgical management for PE is performed. These patients must be urgently transferred to the operating room, and on the operating table TEE should be performed to confirm the diagnosis. Despite these efforts, patients who present with cardiac arrest have a high surgical mortality rate.[206,207]

The mortality rate from pulmonary embolectomy ranges from 30% to 40%. There has been concern that medical therapy may delay definitive surgical therapy and may account for the high mortality rate. Among 1047 patients who underwent pulmonary embolectomy from 1961 to 1984 the average in-house mortality rate was 32%. Using the National Inpatient Sample from 1999 to 2008, recently Stein and colleagues showed that the case fatality rates for unstable patients (shock or ventilator-dependent) with PE undergoing pulmonary embolectomy was 40% and in stable patients 24%, with an overall case fatality rate of 28%. The case



• **Fig. 42.8** Large clot burden removed by pulmonary embolectomy.

fatality rates were lower in patients with the primary diagnosis of PE who had few comorbid conditions. It was observed in both groups that patients with IVC filters had a lower case fatality rate than those who did not have filters.[208,209] More recently the surgical mortality rates for pulmonary embolectomy have decreased at specialized centers (Fig. 42.8, pulmonary embolectomy). A multidisciplinary approach appears to be the key to diagnosis, treatment, and postoperative care, translating to reduced mortality and morbidity rates.[210,211]

Endovascular Therapy in Massive Pulmonary Embolism

In patients with massive PE who are not candidates for either pulmonary embolectomy or systemic thrombolysis, if there is institutional expertise for endovascular management, this should be considered. The goal is to convert a massive PE into a submassive PE with resultant improvement in the patient's hemodynamic and respiratory status. Initially, CDT provides mechanical debulking of the clot, and if indicated because of persistent elevation of PA pressures, infusion of low-dose (1 mg/h) tPA directly into the clot over a 12- to 24-hour period. CDT should be considered and the decision should be made quickly as part of a multidisciplinary discussion.[180–215] Complications of CDT are rare, but when they occur they can be serious. They include perforation of the PA or perforation of the atrium or ventricle with pericardial tamponade. These interventions should be performed only by clinicians who are experienced in catheter-based intervention and within institutions that have defined protocols and multidisciplinary teams to manage these critically ill patients.

The management of high-risk submassive PE is summarized in Fig. 42.9. For the normotensive patient with PE it is important to quickly risk stratify and identify the patient with RVD and large clot burden. If patients in this subset manifest signs of RV injury with persistent elevations in troponin and echocardiographic evidence of RV overloading with impending RV failure, then systemic thrombolytic therapy, local thrombolytic therapy, and surgical management are management options to be considered. In the patient with massive PE, as with submassive PE with RVD, there must be multidisciplinary coordination among the critical care physician, interventional cardiology and radiology, and cardiothoracic surgery to quickly determine the best treatment approach. Both respiratory and hemodynamic support will allow some time to consider the various management options.

Special Populations

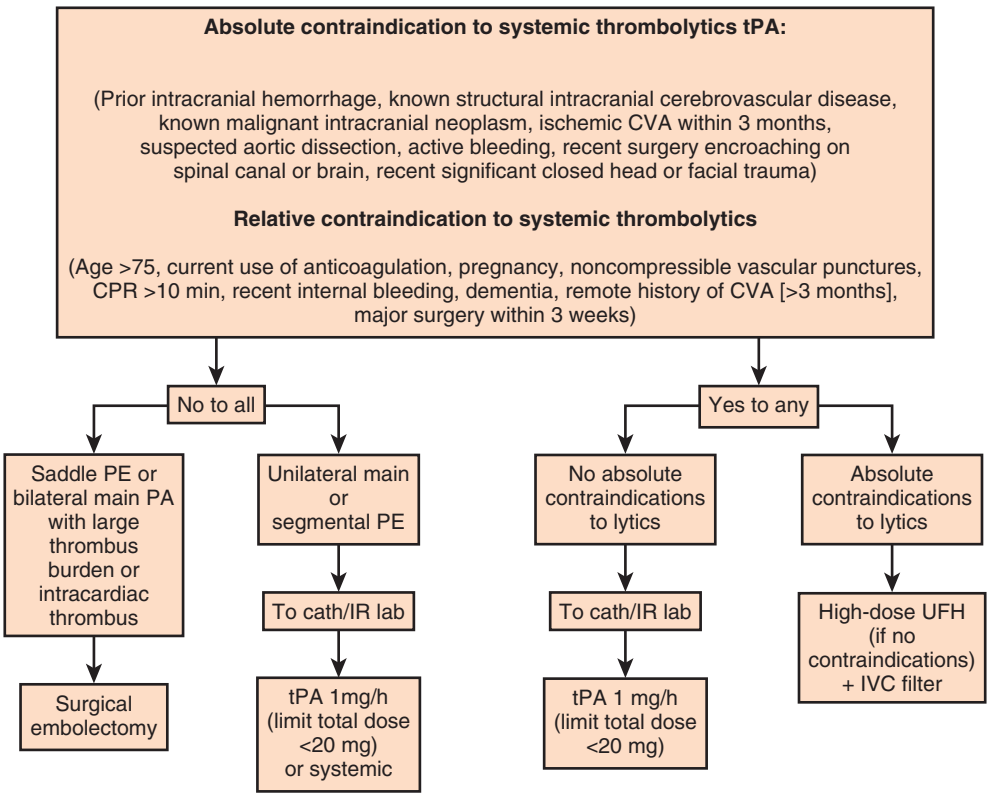
Pregnancy

The incidence of PE during pregnancy ranges between 0.3 and 1 per 1000 deliveries.[216] PE is the leading cause of pregnancy-related maternal death in developed countries. In the United States, maternal death from PE ranks third after hemorrhage and hypertensive disorders.[217,218] There is a fivefold increased risk of VTE in the pregnant woman because of venous stasis, a prothrombotic state as a result of increased levels of coagulation factors, reduced protein S, and fibrinolytic activity.[219] The two major PE risk factors in pregnancy are a personal history of VTE and heritable thrombophilias.[220] The risk of PE is higher in the postpartum period, particularly after a cesarean section. The clinical features of PE are no different in pregnancy compared with the nonpregnant state. There have been no prospective trials that have validated existing prediction models to exclude PE in pregnancy. It is been shown from a maternal death review that pregnant women who died from PE are older than 35 years, are obese (body mass index >30), and have chronic medical conditions.[221]

Diagnosis of Pulmonary Embolism in Pregnancy

Although D-dimer may be elevated in pregnancy, leading to a high rate of false-positive results, a normal D-dimer value has the same exclusion value for PE in pregnant women as in other patients with suspected PE. Because D-dimer is elevated in pregnancy, it has been suggested that D-dimer testing not be used in the evaluation of suspected VTE in pregnancy or the early postpartum period. However, in view of its negative predictive value, it is reasonable to measure the D-dimer even though the probability of a negative result is lower than in other patients with suspected PE.[219]

An elevated D-dimer assay should be followed by CUS of the lower extremities. If CUS demonstrates DVT, then anticoagulation can occur and thoracic imaging is not necessary. If CUS is negative and the diagnosis is still suspected, then thoracic imaging is warranted. It is important to note that the upper limit of radiation with regard to the danger of injury to the fetus is considered to be 50 mSv (50,000 mGy), and all radiologic tests (CT and $\dot{V}/\dot{Q}$) fall well below this limit.[220] In a pregnant or postpartum woman with suspected PE who has a normal chest radiograph, either a $\dot{V}/\dot{Q}$ scan or a perfusion scan alone will be sufficient. A normal lung scan essentially excludes the diagnosis of PE. Perfusion scanning compares favorably with CT as far as exposure of breast tissue to radiation is concerned.[221] If the chest radiograph is abnormal and the lung scan is nondiagnostic, then CTPA is recommended.



• **Fig. 42.9** "High-risk" submassive pulmonary embolus with right ventricular injury algorithm. *CPR,* Cardiopulmonary resuscitation; *CVA,* cerebrovascular accident; *IR,* interventional radiology; *IVC,* inferior vena cava; *PA,* pulmonary artery; *PE,* pulmonary embolism; *tPA,* tissue plasminogen activator.

Treatment of Pulmonary Embolism in Pregnancy

The medical treatment of PE in pregnancy is heparin—either UFH or LWMH, neither of which crosses the placenta nor is found in breast milk in any significant amount. As there are no specific data in the setting of pregnancy, treatment should consist of a weight-adjusted dose of LMWH. Adaptation according to anti-Xa monitoring may be considered in women at extremes of body weight or with renal disease. The heparin treatment should be given throughout the entire pregnancy. From limited data fondaparinux appears efficacious in pregnancy, but bleeding risk is not absent, and care is required when used as second-line therapy.[222]

The new oral anticoagulants are not to be used during pregnancy. Teratogenic effects, reduced fetal viability, hemorrhagic changes, and placental abnormalities have been found in both dabigatran and rivaroxaban. Rivaroxaban is secreted in breast milk.[222] VKAs cross the placenta and are associated with a well-defined embryopathy during the first trimester. Administration of VKAs in the third trimester can result in fetal and neonatal hemorrhage as well as in placental abruption. Warfarin may be associated with central nervous system anomalies in any trimester in pregnancy.[220]

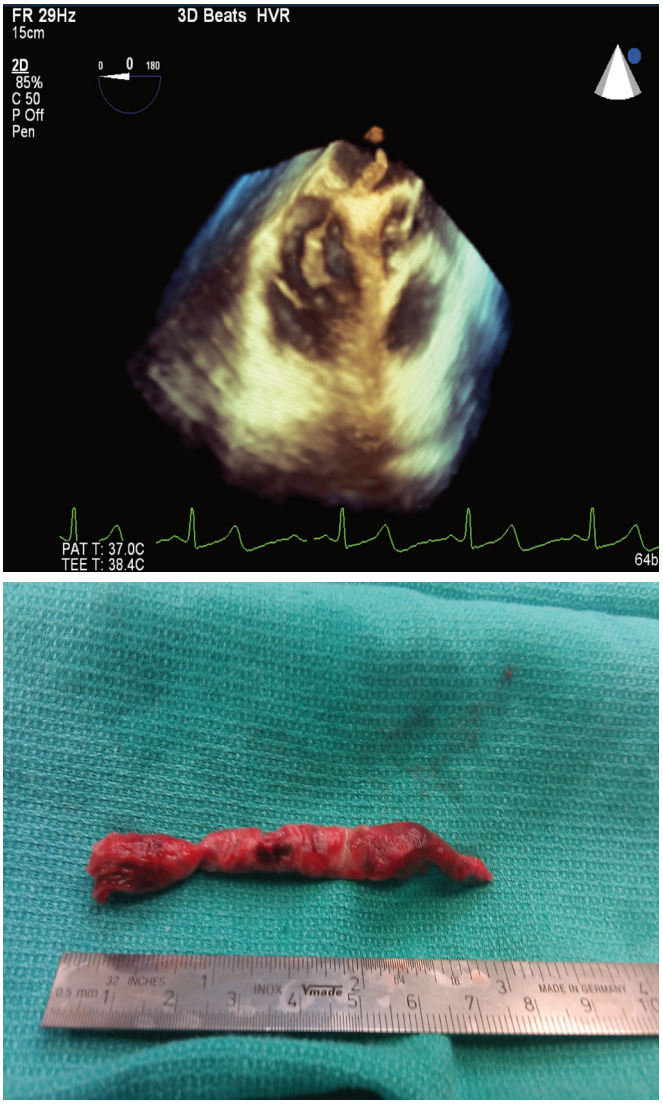
The management of labor and delivery requires particular attention. Epidural analgesia cannot be used unless LMWH is discontinued at least 12 hours before an epidural approach. Treatment can be resumed 12 to 24 hours after withdrawal of the epidural catheter. In any case, close collaboration among obstetrician, anesthetist, and critical care physician is recommended. After delivery, heparin treatment may be replaced by anticoagulation with VKA. Anticoagulant treatment should be administered for at least 3 months after delivery. VKAs can be given even to breastfeeding mothers.[220] Thrombolytic therapy should be used when there is a life-threatening pulmonary embolic event. At the time of delivery, thrombolytic treatment should not be used except in extremely severe cases and if surgical embolectomy is not immediately available. Indications for IVC filters in pregnant women are similar to those in other patients with PE.

In summary, in pregnant women with a clinical suspicion of PE an accurate diagnosis is paramount, as a prolonged course of heparin is required. All diagnostic modalities, including CT scanning, may be used without significant risk to the fetus. LMWHs are recommended in confirmed PE; VKAs are not recommended during the first and third trimesters but could be considered with caution in the second trimester of pregnancy. Anticoagulant treatment should be administered for at least 3 months after delivery.[220]

Right-Sided Heart Thrombi

Echocardiographically documented right-sided heart thrombi occur in approximately 4% of patients with PE.[25,150] These patients have more hemodynamic instability and have a higher mortality rate. In the ICOPER study in patients with acute PE and a free-floating right-sided heart thrombus, the mortality rate was 15% compared with 11% without such thrombi.[150]

In these patients, the treatment of choice is controversial. Both thrombolytic therapy and surgical embolectomy have been used with multiple reports of successful results. In the ICOPER study, thrombolytic treatment was the preferred option, but the 14-day mortality rate was above 20%.[150] In contrast, excellent results with thrombolytic therapy were reported in a series of 16 patients, in which 50%, 75%, and 100% of clots disappeared from the right



• **Fig. 42.10** Embolism in transit through the patent foramen ovale and surgical removal. (Courtesy Dr. Omar Lattouf, Emory University Cardiothoracic Surgery.)

side of the heart within first 2, 12, and 24 hours, respectively, after administration of thrombolytics. All patients survived 30 days.[223] It appears from the literature that treatment with heparin alone is not a treatment option.

For right-sided heart thrombi crossing the interatrial septum (patent foramen ovale) surgical embolectomy is warranted (Fig. 42.10). Whichever therapy is selected, it should be implemented without delay; in the presence of unequivocal echocardiographic visualization of a mobile right-sided heart thrombus, no further diagnostic tests are needed.[25,214,224,225]

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon but serious sequela of PE.

See the online supplement for additional discussion on CTEPH.

Prophylaxis

The VTE event is a common and recognized complication in critically ill patients. A VTE event can have dire consequences for the critically ill patient with preexisting cardiopulmonary compromise. All critically ill patients have significant risk factors for VTE and also are at higher risk for bleeding. Venous thromboembolic prophylaxis decreases the risk of VTE in ICU patients.[17–21] DVT prophylaxis is effective at reducing the risk of death. In several meta-analyses of surgical patients, prophylactic measures reduced the development of thromboembolic events by more than 50% and also the VTE-attributable mortality rate.[236]

Lack of adherence to evidence-based VTE prophylaxis guidelines has been problematic on a national and international scale.[13,236] With the implementation of electronic medical admission order sets universal VTE prophylaxis can be achieved. Extended post-hospitalization prophylaxis has been recommended in orthopedic surgical and medical patients. The advent of safe and effective prophylaxis strategies makes all critical care patients candidates for some form of preventive therapy on the basis of risk factors present in this population of patients. Several studies suggest that more than 85% of hospitalized patients are receiving some sort of DVT prophylaxis. VTE prophylactic measures are growing in ICUs with quality care initiatives targeting this intervention via bundled care pathways.[237,238]

The administration of prophylactic LMWH (or low-dose UFH) can be administered to the majority of critically ill patients. Critically ill patients at high risk for clinically important bleeding should receive mechanical thromboprophylaxis until the bleeding risk decreases. Renal insufficiency is not a contraindication to the use of LMWH or low-dose UFH.

Long-Term Prognosis

Nearly 25% of patients with PE do not survive the first year after the diagnosis. A majority of these patients succumb to underlying conditions, such as cancer or chronic heart disease, rather than PE. After surviving the first year the patient continues facing bleeding complications from anticoagulation therapy, the risk of recurrent VTE, the development of cancer, and the development of CTEPH.[239]

See the online supplement for additional discussion on long-term prognosis.

Pulmonary Embolism Response Team

Recently, a pulmonary embolism response team model was developed, based in part on the model of the rapid response team.[246] Given the continuum of disease represented by submassive PE and the treatment challenges posed by massive PEs, the goal of the PERT is to rapidly bring together the expertise of a multispecialty team in the field of thromboembolic disease to improve the quality of care and the survival in patients with PE. Not only does the team approach bring expert opinion to the bedside quickly, but it also allows hospital resources to be deployed more efficiently and can be foundational for both local and/or regional research. Although the concept is too new as yet to have efficacy data associated with it, its ability to facilitate care of the PE patient while applying multidisciplinary evidence-based treatments to patients with both submassive and massive PEs may someday make it the standard to which other models are compared.[247]

CTEPH is an uncommon but serious sequela of PE. Certain patients with PE develop an aberrant and incomplete resolution of the thrombotic event, resulting in endothelialized thrombi, which if left unchecked will result in the development of a distal, small vessel vasculopathy. This event results in progressive increases in RV afterload and pulmonary hypertension. When small distal vessel disease develops in patients with CTEPH, the patient no longer is a candidate for surgical management.[226] The reasons are unclear for this divergent pathway in thrombus resolution. Acquired and hereditary risk factors are suspected. For example, 20% of patients with CTEPH have antiphospholipid syndrome, and increased levels of factor VIII are found in CTEPH when compared with non-thrombotic pulmonary hypertension and control groups.[214,224,225] Characteristics of the initial acute embolic event may be associated with subsequent development of CTEPH. Persistent RVD at discharge and persistent elevation of pulmonary artery pressures may play a role.[226,227]

In the past it was estimated that the incidence of CTEPH was only 0.1% to 0.5%.[226] Recent prospective studies have shown that CTEPH is much more common, with an incidence ranging from 1% to 3.8% of patients who survived their acute pulmonary embolic event. It is estimated that in the United States 6000 to 22,000 new cases potentially may occur in each year.[226,228–230]

The $\dot{V}/\dot{Q}$ lung scan plays a central role in the evaluation of patients with pulmonary hypertension. The $\dot{V}/\dot{Q}$ scan in a patient with suspected CTEPH will show the "mottled" appearance of subsegmental and segmental perfusion defects. Larger defects can also be seen.[226] The lung scan is superior to CT angiography in screening patients for CTEPH. A single-center retrospective investigation comparing the lung scan with CT angiography and 227 patients with pulmonary hypertension demonstrated a sensitivity of 97.4% for $\dot{V}/\dot{Q}$ scanning but only 51% for CT angiography in detecting chronic thromboembolic disease.[231]

CT or MRA can be used to plan surgical intervention. Right-sided heart catheterization is required to determine the degree of hemodynamic impairment, and conventional pulmonary angiography can determine the proximal location of the thrombotic obstruction.[226]

Surgical removal of the obstructing material requires a true endarterectomy as opposed to a simple embolectomy. The current approach to pulmonary endarterectomy requires median sternotomy, cardiopulmonary bypass, and periods of hypothermic circulatory arrest to provide adequate visibility. The main pulmonary arteries are incised and the correct endarterectomy level within the wall is defined. Thereafter the plane is followed circumferentially down to the segmental and sometimes subsegmental branches of each lobar artery, a procedure that is performed with the help of special suction dissectors.[229,230]

The perioperative mortality rate is related to the severity of the disease, with a mortality rate of 4% in patients with a preoperative PVR less than 900 dynes/s per centimeter^{-5} and 20% in those with PVR above 1200 dynes/s per centimeter^{-5}. The functional results of a successful pulmonary thromboendarterectomy are excellent and generally are sustained over time, with a 3-year survival rate of about 80%.[231–233]

The major causes of postoperative fatality from pulmonary endarterectomy are RV failure related to persistent pulmonary hypertension and acute lung injury. Lifelong anticoagulation and placement of the IVC filter are recommended. In patients who are deemed inoperable because of distal chronic thromboembolic disease or in whom the surgical mortality risk of endarterectomy is high, medical therapy developed for idiopathic pulmonary arterial hypertension has been studied in patients with CTEPH. It is important to identify patients as early as possible, so they may have the opportunity for pulmonary endarterectomy because the hemodynamic and symptomatic benefits provided by medical therapy are modest.[226,234,235]

Long-term prognosis may depend on whether the pulmonary embolic event was provoked or unprovoked (occurring in the absence of known risk factors). The prognosis of unprovoked PE may be more unfavorable than that for patients who experience provoked PE. Studies have shown that compared with their counterparts with unprovoked PE, patients with provoked PE are at higher risk for recurrent PE, arterial cardiovascular events, the occurrence of cancer, and CTEPH.[240–244]

In a recent study Klok and colleagues investigated the long-term prognosis of acute PE in 308 patients with unprovoked PE, 558 patients with provoked PE, and 334 patients without PE for a median follow-up period of 3.3 years. The mortality rate for the acute embolic event was 5.2%. The adjusted HR for recurrent VTE was increased for patients with unprovoked PE versus provoked PE (HR 2.1, 95% CI 1.3–3.1) and unprovoked PE versus patients without PE (HR 10, 95% CI 4.9–28). Recurrent PE was fatal in 19% of the patients and these fatalities usually occurred after 3 weeks from the initial PE episode. The risk for cancer was higher for the patients after unprovoked PE than for the patients with provoked PE (adjusted HR 4.4, 95% CI 2.0–10) and without PE (adjusted HR 2.5, 95% CI 1.1–2). Patients with unprovoked PE experienced severe cardiovascular disease two to three times more often than the patients from the other two study cohorts (adjusted HR 2.6, 95% CI 1.5–3.8; and HR 2.4, 95% CI 1.2–3.7). There was no difference in the pooled risk for adverse outcome of patients with unprovoked and provoked PE, although the risk on all separate endpoints except for malignancy-related death was markedly higher for the patients with unprovoked PE. From this study, in nearly 4 years after the embolic event, half of the patients diagnosed with acute PE died or were diagnosed with cancer, recurrent VTE, CTEPH, or arterial cardiovascular disease. This study sets forth a clarion call for studies to develop and evaluate accurate prediction strategies for duration of treatment and to provide further insight on clinical surveillance and personal prognostication for the patients who have survived their initial embolic event.[245]

Key Points

- It is important to identify patient-related and setting (ICU)-related risk factors for the development of VTE. ICU risk factors associated with massive PE are malignancy, cardiopulmonary disorders, and immobilization.
- Nearly two-thirds of patients who die from pulmonary thromboembolism die within 1 hour of presentation, giving rise to the concept of the golden hour to accomplish both diagnosis and commence treatment. The principal pathophysiologic effects of pulmonary thromboembolism result from the impaction of clot in the pulmonary circulation with resulting vascular obstruction and humoral mediator release.
- The major clinical presentations of life-threatening PE seen in patients coming to the ICU range from signs and symptoms of RVD to frank shock.
- Risk stratification is useful in the assessment of submassive normotensive PE with RVD. RVD can be identified from clinical findings, ECG, cardiac biomarkers, and imaging modalities (echocardiogram and CTPA). The initial hemodynamic presentation of PE is the most powerful predictor of outcome. Central location of a thrombus is an independent risk factor for death.
- The cornerstone of pharmacologic management of VTE is heparin. Heparin therapy should be initiated, if there is no contraindication, as the diagnostic evaluation is being performed. UFH, LMWH, or fondaparinux followed by warfarin is currently the standard treatment for low-risk PE. New oral agents have been recently approved. Thrombolytic therapy, if there are no contraindications, should be used in patients with massive PE and considered in patients with submassive PE with evidence of severe RVD.
- The management of the normotensive submassive PE patient centers on reducing RV afterload and preventing further insult to the right ventricle. Systemic and endovascular delivery of thrombolytic agents can reduce RV strain. The placement of a retrievable IVC filter can prevent further embolic impact on the RV.
- Supportive therapy for massive PE utilizes judicious use of fluids to avoid further increases in RV strain. NE is the vasopressor of choice to maintain perfusion pressure. Dobutamine should be used to improve contractility. These temporizing measures will allow the critical care team to mobilize thrombolytic, endovascular, and surgical management strategies.
- All diagnostic modalities, including CT scanning, may be used without significant risk to the fetus in the pregnant woman. LMWHs are recommended in confirmed PE. Anticoagulant treatment should be administered for at least 3 months after delivery.
- Thrombolytic therapy or surgical intervention should be considered for right-sided heart thrombi. If a patent foramen ovale is present or right-sided heart thrombi cross the patent foramen ovale, surgery should be performed.
- CTEPH is more common than once thought and is best managed with pulmonary endarterectomy. It is important to identify these patients early.
- VTE prophylaxis strategies are necessary for nearly all critical care patients.
- Four years after PE the majority of patients will have either died or had recurrent PE, cancer diagnosis, arterial cardiovascular disease, or CTEPH. We must do more in follow-up of these post-PE patients.
- Pulmonary embolism response teams can bring a multidisciplinary team together and facilitate the deployment of hospital resources in an expedited fashion to best manage the continuum of submassive and massive PEs.

Acknowledgment

Ken Leeper was renowned and beloved for his incredible dedication to patient care, research, and his tireless devotion to teaching medical students, nurses, medical residents, and fellows with the goal of creating the next generation of bedside practitioners. He co-authored the pulmonary embolism chapter for the 4th edition of Critical Care Medicine. Ken died on April 7, 2016. He will be missed and always remembered as an inspirational man and physician and for his lasting contributions to the art and science of medicine.

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Review Questions

1. A 55-year-old man presents to the emergency department (ED) and is diagnosed with a pulmonary embolism (PE) with computed tomography (CT). Which of the following findings are expected changes that this patient may exhibit?

a. An increase in arterial partial pressure of oxygen ($Paco_2$) is a typical finding on arterial blood gas analysis owing to an increase in dead space.

b. Hypoxemia is caused only by a low cardiac output state.

c. Pao_2 and the alveolar-arterial (A-a) gradient are invariably abnormal.

d. The gradient between the end-tidal CO_2 ($etco_2$) and the $Paco_2$ is increased.

Answer: d. Acute PE has a variety of hemodynamic and gas exchange consequences. By occluding the pulmonary vasculature, PE increases ventilation relative to perfusion; it is therefore a dead-space phenomenon. $Paco_2$ is increased in critical illness as a result of either an increase in CO_2 production (Vco_2), a decrease in minute ventilation (VE), or an increase in dead-space ventilation (VD). Using this logic, one would expect PE to cause hypercapnia; typically, however, hypocapnia is present owing to an increase in minute ventilation associated with PE. If a PE is massive enough, especially in patients prone to CO_2 retention (e.g., chronic obstructive pulmonary disease), an increase in CO_2 can occur. This is not the norm, however. Although a problem of dead space, PE typically causes hypoxemia by shunt-type physiology, as local vasoconstriction promotes ventilation-perfusion mismatch. Atelectasis can occur distally to the clot, promoting ventilation-perfusion mismatch as well. Acute increases in right-sided pressures can open a patent foramen ovale, causing intracardiac shunt also. A low cardiac output state can contribute to hypoxemia if mixed venous oxygen saturation falls enough; however, this is not the only cause of hypoxemia, as discussed earlier. Though hypoxemia is common in PE, arterial partial pressure of oxygen (Pao_2) and A-a gradient have been reported to be normal in up to 30% of patients. End-tidal capnography is a useful adjunct in PE. Owing to a drop in cardiac output and an increase in dead space (which will decrease alveolar CO_2), the $etco_2$ waveform area will decrease, widening the gap between $etco_2$ and $Paco_2$.

2. Which one of the following is most correct concerning the diagnosis of PE?

a. D-Dimer has a high positive predictive value and can establish the diagnosis when levels are above 500 ng/mL.

b. Ventilation-perfusion scanning has a very high sensitivity (>90% for the presence of PE) but low specificity.

c. Chest radiographic findings with high sensitivity for PE include pleural-based infiltrates, focal oligemia, and hypovascularity.

d. Pulmonary angiography's high sensitivity as a diagnostic tool is detracted by its lower specificity.

Answer: c. Diagnosing PE has become progressively more sophisticated in recent years. The most important first step is suspicion, and studies have confirmed the usefulness of physicians' pretest clinical suspicion for PE when considering diagnostic testing. Initial evaluation includes chest radiography and blood testing. Pleural-based infiltrates, focal oligemia, and hypovascularity were found to be more common in those diagnosed as having PE but lacked high sensitivity or specificity for this disorder. Similarly, D-dimer testing, which can be positive in many clinical conditions such as recent surgery, trauma, malignancy, severe infection, pregnancy, and liver disease, has been shown to have a very high negative predictive value (94%) and makes PE unlikely if less than 500 ng/mL. Ventilation-perfusion scanning has been the predominant test to help rule in or out disease. Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) data revealed that ventilation-perfusion scans could be diagnostic in two cases: high-probability scans with high pretest probability and normal scans with low pretest probability. However, these two scenarios account for less than 30% of cases and in general, ventilation-perfusion scanning is not diagnostic in up to 80% of patients. Many cardiopulmonary disorders can cause ventilation-perfusion abnormalities, making intermediate- or low-probability scans nondiagnostic. Therefore spiral CT scans of the chest have recently been used more frequently. Specificity for spiral CT scans is better than sensitivity, with much of the difficulty in identifying subsegmental pulmonary emboli. Pulmonary angiogram remains the gold standard, with sensitivity and specificity reaching 95% to 100%.

3. Which of the following is true regarding the hemodynamics and management of the unstable patient with acute PE?

a. An acute increase in pulmonary artery pressures leads to right ventricular (RV) dysfunction and dilatation, causing septal shift into the left ventricular cavity, decreasing left ventricular output, causing shock.

b. Patients with acute PE should be aggressively volume resuscitated to maintain high right-sided pressures and transpulmonary blood flow.

c. Vasoactive medications (i.e., vasopressors) should not be given, as many can increase pulmonary vascular resistance, worsening hemodynamics.

d. Similar to patients with acute respiratory distress syndrome (ARDS), patients with acute RV failure from PE should have their airway pressure limited and allowance for permissive hypercapnia and permissive hypoxemia.

Answer: a. The hemodynamic consequences of acute PE are secondary to RV failure. The RV is accustomed to emptying into a low-pressure circuit—the pulmonary vasculature. Acute embolic obstruction, along with platelet activation and release of humoral mediators (e.g., thromboxane, histamine, serotonin), leads to an acute increase in pulmonary pressures, which the RV cannot overcome. Acute RV failure causes septal shift and progressive decrease in left ventricular cavity size and output (ventricular interdependence).

Preload should be manipulated with caution in acute PE. Volume overloading an acutely pressure overloaded RV will only make things worse. Patients with acute PE still may have recruitable preload, though, and the potential to respond to volume; if volume is given, it should be given judiciously. Management of acute RV failure can be challenging. If arterial hypotension is allowed to go unchecked, coronary perfusion to the RV will fall, worsening RV failure, worsening the entire hemodynamic picture. Knowing this, vasopressors are commonly used in RV failure to maintain arterial pressure and coronary perfusion to the right side. Many vasopressors can increase PVR, but the risk/benefit ratio obviously points to maintaining pressure. Other hemodynamic management decisions that are fairly common include RV afterload reduction with inhaled pulmonary vasodilators and inotropic support with agents such as dobutamine. Finally, an acute failing RV will not tolerate acidosis or hypoxia,

as both will exacerbate acute pulmonary vasoconstriction. Ideally, hypercapnia and hypoxemia could be avoided with as low airway pressures as possible, but priority (at least acutely) should be given to maintaining gas exchange to avoid worsening of RV failure.

4. A 49-year-old woman presents to the ED with chest pain and electrocardiogram (ECG) changes to include a new right bundle branch block and T-wave inversions across the anterior precordium. CT demonstrates acute bilateral proximal PE. Her blood pressure is 120/80 mm Hg and she clinically looks well. Which of the following is true with respect to choices regarding her treatment options?

a. There is a limited role for echocardiography, as the decision to administer thrombolytics is based solely on arterial blood pressure.

b. There is general consensus that normotensive PE patients with RV dysfunction should be administered thrombolytic therapy.

c. An elevation in cardiac biomarkers is associated with concomitant acute coronary syndrome and should be investigated with cardiac catheterization.

d. The decision to administer thrombolyitic therapy should take into consideration not only hemodynamic/blood pressure, but also risk stratification of normotensive patients.

Answer: d. It is generally recommended that patients with acute PE with evidence of hypotension, and no contraindication to thrombolytic therapy, should be given thrombolytics. All other patients should immediately be risk stratified for potential complications. Most importantly, this includes an echocardiogram to assess for RV dysfunction. Normotensive patients with PE without RV dysfunction will overwhelmingly do well and should not be offered thrombolytics. In normotensive patients with RV dysfunction, the decision to administer thrombolytics should be assessed on a case-by-case basis based on risk stratification. This includes how the patient looks clinically, oxygenation and work of breathing, cardiac biomarkers, and ECG and CT scan findings.

43

Pulmonary Hypertension*

BERNARD KIM, KUMAR SATYA, AND ROBERT BERKOWITZ

CHAPTER OUTLINE

Pathophysiology of PH and RV Failure
- Hemodynamic Classification of PH
- Pathology and Cellular Molecular Physiology of PH
- RV Failure

Management of PH and RV Failure in the ICU
- General Management Principles
- Monitoring
- Maintaining SVR and RCA Perfusion
- Afterload Reduction
- Optimizing Preload
- Afterload Reduction
- Pulmonary Vasodilators

Augmenting RV Cardiac Output
- Inotropes
- Rate and Rhythm Control
- Ventilatory Support
- Mechanical Circulatory Support
- Atrial Septostomy
- Prognosis

Pulmonary hypertension (PH) in critically ill patients admitted to the intensive care unit (ICU) may present with rapid deterioration of right ventricular (RV) function, leading to hemodynamic collapse and death. An understanding of the pathogenesis of RV failure secondary to PH is critical for RV rescue and successful treatment of these patients.

Although PH is defined regardless of mechanism as the presence of a resting mean pulmonary artery pressure (mPAP) greater than 25 mm Hg and a pulmonary vascular resistance (PVR) greater than 240 dynes*second/cm[5] (or >3 Woods units) as determined by right heart catheterization, PH is a pulmonary vascular disorder that encompasses a broad spectrum of pathologies classified on the basis of underlying etiology and pathophysiologic factors (Box 43.1).[1]

When decompensated PH is encountered in the ICU, it is most commonly due to elevated pulmonary venous pressure in the setting of left-sided heart disease (World Health Organization [WHO] group 2) or preexisting vascular disease which could span multiple groups.[2] It is also recognized after cardiothoracic surgery, in part related to endothelial dysfunction seen with cardiopulmonary bypass.[3,4] PH is also associated with sepsis,[5] acute respiratory distress syndrome (ARDS) with associated acute RV failure in 10% to 25% of cases,[6,7] and after massive pulmonary embolism (PE) in up to 60% of patients.[8] PH may also develop as a result of reversible factors that occur in critical illness, leading to an increase in PVR, which often precipitates RV failure. Functional residual capacity is one of these important factors.[9] A decrease in lung volume (atelectasis, endobronchial intubations, effusions, insufficient positive end-expiratory pressure [PEEP], pneumothorax, and pneumonia) will increase PVR, as well as excessive lung volumes (excessive PEEP or tidal volume, air trapping; Fig. 43.1).[10] Other reversible causes of PH include hypoxia, hypercarbia, acidosis (Fig. 43.2),[11] hypothermia, and shivering. Use of alpha-antagonists can increase both SVR and PVR.[10]

Several relatively new developments have led to a greater focus on RV function in critically ill patients. The rapid growth in our understanding of pulmonary vascular biology and the development of several new classes of pulmonary vasodilator medications has led to widespread treatment options for patients with pulmonary arterial hypertension and has enhanced our clinical expertise in managing RV failure, especially toward the end of their disease. Technical advances in the development and use of temporary RV mechanical support for advanced patients with either reversible disease or as a bridge to transplant has provided further insight into the management of otherwise intractable late-stage RV failure.[12]

Pathophysiology of PH and RV Failure

Hemodynamic Classification of PH

The following equation relates the mean pulmonary artery (PA) pressure to the pulmonary venous (PV) pressure, PA blood flow (PBF), and PVR:

$$\text{PBF}\,(\text{L}/\text{min}/\text{m}^2) = \frac{(\text{mPAP} - \text{PV})\ \text{mm Hg}}{\text{PVR units}/\text{m}^2}.$$

The difference between the mPAP and the PV pressure (also referred to as the left atrial pressure [LAP]) is the transpulmonary gradient (TPG). Under normal circumstances, the pulmonary circulation is a low-pressure, low-impedance circuit; despite a fourfold rise in PBF, PAPs increase minimally and PVR falls. Normal hemodynamics are shown in Table 43.1. When PAPs are elevated, the TPG helps determine the site of the elevated PAP (Table 43.2), which corresponds to the location of the underlying pulmonary vasculopathy.

*The authors would like to thank Luke Chong, MD and Anthony Lucev, MD for their assistance with this chapter.

• BOX 43.1 Updated Classification of Pulmonary Hypertension

Group 1. Pulmonary arterial hypertension
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
  - 1.2.1 *BMPR2*
  - 1.2.2 *ALK1, ENG, SMAD9, CAV1, KCNK3*
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases
  - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″ Persistent pulmonary hypertension of the newborn

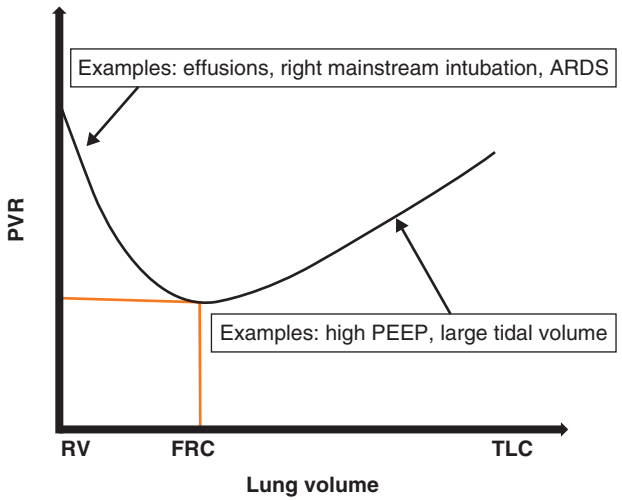
Group 2. Pulmonary hypertension due to left heart disease
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group 3. Pulmonary hypertension due to lung disease and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung disease

Group 4. Chronic thromboembolic PH

Group 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure segmental PH

Groups shown are from the 5th World Symposium on Pulmonary Hypertension, Nice, France, in 2013. BMPR, *Bone morphogenic protein receptor type II;* CAV1, *caveolin-1;* ENG, *endoglin;* HIV, *human acquired immunodeficiency virus;* PAH, *pulmonary arterial hypertension;* PH, *pulmonary hypertension. From Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension.* J Am Coll Cardiol. *2013;62:D34–D41.*



• Fig. 43.1 The relationship between pulmonary vascular resistance *(PVR)* and lung volume. PVR is optimal at functional residual capacity *(FRC)*. *ARDS,* Acute respiratory distress syndrome; *PEEP,* positive end-expiratory pressure; *PVR,* peripheral vascular resistance; *RV,* right ventricle; *TLC*, total lung capacity. (From Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: physiology and perioperative management. *J Cardiothorac Vasc Anesth.* 2011;25:687–704.)

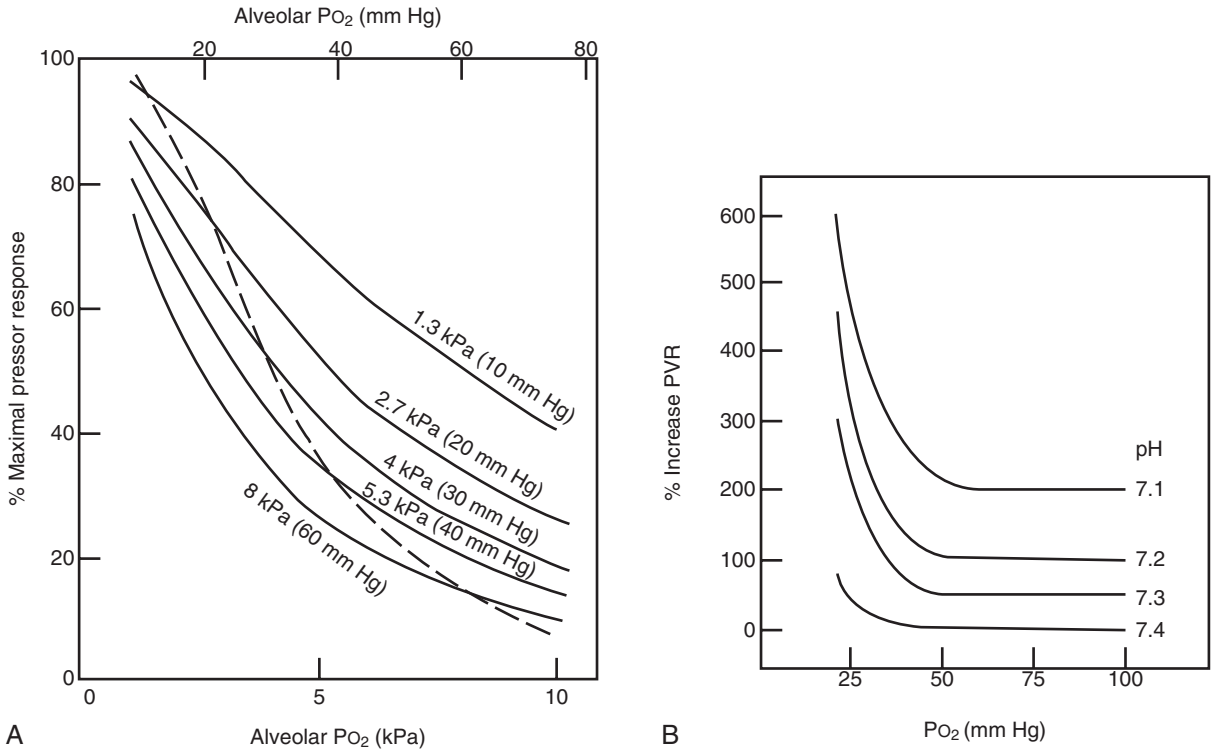
When PAP is normal, the TPG is normally low. In PH, the TPG can be elevated or normal. If the TPG is elevated, there is a precapillary contribution to the PH. If the TPG is normal, then high PAP is due to either high PV pressure or high PBF, and a postcapillary contribution to the PH occurs. With increases in PV pressure and TPG, both postcapillary and precapillary changes are present. In this latter case, combined precapillary and postcapillary PH is present, which may be either fixed or reversible depending on pulmonary vasodilator test results.[13]

In the hemodynamic classification of PH (see Table 43.2) the PV is the LAP and is approximated in clinical practice by the pulmonary capillary wedge pressure (PCWP).

Pathology and Cellular Molecular Physiology of PH

An anatomic overview of precapillary and postcapillary PH is shown in (Fig. 43.3). It is important to recognize that the conditions that raise the postcapillary pressure, such as left-sided heart failure (HF; group 2 PH) differ significantly from conditions that increase the precapillary pressure and primarily affect the pulmonary arteries and arterioles, such as idiopathic pulmonary arterial hypertension (group 1 PH). The former is associated with a relatively small TPG with histopathologic changes in the arterial vessels that consist of mild medial hypertrophy and reversible intimal changes. In the latter, there is an increased TPG or arteriovenous pressure gradient, and histopathologic changes on the pulmonary vasculature are more marked, including significant intimal hypertrophy with fibrosis, marked smooth muscle hypertrophy, vasoconstriction, adventitial proliferation, and thrombosis (Fig. 43.4).[14] These changes cause vascular flow obstruction and eventually lead to abnormal angiogenesis and formation of plexiform arteriopathy. Endothelial dysfunction also develops with imbalances between vasodilation and vasoconstriction and between apoptosis and proliferation, mechanisms that are thought to play the most important role in the development of chronic progressive PH.[15] In patients with combined precapillary and postcapillary PH, marked histopathologic changes may also be present.[13]

In many types of PH, production of endogenous vasodilators (nitric oxide [NO] and prostaglandins) is impaired, and production of vasoconstrictors (endothelin-1, thromboxane A) is increased. The common treatment strategy for PH is to achieve the balance in key molecular pathways by increasing available nitrous oxide (NO) and prostacyclin, and reducing the effects of endothelin-1 (Fig. 43.5).[15] Hypoxic pulmonary vasoconstriction, as occurs in respiratory disorders (World Health Organization group 3), is an important determinant of arterial PH. In ARDS both hypoxemia and the accumulation of intravascular fibrin and cellular debris contribute to subsequent vascular obliteration of PH. RV dysfunction as a complication of ARDS is more gradual than in patients with massive PE and usually



• **Fig. 43.2** Effect of oxygen tension and acidemia on pulmonary vasoconstriction. A, Pulmonary vasoconstriction increases as alveolar oxygen tension (Pa_{O_2}) falls while keeping mixed venous oxygenation constant (mixed venous partial pressure of oxygen *[P_{O_2}]* indicated for each *solid line* from 60 to 10 mm Hg). The combined effect of allowing Pa_{O_2} and mixed venous P_{O_2} to fall is shown by the *dashed line,* where Pa_{O_2} and mixed venous oxygen saturation are the same.[34] Maximal pulmonary vasoconstrictor response was defined as the difference between baseline pulmonary artery pressure when ventilating with a fraction of inspired oxygen (F_{IO_2}) of 0.21 and perfusate F_{IO_2} of 0.06, and the pulmonary artery pressure when both the inspired and the perfusate F_{IO_2} was 0. The pressure response at all other combinations of inspired and perfusate F_{IO_2} was expressed as a percent of the maximum. *B,* Pulmonary vasoconstriction in newborn calves as a function of inspired partial pressure of oxygen under conditions of different levels of arterial blood pH. Hypoxic pulmonary vasoconstriction is increased and occurs as a higher level of inspired oxygen as arterial pH is decreased. *PVR*, Pulmonary vascular resistance. (From Braunwald E. Pathophysiology of heart failure. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine.* Philadelphia: Saunders; 1980, pp 453–471.)

TABLE 43.1 Normal Hemodynamic Values

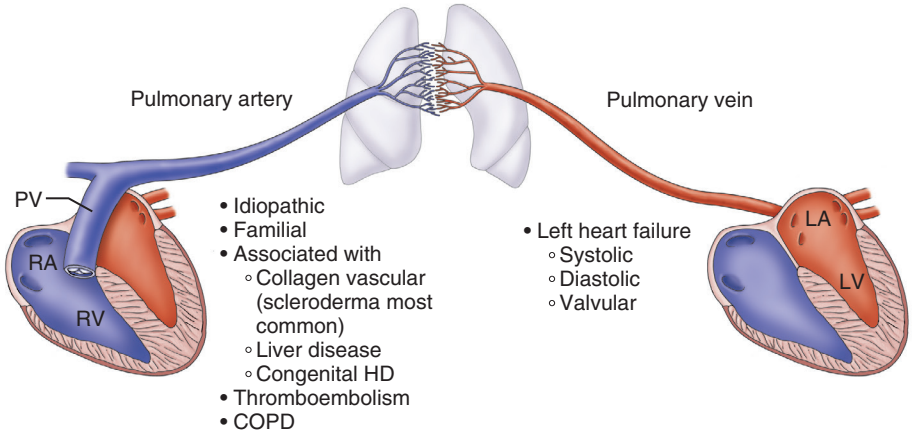
Left atrial pressure	8 mm Hg
Systolic pulmonary artery pressure	25 mm Hg
Diastolic pulmonary artery pressure	10 mm Hg
Mean pulmonary artery pressure	15 mm Hg
Transpulmonary gradient	7 mm Hg
Pulmonary vascular resistance	0.9–1.4 Woods units or 90–120 dynes/s/cm^5

From Hrymak C, Strumpher J, Jacobsohn E. Acute right ventricle failure in the intensive care unit: assessment and management. *Can J Cardiol.* 2017;33:61–71.

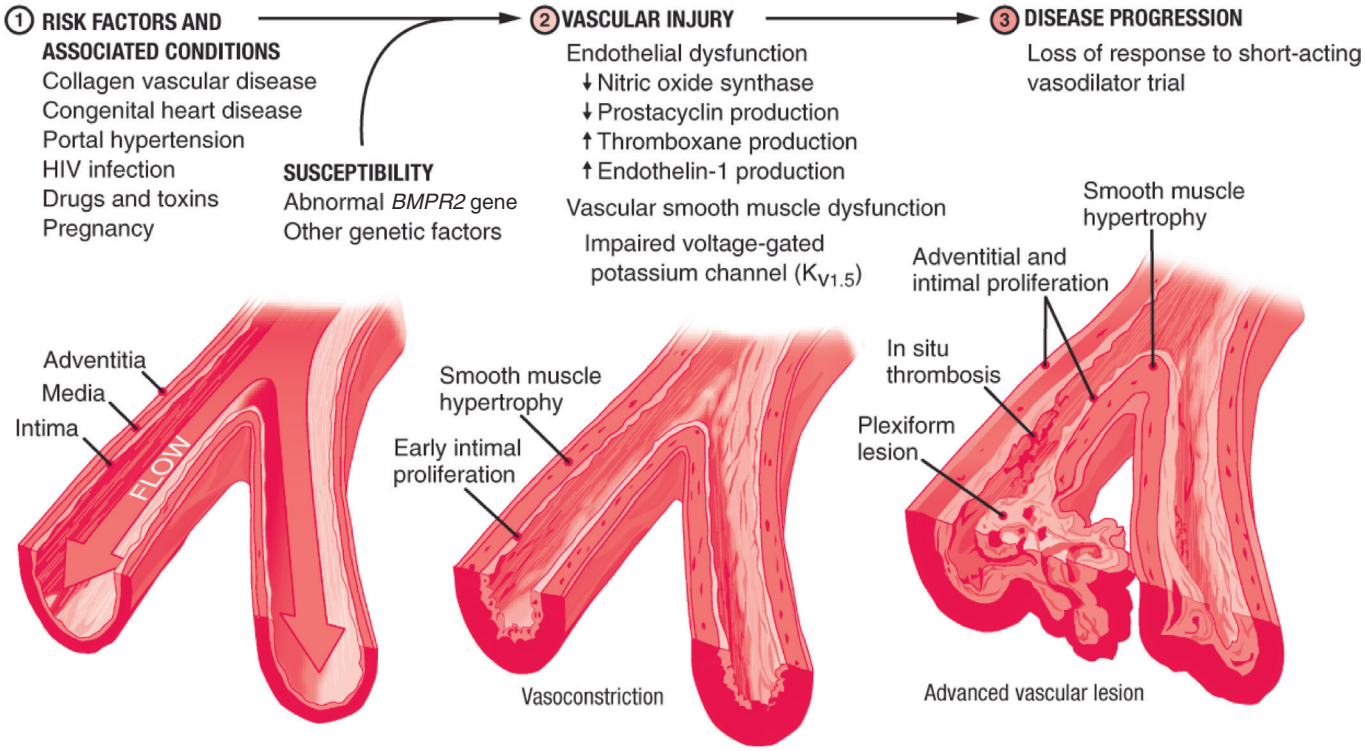
TABLE 43.2 Hemodynamic Classification of Pulmonary Hypertension and the Importance of Transpulmonary Gradient

Pulmonary Hypertension	Expected Measurement
Precapillary PH (↑TPG: >12 mm Hg, normal LAP)	↑mPAP ≥25 mm Hg, PCWP <15 mm Hg, PVR >3 Woods units (240 dynes/s per cm^5), normal or ↓CO
Postcapillary PH (normal TPG: ≤12 mm Hg, ↑ LAP)	mPAP ≥25 mm Hg, PAWP ≥15 mm Hg, PVR ≤3 Woods units (240 dynes/s per cm^5), normal or ↓CO
Mixed precapillary and postcapillary PH (↑TPG: ≥12 mm Hg, and ↑LAP)	mPAP ≥25 mm Hg, PAWP ≥15 mm Hg, PVR ≥3 Woods units (240 dynes/s per cm^5), normal or ↓CO

CO, Cardiac output; *LAP,* left atrial pressure; *mPAP,* mean pulmonary artery pressure; *PAWP,* pulmonary arterial wedge pressure; *PCWP,* pulmonary capillary wedge pressure; *PH,* pulmonary hypertension; *PVR,* pulmonary vascular resistance; *TPG,* transpulmonary gradient.
From Hrymak C, Strumpher J, Jacobsohn E. Acute right ventricle failure in the intensive care unit: assessment and management. *Can J Cardiol.* 2017;33:61–71.



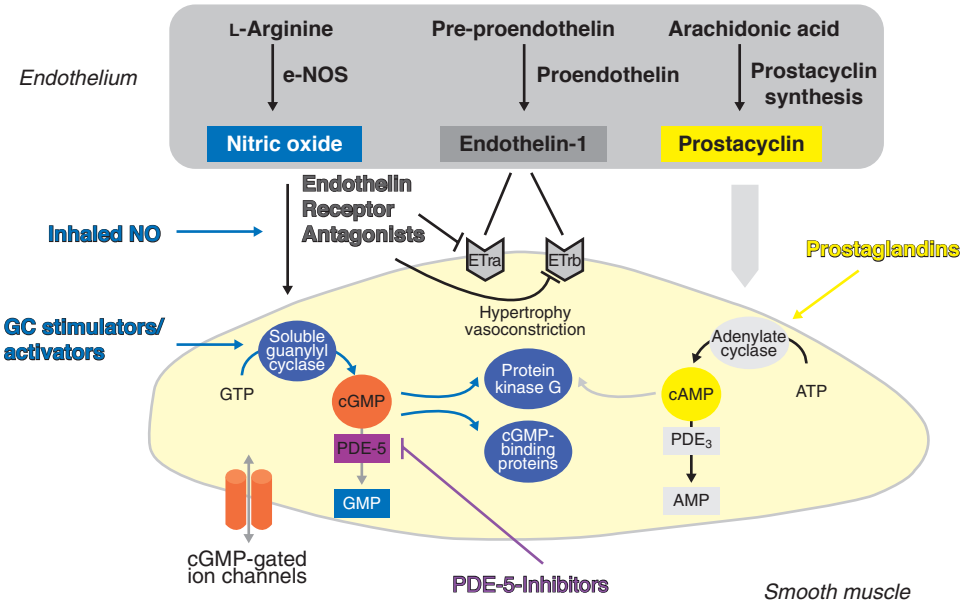
• **Fig. 43.3** An anatomic overview of precapillary or pulmonary arterial hypertension *(left)* and postcapillary or pulmonary venous hypertension *(right)*. *COPD,* Chronic obstructive pulmonary disease; *HD,* heart disease; *LA*, left atrium; *LV,* left ventricle; *PV,* pulmonary valve; *RA,* right atrium; *RV,* right ventricle. (From Zakir RM, Al-Dehneh A, Maher J, et al. Right ventricular failure in patients with preserved ejection fraction and diastolic dysfunction: an underrecognized clinical entity. *Congest Heart Fail.* 2007;13:164–169.)



• **Fig. 43.4** Pathogenesis of pulmonary arterial hypertension. In susceptible patients, pulmonary arterial hypertension occurs as the result of an insult to the pulmonary vascular bed. This insult results in an injury that progresses to produce the characteristic pathologic features. *BMPR2* is the bone morphogenetic protein receptor II gene, which is believed to responsible from the inherited form of the disease. *HIV,* Human immunodeficiency virus. (From Gaine S. Pulmonary hypertension. *JAMA.* 2000;284:3160–3168.)

occurs at least 48 hours after the beginning of respiratory support.[7] The mortality rate and incidence of RV failure have been shown to be related to the level of plateau pressure during mechanical ventilation.[16] The implementation of low tidal volume ventilation in patients with ARDS has significantly lowered not only mortality rates but also the incidence of acute RV failure in this patient population.[17] Although sepsis is a major risk factor for developing ARDS, sepsis itself can sometimes lead to severe acute arterial PH.[16]

Endotoxins and vasoconstrictor mediators related to pulmonary vasoconstriction also play significant roles in the development of PH during sepsis. Endotoxins may not only cause systemic hypotension but also pulmonary biphasic hypertension, with a decrease in compliance and increase in resistance of the respiratory system.[5] Endotoxemia is characterized by constriction of the proximal pulmonary arteries during the early phase followed by decreased compliance of the distal pulmonary vasculature.[18]



• **Fig. 43.5** Endothelial and vascular smooth muscle cell pathways involved in the regulation of pulmonary arterial tone and pharmacologic approaches. Vasorelaxation is mediated by increases in cyclic guanosine monophosphate *(cGMP),* antagonism of the endothelin A and B receptors (*ETra* and *ETrb*), or stimulation of adenylate cyclase by prostaglandins, primarily prostacyclin. Intracellular levels of cGMP can be targeted at different levels by exogenous nitric oxide (inhaled nitric oxide), activators/stimulators of soluble guanylate cyclase, or by inhibiting the catabolism of cGMP by phosphodiesterase 5 inhibitors. *AMP,* Adenosine monophosphate; *cAMP,* cyclic adenosine monophosphate; *e-NOS,* endothelial nitric oxide synthase; *GC,* guanylyl cyclase; *GMP,* guanosine monophosphate; *GTP,* guanosine triphosphate; *NO,* nitric oxide; *PDE-5,* phosphodiesterase-5. (From Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation.* 2012;126:975–990.)

These endotoxin-dependent hemodynamic and respiratory effects are also mediated by an excessive release of inflammatory mediators and an imbalance in the production of NO, prostacyclin, and endothelin-1 as previously discussed.[5,19] In experimental systems, endotoxin infusion can dramatically affect RV function in the very early phase of septic shock; right ventricular-vascular coupling is preserved by an increase in RV contractility. Later, however, myocardial oxygen consumption and the energy cost of RV contractility are increased, which together with progressive endotoxin-induced PH leads to RV dysfunction and failure.[20]

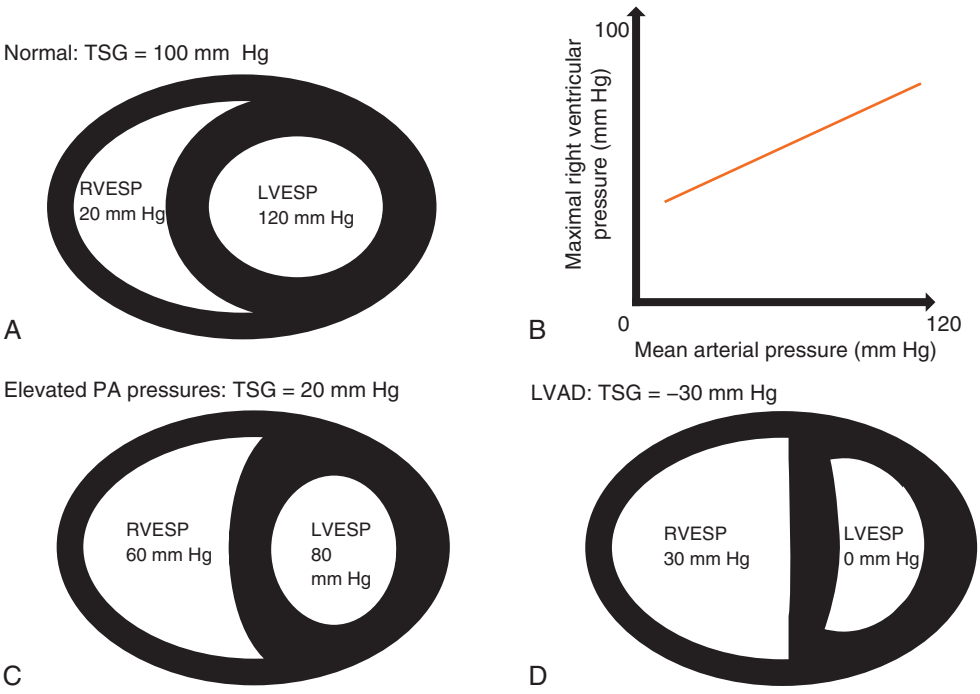
RV Failure

The pump responsible for perfusing the pulmonary circulation is considerably different from its counterpart in the systemic circulation. Unlike the muscular and ellipsoidal left ventricle (LV), which can be considered a four-walled chamber, the RV consists essentially of a thin free wall wrapped around the more muscularized medial wall of the LV.[9] The end diastolic dimension of the RV free wall is 2 to 3 mm in thickness compared with 8 to 11 mm in the LV free wall. Although the smaller mass of the RV produces less contractile force, the RV has a greater end-diastolic volume and surface area per unit of volume of fluid with flattening of the RV free wall during systole. There is a large increase in volume without change in free wall area, allowing the RV stroke volume to match the LV stroke volume with less energy expenditure.[12] The RV bioenergetic requirement is 20% of that of the LV. It is important to mention in this context that forces transmitted from one ventricle to the other through the myocardium and pericardium are termed *ventricular interdependence*. Because of the pericardium, the higher LV pressure is transmitted to the RV through the interventricular septum. This pressure difference, or transseptal gradient (TSG), is present in systole and diastole, and accounts for the normal left-to-right bulge of the septum and creates a scaffold against which the RV free wall contracts (Fig. 43.6A). In a normal heart, 4% to 10% of the LV systolic function depends on the RV, and 20% to 40% of the RV systolic function depends on the LV.[9] Importantly, RV function is dependent on high LV cavity pressure (Fig. 43.6B).[9,12] Coronary perfusion to the RV occurs during both systole and diastole compared with primarily diastolic flow in the LV, making the RV dependent on systolic blood pressure. Therefore right carotid artery (RCA) filling and RV perfusion also depend on a high LV cavity pressure.

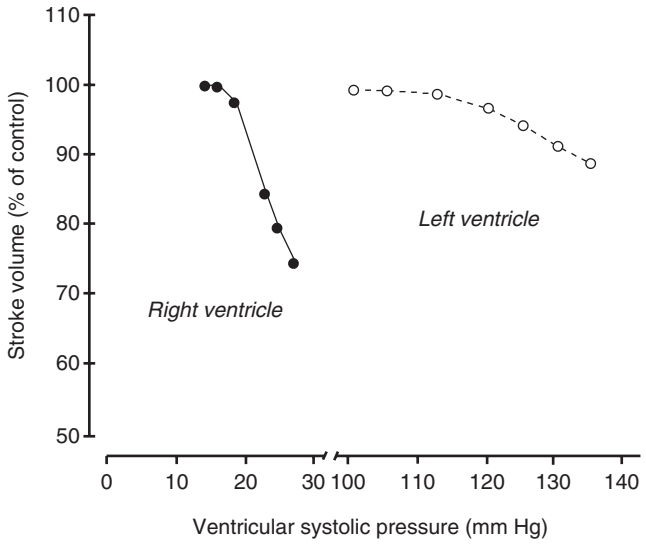
Under normal conditions the RV operates against a low-impedance, high-capacitance, and low-pressure system. Accordingly, and as already described, the RV can accommodate increases in volume overload, but it is exquisitely sensitive to changes in afterload as occurs with an increase in PVR (Fig. 43.7). When there is a chronic increase in PVR (e.g., lung disease, thromboembolic disease, idiopathic pulmonary arterial hypertension), RV hypertrophy occurs. The increased thickness reduces wall stress through Laplace's law[19]:

$$\text{Wall stress} = \text{Pressure} \times \text{Internal radius}/\text{Wall thickness}$$

In acute RV pressure overload, such as that seen in the setting of a massive PE, RV systolic pressure increases to a point where there is no further increase (40 mm Hg) and function begins to decline with decreased cardiac output (CO) and decreased blood pressure (Fig. 43.8). In RV pressure overload, the TSG is decreased (see Fig. 43.6C) and therefore, unlike in the case of volume overload, the septum does not return to its original shape during systole.



• **Fig. 43.6** Relationship between transseptal gradient *(TSG)* and right ventricle (RV) function. A, Normal condition; TSG is 100 mm Hg (normal range 80 mm Hg-120 mm Hg). The shape and position of interventricular septum is maintained. B, Normal physiology; RV pressure development is dependent on left ventricle (LV) pressure. C, Patient with elevated pulmonary artery (*PA*) pressure; TSG is 20 mm Hg. The septum is flattened toward the LV and the RV is dilated. D, Patient with a left ventricular assist device *(LVAD)*; TSG is –30 mm Hg. There is potential for the septum to bulge into the LV or to have a "suction event." *LVESP*, Left ventricular end-systolic pressure; *RVESP*, right ventricular end-systolic pressure. (From Hrymak C, Strumpher J, Jacobsohn E. Acute right ventricle failure in the intensive care unit: assessment and management. *Can J Cardiol.* 2017;33:61–71).



• **Fig. 43.7** Enhanced afterload sensitivity of the right ventricle compared with the left ventricle. Right ventricular stroke volume is impaired to a much greater extent comparison with the left ventricle with comparable acute increases in arterial pressure. (From Lumb AB. The pulmonary circulation. In: *Nunn's applied respiratory physiology.* Woburn: Butterworth-Heinemann; 2000, p 152.)

The RV dilates and the normal helical orientation of the myofibrils is reduced. Mechanical cardiac function is deleteriously affected and RV cardiogenic shock may eventually supervene (Fig. 43.8).[21,22] In this case, acute management then depends on reestablishing the TSG by increasing LV pressure. RV dilatation and failure occur in most conditions that cause an acute decrease in the TSG. In patients with a left ventricular assist device (LVAD), for example, the TSG may become negative as a result of increased LVAD inflow, as with too high a pump speed, leading to further RV dilatation. ("suction events"; see Fig. 43.6D). This situation may be aggravated when hypovolemia is present.

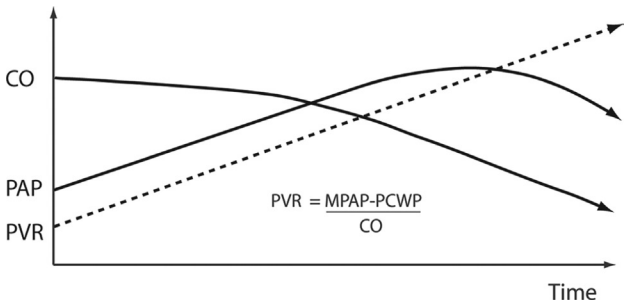
A downstream adverse effect of right-sided HF is the development of systemic venous hypertension that leads to concomitant visceral organ congestion and dysfunction. Regardless of the underlying cause of PH, the final common pathway for hemodynamic deterioration and death is RV failure.

Management of PH and RV Failure in the ICU

General Management Principles

The management of patients with PH associated with RV dysfunction in the ICU is challenging because of the following factors:

1. Multiple etiologies result in similar-appearing clinical scenarios but require subtle differences in approaches to treatment.



• **Fig. 43.8** Right ventricular shock. Relationship between cardiac output *(CO),* pulmonary artery pressure *(PAP),* and pulmonary vascular resistance *(PVR)*. As pulmonary pressures increase, CO will decrease. *MPAP,* mean and pulmonary artery pressure; *PCWP,* pulmonary capillary wedge pressure. (From Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation.* 2008;117:171–131.)

• BOX 43.2 Management Principles of Pulmonary Hypertension With Right Ventricular Failure

1. Maintain SVR and RCA perfusion pressure
2. Optimize preload
   a. Avoid underfilling of RV
   b. Avoid overfilling of RV
   c. Ventilator management to avoid decreased preload
3. Decrease RV afterload and PVR
   a. Pulmonary vasodilators
   b. Reverse metabolic factors
   c. Ventilator settings
4. Augment RV cardiac output
   a. Increase RV contractility
   b. Rate control
   c. Rhythm control, atrioventricular synchronization

PVR, *Peripheral vascular resistance;* RCA, *right carotid artery;* RV, *right ventricle/right ventricular;* SVR, *systemic vascular resistance.*

2. Current guidelines for treatment are based mostly on expert consensus owing to the current lack of evidence-based medicine (i.e., data extrapolated from chronic treatment of PH, animal studies, post–cardiac surgical experience).
3. Treatment requires management of hemodynamics based on knowledge of pathophysiologic principles using a combination of medical and mechanical modalities.
4. The mortality level is high.[2,23]

Therefore patients should be managed at or in conjunction with a center that specializes in PH equipped with all the available specialized medical and mechanical treatment modalities and clinical staff specifically trained to assist in the treatment of these patients.[24–26]

Treatment is hemodynamically directed and has four major goals.

1. Maintenance of SVR and thereby the pressure gradient between aortic and RV pressure in to ensure RCA perfusion and reversal of RV ischemia. This also improves adverse LV conformational changes imposed by a dilated RV via interventricular dependence.[25] In cases of preexisting PH where RV pressures approach or exceed systemic pressures, using drugs that increase contractility before initiating therapies to maintain SVR can lead to an increase in wall tension and increase RV end-diastolic pressure (RVEDP), thus decreasing RV coronary perfusion pressure.[12] Additionally, maintaining perfusion can help mitigate enteric factors that may perpetuate acidemia, which can worsen hypoxic pulmonary vasoconstriction.
2. Optimization of preload, which involves avoiding underfilling of the RV, which leads to low CO via the Frank-Starling mechanism, and avoidance of overfilling to prevent RV overdistention that affects the TSG and myocyte stretch causing suboptimal myofilament placement. With overfilling, increased central venous pressure (CVP) and venous congestion lead to decreased organ perfusion pressure and multiorgan failure.[9]
3. Reduction of RV afterload and PVR.
4. Augmentation of RV cardiac output by improving contractility, rate and rhythm management, and atrioventricular synchronization.[2] This is particularly important in patients with chronic PH when PAP cannot be reversed and management should focus more on optimizing RV function[12] (Box 43.2).

Monitoring

Monitoring of PH and RV pressures, as well as their effects on organ function, is essential in the ICU setting. Close attention to clinical and laboratory markers of organ dysfunction is necessary owing to the deleterious effects of elevated CVP and accompanying venous congestion. Strict recording of fluid intake and output can provide information regarding preload, renal function, or response to diuresis. Laboratory measures such as serum creatinine levels, liver function tests, and lactate levels serve as objective measures of renal and liver impairment and tissue perfusion, respectively, especially when severe RV failure leads to hepatic congestion and decreased end-organ perfusion. Myocardial markers such as natriuretic peptides and troponin can also be used for monitoring.

Although prior studies express concern and controversy about the utility of invasive monitoring,[27,28] the use of PA catheters provides invaluable information on cardiac function in critically ill patients with shock. The ability to readily assess hemodynamic parameters, such as cardiac index (CI), mPAP, PVR, PCWP, and mixed venous oxygen saturation (SvO_2), facilitates the delivery of additional therapies such as vasopressors, inotropes, or vasodilators. The use of serial transthoracic echocardiography (TTE) can lend additional insight into cardiac function by offering a direct glimpse at left and RV filling, interventricular dependence, contractility, and valvular pathology, as well as aid in the assessment of abnormal flow or left-to-right shunting.

Maintaining SVR and RCA Perfusion

Vasopressors

Norepinephrine

Norepinephrine (NE) is widely used in critical care settings to treat hemodynamically unstable patients. Its effects via β_1-receptor agonism are controversial. In animal models there is evidence for increased CO at doses up to 0.5 μg/kg per minute.[29–31] Other studies in patients with septic shock or after cardiac surgery have shown no effect on inotropy and CO.[32–34] NE exerts significant

α_1-receptor–mediated vasoconstriction. Animal studies have shown that α-adrenergic stimulation can cause a disproportionate rise in PVR and worsen PH,[35] with increases in PVR from 2.5 to 3.5 Woods units observed at a dose of 70 μg/min.[34] In a study of patients with septic shock, NE at a dose of 0.7 to 1.2 μg/kg per minute also resulted in increased PVR.[36] However, in patients with chronic PH in whom systemic hypotension developed after induction of anesthesia, it exerted more vasoconstrictive effect in the systemic rather than in the pulmonary circulation, decreasing the PVR/SVR ratio, which is favorable for RCA perfusion pressures and the TSG.[33] Further studies in septic shock showed that NE produced a 26% increase in PVR in contrast to a 35% increase in SVR.[32] Other animal studies have shown that NE causes no increase in pulmonary or renal vasoconstriction.[30] Additionally, in animal models, no increase in PVR was noted at doses less than 0.5 μg/kg per minute.[31] However, in HF patients with pulmonary arterial hypertension (PAH), NE use showed no difference in survival.[37] In post–cardiac surgery patients, NE has been successfully used in combination with prostaglandin for the treatment of patients with acute and chronic PH.[38] Overall, evidence exists for the use of NE in patients with PH and RV dysfunction to increase SVR and RCA perfusion, albeit with care for possible increase in PVR.

Phenylephrine

Phenylephrine is a direct α_1-agonist causing vasoconstriction that can increase SVR.[2] It does not cause tachycardia but may cause reflex bradycardia.[12,39] Phenylephrine has been shown to increase in PVR.[12] In patients with chronic PH with hypotension after induction of anesthesia, phenylephrine was less effective than NE at increasing blood pressure, slightly decreased CI, increased PVR, and had no effect on the PAP/MAP ratio.[33] Thus phenylephrine is not an ideal vasopressor in the setting of PH with RV failure.

Dopamine

Dopamine produces dose-dependent dopaminergic, β-adrenergic, and α-adrenergic effects on cardiac output and vascular tone. In patients with septic shock, dopamine was shown to increase CI without an increase in PVR.[32] Animal studies have shown no increase in PVR up to 10 μg/kg per minute.[2,40] However, dopamine in infants has been shown to increase the PVR/SVR ratio.[2,41] In patients with chronic PH, dopamine infusion led to increases in heart rate, mean pulmonary and systemic pressure, and cardiac index, with a concomitant fall of SVR.[42] Administration of dopamine is associated with an increased risk of supraventricular tachycardia, ventricular tachycardia, and sinus tachycardia with potentially dramatic hemodynamic consequences in patients with severe PH.[39,43] Furthermore, in patients with cardiogenic shock, dopamine was found to increase mortality.[43] Given the evidence, dopamine does not appear to be the ideal agent for treatment of PH with RV dysfunction.

Epinephrine

Epinephrine is a mixed α-/β-receptor agonist. In patients with septic shock, epinephrine at doses of 0.1 to 1.0 μg/kg increased RV ejection fraction but did increase mPAP by 11%.[12,44] In a small animal study of sepsis-induced PH, epinephrine infusion increased SVR and CO and lowered PVR.[45]

Vasopressin

Vasopressin (AVP) is an endogenous hormone with a noradrenergic vasopressor effect on the systemic vasculature and an ability to produce NO-mediated selective pulmonary vasodilation via endothelial V1 receptors.[46] In healthy animals, a linear relationship was observed between vasopressin levels and SVR without significantly affecting PVR.[47] In patients with PH with hypotension postoperatively, a dose of 0.05 to 0.1 U/min increased SVR without affecting PVR or mPAP.[48] However, at a higher dose of 1.16 U/kg per hour, it caused increased PVR and decreased CO with a decrease in RV contractility.[49] Higher doses of 0.08 to 0.4 U/min have also been known to cause pulmonary and coronary artery vasoconstriction.[12] The use of vasopressin at a low dose (0.04 U/min) increased SVR without pulmonary vasoconstriction.[9,50] At lower doses between 0.01 and 0.3 U/min, it can cause pulmonary vasodilation via stimulation of endothelial NO.[12] In animal studies, vasopressin infusion produced significant pulmonary vasodilation and reduction in PVR.[2,51] It can also increase GFR by constricting efferent arterioles. This is in contrast to catecholamine receptor–mediated vasopressors that constrict afferent arterioles and can decrease GFR.[48] This may explain AVP's diuretic effect in vasodilatory shock.[36,52] In patients with vasodilatory shock, AVP in combination with NE was shown to increase CI and SVR without any effect on PVR or mPAP, and the combination also demonstrated a lower incidence of tachyarrhythmias versus NE alone.[52] In contrast, in a different study of patients with sepsis, AVP in combination with NE did not affect CO but decreased mPAP.[53] Overall, the existing literature suggests that low-dose AVP with NE could be a useful combination for the treatment of PH with RV dysfunction.

Optimizing Preload

According to the Frank-Starling law, increasing preload can improve RV stroke volume. However, once the RV is adequately filled, excessive volume loading can be detrimental to the hemodynamics of the RV. In the setting of an elevated PVR, a small increase in preload can cause the right ventricle to dilate, which will increase RV free wall tension. This results in increased myocardial oxygen demand along with a decrease in RV coronary perfusion pressure, which ultimately leads to RV dysfunction and failure. As the right ventricle dilates, the interventricular septum shifts toward the left ventricle, causing impairment in LV diastolic filling and leading to a decline in systemic CO. The tricuspid annulus also begins to stretch as the RV dilates thereby causing tricuspid regurgitation.[9,12,26] Ensuing end-organ damage will result either from poor perfusion, organ congestion, or a combination of the two.

Recognizing RV failure is extremely important. Some classic physical findings are elevated jugular venous distention, hepatomegaly, and peripheral edema. An echocardiogram is useful for assessing size and function of the right ventricle, CO, tricuspid regurgitation, as well as IVC diameter and respiratory collapsibility. The best way to monitor hemodynamics is by inserting a right heart catheter. A rising V wave on a CVP tracing is indicative of increasing RVEDP. Mixed venous oxygen saturation and thermodilution can be used to determine CO while other hemodynamic parameters can also be monitored.

Close monitoring of fluid status is crucial and unmonitored fluid challenges are not advised.[2] In certain cases, RV failure is associated with fluid overload and a negative fluid balance is key to successful therapy.[25] A CVP of approximately 8 to 12 mm Hg is a reasonable preload goal. In the setting of CVP elevation, fluid removal via diuretics or hemodialysis should be the attempted. In contrast, when the CVP is too low, a small fluid bolus of 250 to 500 mL should be administered with careful monitoring of CVP

and markers of systemic perfusion to determine if the right ventricle is fluid-responsive. A modest CVP increase of 2 to 5 mm Hg after a fluid challenge and a resulting improvement in CO indicates that the right ventricle is fluid-responsive, and additional fluid challenges may be attempted. However, if the CVP increases above 20 mm Hg or rises without an improvement in hemodynamic parameters, the right ventricle is not fluid-responsive then further fluid administration should not be attempted.[9,12]

Afterload Reduction

Reversible Metabolic Factors

Proper management of RV failure and PH necessitates identification of reversible factors that incite or perpetuate RV dysfunction. Aside from catheter-assisted or mechanical thrombolysis in the setting of PE, RV afterload reduction in acute RV failure is often challenging because underlying chronic lung or heart disease contributing to increased PVR are not readily reversed by single, definitive treatment modalities. Thus treatment should address ancillary factors that can worsen PVR, such as underlying systemic disease, sepsis, acidosis, and pulmonary hypoxic and hypercapnic vasoconstriction.

Of particular importance is infection, which is a significant predictor of mortality in the ICU setting. In a series of ICU patients with acute right HF and pulmonary arterial hypertension, infection was present in 43% of patients with over a threefold incidence in nonsurvivors compared with survivors.[37] Vasoactive factors such as endothelin are elevated in sepsis and contribute to increased pulmonary arterial hypertension as well as decreased CO.[54,55] In addition, decreased NO synthesis secondary to bacterial endotoxin can lead to an increase in PVR.[12] Low CO after cardiac surgery or in acute decompensated HF is associated with decreased splanchnic perfusion and thus impairment of the intestinal epithelial barrier function. Accompanying changes in pH and gastrointestinal mucosal permeability can lead to increased bacterial translocation and elevated levels of endotoxin and inflammatory cytokines.[56,57] Thus prompt recognition and treatment of infection allows for control of not only source-related pathology, but also management of a critical factor that can affect cardiopulmonary improvement.

Pulmonary Vasodilators

Reduction of RV afterload and PVR is important in the management of patients with PH. Most pulmonary vasodilators can be subdivided according to their action on the pulmonary vasculature via cyclic guanosine monophosphate (cGMP), prostacyclin, or endothelin pathways[17] (see Fig. 43.5). In the chronic setting, most agents are generally only indicated for use in group 1 PH. There is only one agent, riociguat, indicated for use in group 4 PH.[58] Limited data exists for phosphodiesterase-5 (PDE-5) inhibitors in group 2 patients.[59] No agents are indicated for use in group 3 patients because of ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. In trials used as monotherapy or in combination, pulmonary vasodilators were able to improve clinical and hemodynamic outcomes.[60] However, only IV prostacyclin has been shown to improve mortality.[61] Not all of these pulmonary vasodilators can be used in a critical care setting: the route of administration, half-life, and systemic effects significantly affect the choice of the medication. Pulmonary vasodilators with longer half-lives or significant systemic hemodynamic effects can decrease organ perfusion pressure and reduce right coronary artery blood flow with further deterioration of RV performance. Use of pulmonary vasodilators in the ICU setting depends largely on the etiology of PH, as inappropriate use can result in worsening clinical status and hemodynamic deterioration.

Of note, pulmonary vasodilators should be used after optimization of RV perfusion and CO as lowering of SVR may worsen RV ischemia.[2] Increased transpulmonary flow may precipitate pulmonary edema. Additionally, nonselective actions of vasodilators may result in worsening $\dot{V}/\dot{Q}$ mismatch. This risk is reduced with the use of inhaled vasodilators, which selectively affects vessels in ventilated lung units.

Inhaled Nitric Oxide

Inhaled NO (iNO) is a potent vasodilator able to lower PAP, PVR and RV oxygen demand.[62] It improves cardiac performance without altering RV contractility and CO.[63–65] Due to its ability to selectively dilate pulmonary vasculature in ventilated lung areas, it improves $\dot{V}/\dot{Q}$ mismatch and oxygenation.[66] It has a very short half-life, rapid onset, and almost no systemic vasodilatory effects, which is very important in the treatment of hemodynamically unstable patients.[9,66] Use of iNO patients with ARDS showed improvement in oxygenation for 24 to 48 hours and variable improvement in mPAP.[67] A combination of iNO and other interventions, such as PEEP and prone positioning, also had beneficial and additive effects on arterial oxygenation.[68] However, iNO had no favorable impact on the duration of ventilatory support or mortality rate in this patient population.[68,69] Nevertheless, some studies have shown that iNO may have some mortality benefit in patients with RV failure after heart transplantation.[70] When used in post–cardiac surgery patients with a history of PH, iNO use was associated with lower heart rates, higher RV ejection fraction, and a lower requirement for vasopressor agents while decreasing PVR by 36%.[71] iNO has been associated with improved outcomes in critically ill postoperative patients in whom severe PH or RV failure developed.[72,73] In addition to its high applicability in many acute conditions, iNO can be delivered in spontaneously breathing individuals by face mask or even nasal cannula as has been shown in pediatric practice.[74] Studies have shown the efficacy of iNO in varied doses from 5 to 40 ppm.[63,66,69,71] However, trials investigating the use of iNO for reversibility studies in group 1 PH patients demonstrated that maximum effects could be obtained at a level of 10 ppm.[71,75,76] iNO has been shown to provide sy nergistic pulmonary vasodilation when used in conjunction with inhaled and IV prostacyclin as well as PDE-5 inhibitors.[2] iNO treatment is associated with some side effects, including methemoglobinemia, nitrogen dioxide formation, damage to surfactant, and possible genotoxicity to cell DNA.[75,77] Abrupt withdrawal of iNO has been associated with rebound PH, a significant drop in the partial pressure of arterial oxygen (PaO_2), and life-threatening hemodynamic deterioration.[77,78] Rebound PH may be attenuated by the use of PDE-5 inhibitors during weaning.[79] Close monitoring and gradual discontinuation are important to prevent and detect rebound PH. iNO is the prototypical ideal agent to be used in a variety of causes of PH with RV dysfunction.

Prostanoids

Prostanoids are able to produce significant pulmonary vasodilatation and lower mPAP and PVR. They also possess antithrombotic, antiproliferative, and antiinflammatory properties. IV prostacyclin is highly effective in cases of severe PH and is also associated with a significant survival benefit.[80,81] In ARDS, IV prostacyclin reduced PVR and improved RV function but increased $\dot{V}/\dot{Q}$ mismatch.[2] Prostacyclin (PGI_2) and its analogs (iloprost, epoprostenol, and treprostinil) are available in inhaled forms for patients with

chronic PAH.[82,83] Inhaled forms of prostacyclin are delivered to ventilated lung units, decreasing the degree of V̇/Q̇ mismatch and hypoxia. However, prostanoids can significantly affect systemic hemodynamics, especially in the IV form, which limits their use in critically ill or hemodynamically unstable patients. Case reports have shown that inhaled prostacyclins have no significant effect on SVR.[84] However, in another case report, the use of inhaled prostacyclin after cardiac bypass was associated with systemic hypotension. Inhaled iloprost effectively decreased mPAP, the PVR/SVR ratio, and improved RV performance immediately after separation from cardiopulmonary bypass.[85] Inhaled iloprost was also successfully used in the treatment of acute RV dysfunction in the setting of acute PE and ARDS by improving PVR and oxygenation without affecting SVR.[2] It has been estimated that only 10% to 20% of inhaled prostaglandin (PG) I2 reaches the alveoli. In patients with ARDS, iloprost improved oxygenation, decreased PVR, and did not produce V̇/Q̇ mismatch or rebound PH when compared to iNO.[86] Concerns exist owing to the side effects of thrombocytopenia and platelet aggregation associated with prostanoids. After cardiac surgery and bypass, platelet function was affected by inhaled prostacyclin but no increase in clinical bleeding was noted.[87] Prostacyclins have a role in the treatment of patients with PH who have RV dysfunction but should be used with care given the potential for V̇/Q̇ mismatch and hypotension.

Phosphodiesterase-5 Inhibitors

Sildenafil and tadalafil are specific PDE-5 inhibitors. They inhibit the metabolism of cGMP, the second messenger that mediates the vasodilatory effects of NO and the natriuretic peptides. They have the ability to lower PVR and mPAP and to increase CO in patients with different forms of chronic PH.[88–90] In patients with systolic or diastolic HF with secondary PH, sildenafil reduced PVR/mPAP and increased CO without an increase in PCWP or decrease in SVR.[91,92] In the chronic setting, it is highly effective alone or in combination with other pulmonary vasodilators: prostacyclins,[93] endothelin receptor antagonists,[60] milrinone,[23] and iNO.[94] Sildenafil was able to improve central hemodynamics and RV function in ventilated patients with PH who required dobutamine administration.[95] PDE-5 inhibitors have been successfully used to minimize rebound PH after iNO discontinuation,[96] in weaning from IV vasodilators in patients after cardiac surgery,[79] as well as in chronic PH therapy[97] and in severe RV dysfunction related to chronic PH.[96] In post-LVAD placement, sildenafil facilitated weaning from iNO and inotropes without deleterious effects on systemic hemodynamics.[98] In patients with PAH, both sildenafil and iNO increased CO; however, sildenafil did so without a rise in PCWP, which is beneficial in patients with concomitant diastolic dysfunction.[88] However, in patients with bowel edema, oral sildenafil may not be well absorbed. In this case, 10 mg of IV sildenafil can be administered as the equivalent of 20 mg PO.[99] Additionally, PDE-5 inhibitors have long half-lives and can potentially cause hypotension and worsen hypoxemia, leading to pulmonary hypoxic vasoconstriction and V̇/Q̇ mismatch.[9]

Calcium Channel Blockers

Calcium channel blockers have been used in hemodynamically stable patients with PAH who demonstrated a pulmonary vascular response to acute vasodilator challenge.[100,101] There are limited data on use of calcium channel blockers in critically ill patients with acute PH. Acute administration of nifedipine in PAH patients did not cause pulmonary vasodilatation, increased RVEDP, and decreased RV contractility.[81] Prolonged half-life and negative inotropic effects, which may precipitate fatal worsening of RV failure, limit the use of calcium channel blockers in the treatment of acute PH.[102]

Endothelin Receptor Antagonists

Endothelin receptor antagonists (bosentan, macitentan, ambrisentan) appear to be highly effective in the treatment of group 1 PH in the outpatient setting with evidence for decreasing time to clinical worsening.[100,103,104] They have not been adequately studied in acute care settings. In an animal model, pretreatment with bosentan completely abolished endotoxin-induced acute PH and changes in pulmonary compliance and resistance.[18] Currently, the only possible implication in critically ill patients would be weaning or conversion from inhaled or IV pulmonary vasodilators to oral medication. Concerns also exist regarding the potential for liver toxicity and anemia.

Natriuretic Peptides

Natriuretic peptides have diuretic and vasodilatory properties and are able to counteract the renin-angiotensin system. In patients with RV failure, they produce dose-related pulmonary vasodilatation without worsening oxygen saturation or systemic hemodynamic and exert favorable neurohormonal effects by suppressing aldosterone.[105] Brain natriuretic peptide significantly attenuated the mPAP and acute hypoxic pulmonary vasoconstriction in otherwise healthy individuals, but they had no effect on mPAP or PVR in patients with PH.[106] In a study of precapillary and postcapillary PH, nesiritide decreased mPAP and PVR in patients with postcapillary PH but not those with precapillary.[107] Use of nesiritide in hemodynamically unstable and hypotensive patients is limited, mainly because of reduction of SVR and resulting profound systemic hypotension.[108]

Nitrates

Nitroprusside and nitroglycerin both can cause significant pulmonary vasodilation. However, nitroprusside has a longer half-life and can cause acute reduction of SVR leading to systemic hypotension, limiting its use in hemodynamically unstable and hypotensive patients.[63] The significant venodilator effect of nitroglycerin can decrease RV preload, leading to adverse consequences in patients with RV failure. Inhaled nitroglycerin may be a safer therapeutic option shown to decrease PVR without significant adverse effects on SVR.[109]

Novel Agents

Riociguat is a novel vasodilator approved for use in group 1 PH and the only vasodilator approved for the treatment of chronic thromboembolic PH.[58,110,111] Riociguat has a dual mechanism of action: it sensitizes soluble guanylate cyclase to endogenous NO, and it directly stimulates soluble guanylate cyclase receptors independent of NO availability, resulting in vasorelaxation and antiproliferative effects. This is in contrast to PDE-5 inhibitors, which target a component of the NO signaling pathway further downstream and have restricted efficacy in the presence of reduced NO levels. This quality may be useful in sepsis as endotoxin has been shown to increase PVR via suppression of NO synthesis.[12,112] In patients with systolic HF with group 2 PH, riociguat decreased PVR and SVR with an increase in CI.[113] There are few data on the use of riociguat in the acute care setting; however, potential exists for similar use in weaning as for endothelin receptor blockers and PDE-5 inhibitors.

Selexipag is a prostacyclin receptor agonist that decreases time to clinical worsening for patients with group 1 PH.[114] Its use in the critical care setting has not been evaluated. Theoretic concerns for hypotension exist as for the prostanoids; however, in a trial involving patients with chronic PH, no clear hypotension was noted.[114]

Augmenting RV Cardiac Output

Inotropes

Dobutamine

Dobutamine is a commonly used inotropic agent in patients with PH. It augments myocardial contractility via β_1-receptor stimulation.[115] In animal models of PH at doses of 5 to 10 μg/kg per minute, dobutamine caused increased blood pressure and CO without a change in PVR.[31] In another animal study, dobutamine at doses of 2.5 to 20 μg/kg per minute increased CO and decreased mPAP and PVR.[116] In patients with secondary PH awaiting lung transplant, dobutamine did not affect MAP and increased CO, but it increased heart rate and mPAP.[117] In patients with RV infarction, dobutamine at doses of 5 to 10 μg/kg per minute increased CO without affecting SVR or PVR.[118] In HF patients, dobutamine doses of 2.5 to10 μg/kg per minute increased CO and reduced PVR and SVR.[119] In studies in which dobutamine was combined with iNO, the effect on the rise in mPAP was neutralized.[116,117] Dobutamine can cause peripheral vasodilation owing to β_2 effects. At doses of 2.5 to 5 μg/kg per minute there is less chance of vasodilation.[9] Animal studies of PH have shown that dobutamine at doses above 10 μg/kg per minute increased PVR and HR with more hypotension.[2,116] In cases of systemic hypotension, patients may require concomitant use of vasopressors to maintain appropriate systemic perfusion pressures. Dobutamine also increases the risk of tachyarrhythmias, which can affect diastolic filling time in the setting of already elevated RV diastolic pressures.[37]

Levosimendan

Levosimendan sensitizes troponin C to calcium and selectively inhibits PDE-3, thereby improving myocardial contractility and vasodilation without increasing oxygen consumption. In animal studies of PE with RV failure, levosimendan increased CO and decreased PVR. This makes it particularly effective in the treatment of RV dysfunction related to PH.[120,121] In this setting, it restored RV function even better than dobutamine, mainly because of more efficient pulmonary vasodilation on top of similar inotropic effects. A study of patients with ARDS in association with septic shock showed that levosimendan improved RV performance mainly through pulmonary vasodilator effects.[122] It was also effective in restoring RV function in patients with cardiogenic shock after myocardial infarction.[123] In patients with HF who have group 2 PH, levosimendan decreased mPAP and PVR while increasing CO without a change in right atrial pressure or PCWP.[124,125] However, in trials of patients with HF, it has been associated with increased risk of cardiac arrhythmias and hypotension, which may negatively affect mortality.[126,127]

Milrinone

Milrinone is a selective PDE-3 inhibitor with significant inotropic and vasodilatory effects in both pulmonary and systemic circulation. It is widely used in patients with decompensated systolic HF [128,129] and those after cardiac surgery.[17,130] In animal models of both acute and chronic PH, milrinone significantly reduced PVR and improved RV function.[131] In combination with iNO, milrinone produced additive pulmonary vasodilatation in acute PH.[64,132] In another animal model of PH, addition of sildenafil to milrinone produced more effective pulmonary vasodilation than either agent alone without significant systemic hypotension. CO and RV performance were significantly improved after milrinone alone or in combination with sildenafil, but not with sildenafil alone.[133] The systemic vasodilatory effects of milrinone along with its relatively long half-life are the major limiting factors against its use in conditions associated with systemic hypotension or hemodynamic instability. Systemic vasopressors (norepinephrine and low-dose vasopressin) were effective in the treatment of the milrinone-induced systemic hypotension after cardiac surgery. However, a milrinone-vasopressin combination was associated with better hemodynamics than a milrinone-norepinephrine combination during the management of RV failure via a decrease in the PVR/SVR ratio.[134] A case series of patients with LVAD who had PH showed increased CO and decreased PVR with IV milrinone.[135] In animal models, inhaled versus IV milrinone after cardiac bypass caused less hypotension and tachycardia, but it decreased PVR to a lesser degree. Inhaled milrinone predominantly dilated pulmonary blood vessels, resulting in a reduced PVR/SVR ratio, improvement in hemodynamic and oxygenation profiles, and prevention of pulmonary endothelial dysfunction.[136] When compared with intravenous milrinone in patients with PH after cardiac surgery, inhaled milrinone demonstrated less systemic hypotension, less $\dot{V}/\dot{Q}$ mismatch, decreased mPAP, and increased CO and improvement in the Pa_{O_2}/F_{IO_2} (fraction of inspired oxygen) ratio.[130,137,138] In heart transplant candidates with PH, inhaled milrinone selectively dilated pulmonary vasculature. It decreased mPAP, PVR, and PCWP and increased RV ejection fraction without any change in SVR or CO.[139] The combination of inhaled milrinone and inhaled prostacyclin was found to be synergistic in post–cardiac surgery patients.[140] Although arrhythmias are a potential side effect, milrinone tends to be less arrhythmogenic than dobutamine.[12]

Rate and Rhythm Control

Maintaining sinus rhythm is essential to preserve appropriate CO. Irregular rhythms such as atrial fibrillation or conduction abnormalities are not well tolerated, as atrial contractility is an important contributor to RV filling in patients with noncompliant RVs.[9,25,141] In the setting of RV dysfunction, tachycardia causes further increases in RVEDP and CVP, with resulting venous congestion leading to decreased organ perfusion.[9]

Patients with RA dilatation or remodeling after surgery, chronic PH, or long-standing lung disease are more susceptible to developing foci for atrial fibrillation or flutter, whereas patients with infiltrative disease or RV myocardial infarction are at higher risk for conduction abnormalities.[22] Increases in RV afterload and elevated PAPs have been postulated to contribute to the increased risk of atrial fibrillation, with atrial fibrillation present in 14% to 18% of cases of acute PE.[142,143] Persistent atrial fibrillation in PAH has a 2-year mortality above 80%.[144]

Supraventricular arrhythmias are more common than ventricular arrhythmias in PAH. One single-center 6-year retrospective study reported 31 supraventricular arrhythmias among 27 of 231 patients for a cumulative 11.7% incidence and 2.8% annual risk per patient, with atrial flutter and atrial fibrillation accounting for 90% of

the arrhythmias.[145] A separate multicenter 4-year retrospective analysis reported ventricular fibrillation in 10 of 132 cardiac arrests (8%).[146]

In the setting of RV dysfunction, tachyarrhythmias and bradyarrhythmias can precipitate acute hemodynamic instability and require prompt cardioversion or pacing, respectively. Acute RV failure is associated with tricuspid regurgitation resulting from RV distention and stretch on the tricuspid annulus. Atrial pacing may be required at higher rates above 80 beats/min to reduce tricuspid regurgitation and RV distention and thus improve RV CO.[9] After sinus rhythm is restored, the use of pressors and inotropes to improve CO and systemic perfusion can sometimes exacerbate these rhythms and consequently cause clinical worsening.[25]

In tachycardia, the choice of rate-control agents can be challenging because calcium channel blockers and β-blockers can contribute to further RV dysfunction by their negative inotropic effects, which lead to reduced RV CO. The role of β-blockers in right HF is not as well defined as their role in left HF. One small study of patients with moderate to severe portopulmonary hypertension using β-blocker therapy for prophylaxis against variceal bleeding revealed that discontinuation of β-blockers led to decreases in PVR, increased CO, and improved exercise capacity.[147] Digoxin may be a useful alternative for rate control, and antiarrhythmic agents such as amiodarone may be beneficial for maintenance of sinus rhythm after cardioversion.[25]

Ventilatory Support

The goal of the heart and lungs is to maintain adequate oxygen delivery to all tissues while removing metabolic waste. It is important to remember that the heart and the lungs cannot in isolation fulfill this obligation but must function as a heart-lung unit. They are both confined to the same body cavity, which has critical implications in ventilated patients. Because the right ventricle, the lungs, and the left ventricle are arranged in a continuous series, an acute insult to one component can affect the function of all elements. Adopting proper ventilation strategies helps to maintain the function of this system and avoids cardiopulmonary conflicts. Noncardiopulmonary elements of oxygen consumption and delivery should be optimized concomitantly while delivering ventilatory or cardiac support therapies.

Supplemental oxygen remains important in hypoxemia. Lung hypoxemia is a powerful vasoconstrictor that can increase RV afterload. Correcting hypoxemia can mitigate cor pulmonale. The response of lung ventilation and perfusion to high F_{IO_2} depends on disease states and must be carefully monitored in ICU patients. For instance, patients with ARDS and chronic obstructive pulmonary disease can react unfavorably to 100% oxygen.

Hypercapnia and acidemia also increase RV afterload and should be corrected to near-normal levels if the overall ventilation strategy allows. Except when low-volume ventilation is necessary (e.g., ARDS), functional residual capacity should be the target of lung volumes.[20] Certain strategies can minimize RV functional compromise, especially in the setting of ARDS, such as using an intermediate tidal volume (8 mL/kg) with a PEEP below 10 mm H_2O, prone positioning, and low respiratory rate.[148] Additionally, maintaining plateau pressure below 27 mm H_2O, adapting PEEP to RV function, and maintaining the partial pressure of arterial carbon dioxide ($PaCO_2$) below 60 mm Hg are other strategies recommended to prevent or mitigate acute RV failure in ARDS.[26] Air trapping and ventilator dyssynchrony can also contribute to increasing RV afterload and should be treated expeditiously.[9]

Certain subgroups of patients with PAH (those with severe PAH) do not tolerate intubation and associated sedation well; such measures should be avoided as much as possible. If intubation is needed, consideration should be given to presedation catecholamine use to mitigate loss of RV contractility and autonomic tone.[25]

Mechanical Circulatory Support

Mechanical ventricular support should be instituted with clear goals in mind using a multidisciplinary team approach. Common goals include anticipated recovery or transplantation. In an otherwise unsalvageable condition, mechanical support will not avert mortality. Frequently, "failure" of mechanical support is due to late intervention, so timely therapy can be lifesaving.

Mechanical support may be needed in case of primary RV failure or in an overwhelmed, chronically compromised ventricle. In any event, all aspects of ventricular performance—namely, preload, afterload and contractility—must be balanced, and mechanical support augments or replaces pump function.

Three cardiopulmonary elements that should be considered in selecting mechanical support are the right ventricle, the lungs, and the left ventricle. If RV failure and lung failure co-exist then an extracorporeal support, such as venoarterial extracorporeal membrane oxygenation (VA-ECMO) or a right-sided tandem with oxygenator spliced in the circuit should be considered. If only RV support is needed, then an Impella device (Abiomed, Danvers, MA) would be suitable. If support is anticipated for a longer duration, then a surgically implanted RV assist device would be indicated so that extubation and mobility can be maintained. There are other iterations of surgically implanted devices that can either replace lung function or heart function. In cases of biventricular failure, bilateral Impella devices, bilateral Tandems, or VA-ECMO are options for short-term support and a surgically implanted biventricular assist device for longer-term support. An oxygenator can be spliced in several extracorporeal circuits if needed.

Placing percutaneous devices is a vascular-anatomic commitment because removal of the arterial limb often requires surgical repair. Some of these devices are better delivered from right-sided veins (e.g., venovenous ECMO dual-lumen cannula (Impella or Tandem) devices); thus access planning in an ICU patient is key. Frequently, a mechanical device is a bridge to another device and access can become a limiting factor.

Atrial Septostomy

Atrial septostomy can be used in centers with experience as a palliative or bridging procedure. Graded balloon septostomy has been reported to have lower risk than a blade septostomy. Because it is infrequently performed, guidelines have not included them in their recommendations.[25] Short-term hemodynamic improvement has been documented as improvement in the 6-minute walk test but long-term outcomes are not known. Atrial septostomy is generally used in patients with functional class IV disease with advanced right HF when medical therapy is not sufficient or is not available, and bridging to transplant or palliation are goals. One set of guidelines recommends against using atrial septostomy in patients with end-stage disease with a right atrial pressure above 20 mmHg and an oxygen saturation of less than 85%.[25] Atrial septostomy techniques, other indications, and contraindications have been reviewed elsewhere.[149]

Prognosis

PH in the ICU has an overall high morbidity and mortality and is challenging to manage. RV dysfunction and cardiogenic shock are believed to be the pathways for multiorgan failure and carry a significant burden.

Patients with PAH who have acute RV failure admitted to an ICU have been shown to have mortality rates as high as 41%. Low levels of natriuretic peptides, inflammatory markers, as well as relatively normal serum sodium and creatinine were demonstrated in one study to be associated with improved survival. Infection was not well tolerated.[37]

In patients with ARDS with protective ventilation, cor pulmonale is frequent (22%) and is associated with worse outcomes, higher needs for vasoactive medications for shock, and has a higher 28-day mortality.[150] Plateau pressure in this study was below 30 mm H_2O and mean PEEP was 8.8 mm H_2O.

Other subsets of patients such as those with acute PE and left HF who develop RV dysfunction from PH also have higher morbidity and mortality. Prognosis in the acutely decompensated patient can be modified by early recognition of worsening clinical status and prompt correction of acute insults while providing support to the failing ventricle.

Acknowledgment

The authors would like to thank Luke Chong and Anthony Lucev for their assistance with this chapter.

Key Points

- Pulmonary hypertension (PH) factors. PH is defined as a resting mean pulmonary artery pressure (mPAP) above 25 mm Hg and a pulmonary vascular resistance (PVR) greater than 240 dynes/sec per centimeter[5] (or >3 Woods units) as determined by right heart catheterization.
- Identifying the site of the underlying pulmonary vasculopathy allows determination of precapillary, postcapillary, or a combination of both precapillary and postcapillary factors responsible for PH.
- Determining the transpulmonary gradient (TPG) allows identification of precapillary or post capillary causes of PH. An elevated TPG indicates a precapillary contribution to the PH. If the TPG is normal, then high pulmonary artery pressure (PAP) is due to either high pulmonary vein pressure or high pulmonary blood flow, and a postcapillary contribution to the PH occurs. With increases in pulmonary vein pressure and TPG, both postcapillary and precapillary changes are present. In the latter case, combined PH is present. This may be either fixed or reversible depending on pulmonary vasodilator testing results.
- Treatment of PH and right ventricular (RV) failure should be dictated by four major goals:
  - Maintaining systemic vascular resistance and the pressure gradient between the aorta and right carotid artery (RCA) to ensure RCA perfusion
  - Optimizing preload. RV underfilling can lead to low cardiac output, whereas overfilling can cause elevated central venous pressure and venous congestion, which leads to decreased end-organ perfusion.
  - Reducing RV afterload and PVR
  - Augmenting RV cardiac output (CO)via improving contractility, rate and rhythm control, and atrioventricular synchronization
- The choice of vasopressor agents in patients with PH and RV failure requires careful consideration of associated factors (e.g., septic shock, postsurgical PH). Norepinephrine and vasopressin, or a combination of both agents, are preferred based on existing literature. Monitoring of hemodynamic parameters can help the intensivist gauge the response to therapy or become aware of untoward effects.
- Pulmonary vasodilators should be carefully applied after optimizing RV perfusion and CO. Intravenous (IV) prostanoids, nitroglycerin, and nitroprusside can affect systemic hemodynamics, thus limiting their use in critically ill and unstable patients. It is important to be mindful of side effects of vasodilators such as rebound PH or ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch with use of these agents. Inhaled nitric oxide can lower PAP, PVR, and RV oxygen demand in almost all etiologies of pulmonary hypertension owing to its properties of $\dot{V}/\dot{Q}$ matching. Inhaled prostacyclins may also have similar benefit.
- Inotropes can improve RV CO by either improving contractility or by pulmonary vasodilator effects. Although dobutamine has an established role in cardiogenic shock, the risk of tachyarrhythmias as well as mixed evidence regarding its effect on increasing mPAP and PVR may limit its use. Levosimendan is a promising agent that can improve CO without increasing mPAP, PVR, or pulmonary capillary wedge pressure, but certain trials show that is has an increased risk of arrhythmias and hypotension. Milrinone can augment RV output via inotropic as well as pulmonary vasodilatory effects. In combination with other agents such as sildenafil or vasopressin, IV milrinone can lead to favorable hemodynamic improvements. Furthermore, the use of inhaled milrinone offers the beneficial effect of pulmonary vasodilation with less systemic hypotension.
- Careful ventilator management is essential to address hypoxemia and hypercapnia, which can perpetuate pulmonary vasoconstriction and increase afterload, respectively. Application of low-tidal volume ventilation in acute respiratory distress syndrome can help to prevent further worsening of RV function.
- Anticipation of further decompensation and early initiation of advanced modalities of treatment such as mechanical circulatory support can be lifesaving.

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Review Questions

1. A 40-year-old moderately obese man is admitted for same-day cardiac catheterization after presenting with 6 months of worsening chest tightness, dyspnea on exertion, and cough. His electrocardiogram examination did not show ischemic changes. Echography was technically difficult, precluding assessment of the left ventricle, but the right ventricle appeared mildly dilated with significant elevation of the pulmonary artery systolic pressure. Left heart catheterization showed non-obstructive coronary artery disease. Right heart catheterization revealed a mean pulmonary artery pressure (mPAP) of 45 mm Hg (pulmonary artery 60/30 mm Hg) with a pulmonary capillary wedge pressure (PCWP) of 10 mm Hg and a cardiac output of 5 L/min. Which condition is described best by this hemodynamic profile?

a. Severe mitral stenosis
b. Left heart failure owing to grade 3 diastolic dysfunction
c. Chronic thromboembolic pulmonary hypertension (CTEPH; group 4 denoted in the clinical classification of PH; see Box 43.1)
d. Combined precapillary and postcapillary pulmonary hypertension (PH) owing to left ventricular combined systolic and diastolic dysfunction

Answer: c. The patient has an elevated TPG of 35 (normal is less than 12) and this is associated with a PCWP of <15 mm Hg. The pulmonary vascular resistance, which is calculated from the mPAP-PCWP gradient (the TPG), divided by the CO is 7 Wood units > 3 Woods units and therefore meets all hemodynamic criteria to be classified as precapillary PH (see Table 43.2). CTEPH is a precapillary form of PH. A patient with severe mitral stenosis (choice a) would have a severely elevated mPAP as would a patient with left heart failure and advanced diastolic dysfunction (choice b) However in the setting of heart failure, the PCWP will be extremely elevated (≥15 mm Hg and the TPG will be 12 mm Hg or lower. These latter two patients have all the hemodynamic criteria to be classified as postcapillary PH. Similarly, a patient with left heart disease with combined precapillary and postcapillary PH (choice d) would have a severely elevated mPAP and a large TPG and a PVR or 3 Woods units or higher, but the PCWP would be at least 15 mm Hg or higher.

2. A 27-year-old female with a past medical history of scleroderma with associated pulmonary hypertension diagnosed 5 years ago presents with syncope. Her current medical regimen includes inhaled prostacyclin, an endothelin receptor blocker, and a phosphodiesterase inhibitor. Her vital signs show a blood pressure of 70/50 mm Hg and a heart rate of 88 beats/min. She is using chronic oxygen therapy and her oxygen saturation is 96% on 3 L (via nasal cannula). Owing to hypotension, she is transferred to the intensive care unit and a Swan-Ganz catheter is placed to assist in management. Hemodynamics reveal the following: central venous pressure (CVP) 20 mm Hg, pulmonary artery pressure (PAP) 90/40 mm Hg, and PCWP 12 mm Hg with cardiac output (CO) 3.9 L/min, and peripheral vascular resistance (PVR) 12 Woods units.

What is the next best step in management?

a. Inotropes to increase cardiac output
b. Decrease afterload with nitric oxide
d. Vasopressors to increase systemic vascular resistance (SVR)
d. Bolus intravenous (IV) fluid

Answer: c. The patient has group 1 PH associated with scleroderma. She presents with syncope and borderline cardiac output with hypotension. The best first step is to maintain the pressure gradient between aortic and right ventricular (RV) pressure to ensure right coronary artery (RCA) perfusion and reversal of RV ischemia by increasing the SVR with vasopressors. Bolus of IV fluid (choice d) is incorrect as her CVP is elevated and would result in overfilling of the RV, an increased transseptal gradient, and increased venous congestion. Choice a is incorrect as increasing contractility before correcting SVR can lead to an increase in right ventricular end-diastolic pressure and a decrease in RV coronary perfusion pressure. Choice c is a reasonable intervention to decrease PVR and improved CO but only after right carotid artery perfusion is restored.

3. You are asked to consult on a 35-year-old patient with idiopathic pulmonary artery hypertension (PAH) who was admitted to the ICU a few days ago with worsening respiratory status. Her condition was diagnosed 5 years ago and no associated conditions were found for her PAH. Her outpatient treatment needed escalation over time such that now she is receiving treprostinil subcutaneous infusion of 100 μg/kg per minute, ambrisentan 10 mg daily, sildenafil 40 mg 3 times a day, spironolactone 50 mg 2 times a day, digoxin 250 μg once a day, and torsemide 40 mg 2 times a day. Doses could not be uptitrated any further because of side effects. Her functional class at best was NYHA class II as an outpatient.

Since presenting to the hospital, her breathing worsened and she needed mechanical ventilation. IV catecholamines were started because of persistently decreased blood pressure. Her current vital signs are as follows: heart rate 110 beats/min, arterial blood pressure 93/67 mm Hg, oxygen saturation measured by pulse oximetry (SpO_2) 94%, CVP 23 mm Hg, and central venous saturation 45%. Urine output has been less than 20 mL/h for the past 6 hours. Echocardiogram shows severe right ventricular dilatation and hypokinesis. Chest radiography shows dilated pulmonary arteries.

The next step in her management is which of the following?

a. Continue the current course and allow her some more time to respond to therapy.
b. Stop treprostinil because one of the side effects is hypotension.
c. Insert a pulmonary artery catheter to obtain accurate hemodynamics and support her with an inotrope; if that approach fails, begin mechanical support.
d. Pulmonary artery catheter and mechanic support therapies are not indicated for right ventricular decompensation.

Answer: c. The current course is not sustainable and available data suggest decline. Stopping treprostinil (choice b) in such a setting could be detrimental, so it should be continued as it is playing a role in afterload reduction. Placement of a Swan-Ganz catheter is the next appropriate step. Inotrope and mechanical support should be considered, as should be candidacy for lung transplantation in this young patient without overt contraindications.

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Massive Hemoptysis

JANICE L. ZIMMERMAN AND RAUL SANCHEZ

CHAPTER OUTLINE

Anatomic Considerations
- Pulmonary Circulation
- Bronchial Circulation
- Nonbronchial Systemic Collateral Circulation
- Pulmonary Venous Abnormalities

Causes of Hemoptysis
- Bronchiectasis
- Tuberculosis
- Lung Malignancy
- Lung Abscess
- Chronic Bronchitis
- Other Pulmonary Infections
- Pulmonary Embolism
- *Aspergillus* Fungus Balls
- Cardiovascular Causes
- Interstitial Lung Disease
- Broncholithiasis
- Diffuse Alveolar Hemorrhage
- Vascular Abnormalities
- Trauma
- Vascular Monitoring Catheters

Invasive Pulmonary Interventions

Management
- Airway and Lung Protection
- Localization of Bleeding
- Hemorrhage Control
- Surgery
- Other Therapies

Hemoptysis varies in amount from intermittent blood-streaked sputum to massive arterial bleeding with asphyxiation or exsanguination. Massive hemoptysis is defined as the expectoration of blood from the respiratory tract in life-threatening quantities. Clinical definitions of massive hemoptysis focus on selected quantities of coughed blood between 200 and 1000 mL over 24 hours or less, with greater than 600 mL as the most common criterion.[1] Quantification of the amount of coughed blood is unreliable, often subjective, and fails to account for blood remaining in the lungs. The adverse clinical effects of hemoptysis, such as impaired gas exchange, airway obstruction, or hypotension, may be more relevant for defining a life-threatening condition.[2]

Fortunately, massive hemoptysis is rare and accounts for 4% to 18.5% of all cases of hemoptysis in recent studies.[3–5] Incidence studies are problematic because of the use of variable definitions. Although mortality rates as high as 71%[6] were reported in the past, mortality rates in recent studies of massive hemoptysis range from 0% to 38%.[2,3,7]

This chapter focuses on the most common causes of massive hemoptysis, clinical manifestations, and options for management.

Anatomic Considerations

The lung is unique among the visceral organs in that it receives a dual blood supply from different circulations. Because hemoptysis can occur from either the pulmonary or bronchial circulation, an anatomic understanding of these systems is important.

Pulmonary Circulation

The pulmonary artery bifurcates into left and right main pulmonary arteries after it leaves the right side of the heart. The pulmonary circulation is a low-pressure system, but pulmonary artery pressures may rise to approach systemic pressures in pulmonary parenchymal and pulmonary vascular diseases. Nevertheless, pulmonary hypertension alone rarely causes hemoptysis.

Prospective angiographic studies for hemoptysis in which both pulmonary and bronchial circulations have been imaged do not exist. Bleeding from the pulmonary arterial circulation accounts for less than 10% of massive hemoptysis cases and has been noted in a variety of destructive pulmonary lesions, including tuberculosis, lung abscess, and aspergillosis.[2,8] Aneurysms of the pulmonary artery, arteriovenous malformations (AVMs), and pulmonary artery rupture have also been reported.

Bronchial Circulation

Bleeding from the higher-pressure bronchial circulation has been estimated to cause 88% of the cases of massive and submassive hemoptysis.[9] The bronchial arteries arise from the descending aorta

with considerable anatomic variation. The one or two bronchial arteries that supply each lung in the majority of individuals[10] arise from the area near the first and second intercostal arteries. Particularly on the right side, the bronchial arteries may arise directly from the proximal first intercostal artery. The arteries course along the trachea, major bronchi, and bronchioles and have terminal communications with the pulmonary capillaries or pulmonary venules. The small-vessel bronchial supply to the trachea and major bronchi drains into the azygos vein with direct communication to the superior vena cava. Aneurysmal dilation of bronchial arteries (Dieulafoy vascular malformation) has been noted in some patients with hemoptysis, and it can occasionally be visualized endobronchially and noted on bronchial arteriography.[11]

A direct anastomotic communication between the bronchial and pulmonary arterioles has been sought to explain the preservation of lung parenchyma after injuries to the pulmonary vascular supply. Anatomic studies have found that intermeshing of pulmonary and bronchial capillary networks is the most common anastomotic arrangement that prevents pressurization of the pulmonary arterioles with systemic pressures.[12] However, in chronic inflammatory diseases of the airways, anatomic anastomoses have been found that allow direct pressurization of the pulmonary artery with systemic pressures.[13] The extent to which these vascular communications are related to hemoptysis remains unknown.

Bronchial arteries vasodilate in the presence of cholinergic, β_2-adrenergic, and some nonadrenergic, noncholinergic agonists. Although the effect of β_2-agonists on the course of hemoptysis remains unstudied, the balance between improved mucociliary clearance of blood affected by β_2-agonists and detrimental bronchial artery dilation should be considered.[14] Other physiochemical maneuvers can influence bronchial blood flow—cold air causes blanching of the human airway,[15] humidified air decreases bronchial blood flow compared with dry gas,[16] and increased alveolar pressure decreases bronchial blood flow by applied pressure at the capillaries.[12]

Nonbronchial Systemic Collateral Circulation

In diseases of the lung associated with inflammation, neovascularization of the lung parenchyma can occur. Although proliferation of the bronchial circulation is the most common mechanism to extend the vascular supply, an extensive network of systemic arteries may neovascularize the lung after crossing the pleural space. This most commonly occurs in diseases that produce pleural scarring, such as in aspergillomas and cystic fibrosis (CF). Anatomically these collateral vessels commonly arise from the intercostal, subclavian, axillary, and phrenic arteries. However, nonbronchial collaterals have also been described from the internal mammary, thyrocervical, carotid, and even the coronary arteries. Suspicion that these vessels may be involved is heightened by recurrence of hemoptysis after bronchial artery embolization (BAE), the presence of pleural disease, and the absence of bronchial arteries supplying an area of lung parenchyma on initial bronchial arteriography.

Pulmonary Venous Abnormalities

Bleeding from the pulmonary veins is most likely in cardiac disease such as mitral stenosis or mitral regurgitation. Focal varices of the pulmonary veins that are occasionally visualized on chest radiography, but are best identified on the venous phase of pulmonary arteriography, have been described.[17,18] More recently, massive hemoptysis owing to pulmonary vein stenosis has been reported as the result of atrial fibrillation ablation procedures.[19,20]

Causes of Hemoptysis

Bronchiectasis, tuberculosis or its sequelae, lung cancer, and aspergilloma (mycetoma) account for the largest proportion of massive hemoptysis cases. However, almost any of the many causes of hemoptysis (Box 44.1) can become massive on rare occasions. Clues to specific diagnoses are obtained by history, physical examination, chest radiography, and chest computed tomography (CT). Additionally, it is important to consider the demographics of the patient population when considering the cause of hemoptysis. For example, there is a predominance of causes related to infectious diseases (i.e., mycobacterial or parasitic) and their long-term complications in individuals from developing and impoverished countries. In contrast, malignancies and bronchiectasis are more common causes of massive hemoptysis in developed countries.

Bronchiectasis

Bronchiectasis is characterized by abnormal dilation of the bronchi with altered mucociliary clearance, persistent bacterial colonization, chronic inflammation of the bronchial mucosa, and submucosal neovascularization that predisposes to hemoptysis. Hemoptysis in bronchiectasis can present as a single life-threatening episode but is more commonly heralded by intermittent blood streaks intermixed with purulent sputum. In patients without a previous diagnosis, the evaluation can be difficult because chest radiographs can be normal or alveolar filling with blood can obscure abnormalities. Diagnosis can usually be confirmed with high-resolution chest CT. Suspicion of the diagnosis warrants broad-spectrum antibiotics to cover the multiple organisms causing infection in addition to management of the hemoptysis.

Bronchiectasis is the usual cause of massive hemoptysis in patients with CF and occurs in approximately 4.1% of patients during their lifetime.[21] It is the second leading cause of death in CF patients who have not undergone transplantation.[22] Massive hemoptysis is more common in patients older than 18 years of age and has been associated with pancreatic insufficiency, *Staphylococcus aureus* colonization, *Pseudomonas aeruginosa* colonization, reduced lung function, and diabetes.[21,23] The origin of the bleeding is most often upper lobe bronchial or systemic arteries. These patients are difficult to treat because of minimal pulmonary reserve in the majority of patients at the time of hemoptysis. Guidelines for treatment of massive hemoptysis in CF patients recommend empiric antibiotic coverage to include *S. aureus*, discontinuation of nonsteroidal antiinflammatory drugs, discontinuation of airway clearance therapies, discontinuation of aerosolized hypertonic saline solution, and use of BAE to control bleeding.[24] Although inhaled tobramycin and dornase alfa use were associated with a lower hemoptysis incidence,[21] consensus was not reached on whether to discontinue these therapies in massive hemoptysis.[24]

Tuberculosis

The resurgence of tuberculosis in many parts of the world and the prevalence of global travel mandate consideration of the disease whenever hemoptysis occurs. Hemoptysis can occur with active cavitary disease or as late sequelae of lung destruction causing bronchiectasis. Hemoptysis has also been reported in miliary

• BOX 44.1 Causes of Focal Pulmonary Hemorrhage

Iatrogenic Disorders
Bronchoscopy
Lung biopsy
Pulmonary artery catheterization
Transtracheal aspiration
Radiofrequency ablation
Brachytherapy

Infectious Disorders
Lung abscess
Mycetoma
Necrotizing pneumonia (*Staphylococcus aureus,* gram-negative aerobes, *Legionella, Actinomyces* species, *Stenotrophomonas, Kytococcus sedentarius, Leptospira* species, *Yersinia pestis, Francisella tularensis*)
Parasitic infection (paragonimiasis, amebiasis, ascariasis, clonorchiasis, echinococciasis, hookworm infestation, strongyloidiasis, trichinosis, schistosomiasis)
Parenchymal fungal infection (aspergillosis, mucormycosis, coccidioidomycosis, histoplasmosis, maduromycosis, botryomycosis)
Tuberculosis (active or inactive)
Viral tracheitis
Herpetic tracheobronchitis

Interstitial Lung Diseases
Lymphangioleiomyomatosis
Sarcoidosis
Tuberous sclerosis
Pneumoconiosis
Langerhans cell granulomatosis

Miscellaneous Disorders
Amyloidosis
Bronchogenic cyst
Broncholithiasis
Bronchopleural fistula
Thoracic endometriosis
Foreign body
Tracheopathia osteoplastica
Lipoid pneumonia
Organophosphate aspiration
Chronic pancreatitis

Neoplastic Disorders
Bronchial adenoma
Lung cancer
Tracheal tumors (mucoepidermoid, squamous cell, adenoid cystic, glomus)
Pulmonary blastoma
Pleuropulmonary angiosarcoma
Sarcoma (synovial, myofibroblastic)
Clear cell tumor
Metastatic disease (prostate, renal, breast, ovarian)
Tracheobronchial schwannoma

Pulmonary Airway Diseases
Bronchiectasis
Bronchitis
Granulomatous tracheobronchitis (ulcerative colitis, Crohn disease, Wegener granulomatosis)
Cystic fibrosis
Bullous emphysema

Traumatic Injury
Blunt chest trauma
Penetrating injury
Ruptured bronchus
Lightning injury
Thoracic splenosis

Vascular Disorders
Pulmonary embolism, infarction
Systemic cholesterol emboli
Intralobar sequestration
Pulmonary artery aneurysms
Behçet disease, Hughes-Stovin syndrome, traumatic pseudoaneurysms
Acquired arteriovenous malformations
Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
Takayasu arteritis
Aortic aneurysms
Trachea–innominate artery fistulas
Scimitar syndrome
Vena caval–bronchial
Dieulafoy disease of bronchus
Ventriculopulmonary fistulas
Hemangioma (sclerosing, cavernous, tracheal)

tuberculosis, although the mechanism is unknown. The pathologic lesion that causes hemoptysis in tuberculosis is often a Rasmussen aneurysm, a small aneurysm of the pulmonary circulation positioned within a cavity wall. Bleeding from the bronchial circulation can also complicate bronchial erosions in active tuberculosis, and study of both circulations is occasionally necessary when resection for local disease is not possible. Although all patients suspected of having hemoptysis secondary to tuberculosis should be placed in respiratory isolation, active pulmonary tuberculosis is found in only one third of such cases. Posttuberculous bronchiectasis requires antibacterial therapy.

Lung Malignancy

Lung cancer is associated with hemoptysis in 20% to 30% of cases and may be the presenting manifestation. Although the clinical course of hemoptysis is often that of chronic blood-streaked sputum, massive hemoptysis may occur with disease progression. Massive hemoptysis is most commonly associated with squamous cell type[25]; cavitation within the carcinoma[26]; and central endobronchial position, occasionally with invasion into the pulmonary arteries. The blood supply to most lung carcinomas is derived from diffuse neovascularization from the bronchial circulation, making BAE effective in some cases.

Other less common cancers can bleed when found in the lung. Kaposi sarcoma has a high incidence of bloody pleural effusions and hemoptysis. Angiosarcomas are vascular tumors that may bleed continuously from small tumor sites.[27] Choriocarcinomas may bleed profusely, particularly after initiation of chemotherapy. Metastatic disease, including renal, ovarian, and breast cancer, has rarely been associated with hemoptysis.

Massive hemoptysis may also result from interventions that treat lung malignancies. Endobronchial brachytherapy has resulted in massive, fatal hemoptysis and was found to be associated with direct contact of the brachytherapy applicator and tracheobronchial walls near great vessels.[28] Radiofrequency ablation of lung neoplasms

has been associated with massive bleeding owing to intraparenchymal hemorrhage and pulmonary artery pseudoaneurysm.[29,30] Bevacizumab, an angiogenesis inhibitor used in treatment regimens of non–small-cell lung cancer, is associated with an increased incidence and severity of hemoptysis.[31] Risk factors may include exposure to prior thoracic radiotherapy, the presence of tumor exposure in the central airway, and concomitant radiotherapy.[31] A consensus group suggested that patients with squamous histology and/or a history of hemoptysis of greater than or equal to 2.5 mL per event should not receive bevacizumab.[32]

Lung Abscess

Lung abscesses are commonly found in parenchymal areas prone to aspiration. The indolent course of these infections allows time for hypertrophy of the bronchial circulation within the walls of the abscess cavity. Additionally, these cavities may enlarge and erode into major pulmonary arteries and other thoracic vessels, including the aorta.[33] With either of these abnormalities, bleeding can be massive and recurrent. Although the abscesses are focal and amenable to surgery, the patient who chronically aspirates because of alcoholism or dementia may have other contraindications for surgery.

Chronic Bronchitis

Chronic bronchitis rarely causes massive hemoptysis, but it is a frequent cause of mild hemoptysis. The pathologic lesions responsible for bleeding are likely dilated bronchial arteries that are eroded during active inflammation of the airways. A comprehensive management approach is required to treat hemoptysis and ensure that other lesions such as lung cancer are not present.

Other Pulmonary Infections

Although hemoptysis can complicate any bacterial or fungal pneumonia, massive hemoptysis is rare unless tissue necrosis is present. Tissue necrosis is a hallmark of anaerobic, staphylococcal, and actinomycotic[34] pneumonias, but it can occur with many different bacterial causes. Septic pulmonary emboli, particularly from staphylococcal species, have a high incidence of concomitant lung cavitation. Mycotic pulmonary artery aneurysms may also be hidden within pneumonias and can be diagnosed by pulmonary arteriography or multidetector CT angiography.[35]

Hemoptysis is particularly common in fungal pneumonias that invade the vasculature. Invasive *Aspergillus* can be found in nonimmunosuppressed patients with chronic obstructive pulmonary disease[36] but is more commonly found in the persistently neutropenic patient. A characteristic radiographic pattern of cavitation and hemoptysis follows the recovery of neutrophils and should be anticipated in at-risk patients.[37,38] The use of prophylactic surgery to resect areas of infarcted lung tissue has been advocated[39] because of the high mortality rate associated with medical management of the hemoptysis. However, such surgery remains high risk. Although it is more rare, invasive pulmonary mucormycosis[40] may produce similar findings. Hemoptysis complicates primary coccidioidal infections in 15% of cases and may approach a 50% incidence in patients with chronic coccidioidal cavities. Histoplasmosis, cryptococcosis, and blastomycosis can also cause hemoptysis. Frequent and sometimes massive hemoptysis can occur with the parasitic diseases paragonimiasis,[41] echinococcosis,[42] strongyloidiasis, and ancylostomiasis.

Pulmonary Embolism

Hemoptysis occurs in approximately 30% of patients with thrombotic pulmonary emboli. Characteristically, hemoptysis is mild and requires no specific therapy. Hemoptysis usually implies some degree of pulmonary infarction with potential disruption of either vascular supply. The suspicion for pulmonary emboli is increased in the presence of risk factors for thrombosis, multicentric bleeding, and pleuritic chest pain. Paradoxically, this cause of hemoptysis must be treated with anticoagulants to prevent propagation of venous thromboemboli. The incidence of worsening hemoptysis after heparin or thrombolytics has not been documented. Nonthrombotic emboli have also been associated with hemoptysis. Septic emboli usually respond to antibiotics alone.

Aspergillus Fungus Balls

Hemoptysis occurs in more than half of patients with pulmonary *Aspergillus* fungus balls.[43] The cavity walls are richly vascularized by branches of the bronchial circulation, and enlargement of these cavities may also extend into large branches of the pulmonary artery. The mechanism of hemoptysis is likely multifactorial from secondary bacterial invasion of the fungal cavity, microinvasion of the cavity wall by *Aspergillus* (semi-invasive aspergillosis), or less commonly by truly invasive disease. Therapy of hemoptysis depends on the underlying cause for the cavitary lung disease.

Systemic antifungal therapy remains controversial because there is not a well-defined means to diagnose semi-invasive disease.[44] Intracavitary amphotericin B, however, instilled via a transthoracic catheter has proved successful at dissolution and sclerosis of the cavity with control of hemoptysis and is a viable option in patients who are poor surgical candidates.[45,46] Alternatively, antifungal therapy with ketoconazole,[47] miconazole,[48] or amphotericin B[49] has been given endobronchially for fungus ball dissolution and hemoptysis control, but these techniques are effective in less than half of patients.[50] A more recent study found better outcomes with bronchoscopic voriconazole installation resulting in significant improvement of hemoptysis in 68% of patients.[51] External radiotherapy has also been used as an adjunctive measure in nonoperable patients.[52]

Surgery remains the therapy of choice in patients with adequate pulmonary reserve owing to the recurrent nature of hemoptysis. Simple aspergilloma (no abnormality in surrounding lung) has an excellent response to surgical resection, most commonly a lobectomy. Complex aspergilloma with surrounding pleural and parenchymal involvement usually requires pneumonectomy and is associated with variable success.[53] Fungus balls complicating sarcoidosis usually occur in patients with bilateral upper lobe cavitary disease (stage IV), in which underlying lung function prohibits resection.

Cardiovascular Causes

Mitral stenosis is one of the most common cardiac abnormalities that can present with hemoptysis. The risk of hemoptysis is likely related to the elevation of pulmonary venous pressure and the rapidity with which the stenosis developed. An echocardiogram should be obtained for definitive diagnosis.

Other causes of increased pulmonary venous pressure, such as mitral regurgitation or severe congestive cardiomyopathy, may also produce hemoptysis that usually presents with radiographic pulmonary edema and a prodrome of pink frothy sputum. Fibrosing mediastinitis,[54] pulmonary veno-occlusive disease,[55] and congenital

pulmonary venous stenosis[56] are less common causes of pulmonary venous congestion.

Rarely, hemoptysis will occur from systemic venous hypertension in severe biventricular heart failure by azygous vein hypertension and dilation. Because the azygous vein drains the trachea and major bronchi, the submucosal dilated venous plexus of the trachea can be friable and produce major hemoptysis.

Interstitial Lung Disease

Only a few interstitial lung diseases are prone to hemoptysis. Lymphangioleiomyomatosis is a disease of smooth muscle proliferation around pulmonary lymphatics, airways, and vasculature. Any of the triad of hemoptysis, pneumothorax, and chylothorax should suggest the diagnosis in a woman of childbearing age.[57] The airway granulomas of sarcoidosis have also been associated with hemoptysis, although the presence of traction bronchiectasis may be a more common cause. Additionally, the erosion of calcified hilar lymph nodes into the vasculature can produce hemoptysis. Other interstitial lung diseases that cause hemoptysis usually have diffuse alveolar hemorrhage.

Broncholithiasis

Broncholithiasis is an infrequent cause of hemoptysis. The typical patient usually has an established diagnosis of mediastinal calcification from granulomatous disease. Previous infections of histoplasmosis, sarcoidosis, or tuberculosis are most common. Broncholithiasis is diagnosed by bronchoscopy when any degree of lymph node calcification is visualized in the bronchial lumen. Symptoms of cough, chest pain, airway obstruction, and hemoptysis can be seen. Lithoptysis, coughing out a broncholith, can also confirm the diagnosis.

Therapy of hemoptysis involves broncholith removal. Broncholith removal by rigid or flexible bronchoscopy is usually successful when the broncholith is free. When broncholiths are partially embedded in the airway wall, removal is best facilitated by rigid bronchoscopy[58] or by thoracic surgery. Surgical options include lymph node resection with or without bronchoplasty or lobectomy.[59]

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) most commonly presents abruptly and may or may not be associated with frank hemoptysis. The early manifestations are often confused with other alveolar filling processes such as pulmonary edema, bacterial pneumonia, or acute respiratory distress syndrome. Consideration of DAH is prompted by the presence of diffuse infiltrates on chest radiograph, the presence of systemic manifestations of vasculitis, the association of hemoptysis, hypoxemic respiratory failure, and the common finding of anemia. Unfortunately, the many causes of DAH are often differentiated on the basis of laboratory tests that may not be routine in many hospitals. Furthermore, specific therapy is often not initiated until a definitive diagnosis has been established by biopsy.

The differential diagnosis of DAH is listed in Box 44.2. Although some of these diseases have no specific therapy, establishing a diagnosis and instituting supportive care help to avoid unnecessary diagnostic and therapeutic maneuvers. Many of the vasculitides are stabilized only with aggressive immunosuppressive therapy, which would not be appropriate for infectious diseases that can present with the same features in a chest radiograph. DAH caused by infection is less common and specific etiologies vary with immunocompetency.[60]

Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL) are usually performed in a patient with unknown pulmonary infiltrates if respiratory compromise is not severe. Although often not sufficient to establish a specific diagnosis, finding a bloody lavage, hemosiderin-laden macrophages, and the lack of specific pathogens can presumptively yield a diagnosis of DAH. The diagnosis of DAH is best made by quantitation of hemosiderin in alveolar macrophages obtained by BAL. A Prussian blue stain is graded by the methods of Kahn and colleagues[61]; hemosiderin scores above 100 are virtually diagnostic of alveolar hemorrhage. Hemosiderin-laden macrophages may not appear in BAL fluid until 48 to 72 hours after acute hemorrhage, resulting in a low sensitivity for hemosiderin scores in this setting.[62]

Immunologic Lung Disease

The differential diagnosis of DAH is narrowed significantly if renal abnormalities are present. Although pulmonary-renal syndromes can often be stabilized with high-dose corticosteroids alone pending further evaluation, directed therapy depends on the measurement of specific autoantibodies and evaluation of a renal biopsy. Alveolar hemorrhage is a hallmark of anti–glomerular basement membrane antibody disease (Goodpasture disease). This disease is 75% male-predominant and follows a flulike prodrome in 30% of patients. Pulmonary hemorrhage is the initial manifestation in 90%, and an abnormal urinalysis is found in 80%. An iron deficiency anemia from sequestration of iron within pulmonary alveolar macrophages is commonly associated with the disease. The immunoglobulin (Ig) G antibodies reacting to a component of type IV collagen are found in linear deposits on the basement membrane of both alveoli and glomeruli and are circulating in 90% of cases.[63] In the appropriate clinical setting, the presence of circulating anti–glomerular basement membrane antibodies is sufficient to make a diagnosis without biopsy and institute plasmapheresis with or without plasma exchange for severe pulmonary or renal disease. After initial stabilization, corticosteroids and immunosuppressive medications usually prevent further antibody production.

Steroids alone are usually sufficient to treat alveolar hemorrhage associated with the immune complex vasculitides. These disorders are usually associated with hypocomplementemia and an elevated titer of antinuclear antibody. Systemic lupus erythematosus (SLE) is the most frequent of the immune complex disorders causing alveolar hemorrhage. SLE rarely presents with alveolar hemorrhage without other manifestations of active disease. Although the alveolar hemorrhage of SLE usually occurs from acute lupus pneumonitis, the high incidence of pneumonia, congestive heart failure, and aspiration in these patients makes a presumptive diagnosis problematic. Lupus pneumonitis usually stabilizes with a regimen of 1 to 1.5 mg/kg per day of methylprednisolone.

DAH also complicates other connective tissue diseases and systemic vasculitides with or without immune complex deposition. Mixed connective tissue disease, cryoglobulinemia, polyarteritis nodosa, progressive systemic sclerosis, rheumatoid arthritis, Behçet disease, endocarditis and tumor-related vasculitis, Schönlein-Henoch purpura, and systemic necrotizing vasculitis have all been described in association with DAH. Specific diagnosis depends on the nonpulmonary features of disease presentation.

Alveolar hemorrhage is an unusual manifestation of Wegener granulomatosis.[64] The classic triad of renal dysfunction, upper airway disease, and pulmonary infiltrates is present in less than

• BOX 44.2 Causes of Diffuse Alveolar Hemorrhage

Immunologic Diseases

Anti–glomerular basement membrane antibody disease (Goodpasture syndrome)
Vasculitides associated with circulating or in situ immune complexes
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Schönlein-Henoch purpura
- Essential mixed cryoglobulinemia
- Tumor-related vasculitis
- Endocarditis-related vasculitis
- Polyarteritis nodosa
- Systemic necrotizing vasculitis

Vasculitides associated with antineutrophil cytoplasmic antibodies
- Wegener granulomatosis
- Microscopic polyangiitis
- Idiopathic necrotizing crescentic glomerulonephritis

Rapidly progressive glomerulonephritis
Associated with other connective tissue diseases, pathophysiology unknown
- Rheumatoid arthritis
- Progressive systemic sclerosis
- Behçet disease

Associated with other renal diseases
Immunoglobulin A nephropathy
Diabetic nephropathy
Associated with precipitating antibodies to milk (Heiner syndrome)
Idiopathic pulmonary hemosiderosis
Primary antiphospholipid antibody syndrome

Chemical or Drug-Related Causes

Amiodarone
D-Penicillamine
Isocyanates
Nitrofurantoin
Retinoic acid
Trimellitic anhydride
"Crack" cocaine
Sirolimus
Everolimus
Propylthiouracil-induced vasculitis
Erlotinib
Bevacizumab
Gemcitabine
Infliximab

Transplant-Related Causes

Bone marrow transplant
Renal transplant
Lung transplant

Bleeding Diathesis

Thrombocytopenia
Leukemia with diffuse alveolar damage
Viral pneumonia
Bacterial or fungal sepsis
Radiation
Chemotherapy toxic to lung
Blast counts >80,000/μL
Extrinsic anticoagulants/thrombolytics
Warfarin overdose
Tissue plasminogen activator
Platelet glycoprotein IIb/IIIa inhibitors
Coagulopathies
Cirrhosis
Disseminated intravascular coagulation

Infections

Adenovirus
Aspergillosis (invasive)
Cytomegalovirus
Dengue
Hantavirus
Influenza
Legionella
Leptospirosis
Malaria
Mycoplasma
Staphylococcus aureus

Pulmonary Venous Hypertension

Mitral stenosis
Mitral regurgitation
Pulmonary capillary hemangiomatosis
Pulmonary veno-occlusive disease
Fibrosing mediastinitis
Congenital heart disease

Diffuse Lung Injury

Negative-pressure pulmonary hemorrhage
Breath-hold diving
Postictal neurogenic pulmonary edema

20% of patients at presentation; however, pulmonary infiltrates are present in 45%.[65] The pulmonary findings are characterized by nodules that may cavitate, lobar infiltrates that are often transient, upper airway obstruction from the granulomatous inflammation that follows airway ulceration, prominent interstitial markings with or without hilar and mediastinal adenopathy, or alveolar hemorrhage. Antineutrophil antibodies against proteinase 3 in cytoplasmic granules (c-ANCA) are found in the serum of 85% to 90% of patients with active Wegener granulomatosis and are 97% specific for the diagnosis.[66]

Among the many causes of rapidly progressive crescentic glomerulonephritis are small-vessel vasculitides such as microscopic polyangiitis that are associated with pulmonary hemorrhage in a third of patients.[67] Therapy of these vasculitides and Wegener granulomatosis usually includes corticosteroids and immunosuppressive therapy. In patients with life-threatening respiratory failure, extracorporeal membrane oxygenation has proved lifesaving in patients with ANCA-positive vasculitides and SLE awaiting onset of systemic therapy.[68,69] Use of recombinant factor VIIa has also been reported in this setting.[70,71]

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis is characterized by repetitive episodes of hemorrhage that occur without obvious precipitating factors. Open lung biopsy fails to demonstrate immune complexes, and no other organ system is affected. Therapy with corticosteroids

and occasionally cyclophosphamide has been attempted, although no controlled trials have been performed.

Immunocompromised Host

DAH is a serious complication of autologous and allogeneic bone marrow transplantation.[72] Risk factors include age younger than 40 years, the presence of underlying solid tumors, renal insufficiency, and severe mucositis. The typical presentation is characterized by onset near the time of leukocyte recovery and is heralded by high fever and diffuse pulmonary infiltrates. Typically lavage fluid appears progressively bloody over serial aliquots, and no pathogenic organisms are recovered on bacterial, fungal, or viral culture. The mortality rate has been reported to range from 80% to 100% despite aggressive supportive care[73] but may be improved with corticosteroid therapy.[74] The optimal dosage and duration of corticosteroid treatment remain controversial, but standard regimens include 1 g/day methylprednisolone administered for 3 days and thereafter tapered over 2 months.[74] The use of recombinant factor VIIa in patients with life-threatening DAH refractory to steroids has been reported.[71] More recent reports reveal a favorable prognosis in patients with early (first 30 days) versus late DAH and autologous versus allogeneic transplants with an overall mortality rate of 48%.[72]

A similar syndrome characterized by fever and pulmonary infiltrates has been noted in 5% of transplant patients, but hemoptysis is rare. Pulmonary capillaritis after lung transplant also can result in DAH. Hemoptysis is seen in up to 25% of cases, with fulminant respiratory failure seen in 18%.[75] This form of acute allograft rejection appears less responsive to corticosteroid therapy than acute lung rejection but has a more favorable response to plasmapheresis. No long-term adverse effects on allograft function are apparent.

Bleeding Diathesis

Although hemoptysis may occur with intrinsic coagulopathies, extrinsic anticoagulants and antiplatelet agents, thrombocytopenia, and fibrinolytics, patients at risk should undergo bronchoscopy to exclude other lesions such as neoplasm. Usually, the disorders of hemostasis are not in themselves solely responsible for hemoptysis, and bleeding can usually be ascribed to the combined presence of another cause, often as insignificant as an upper respiratory infection.

Leukemia patients may be particularly susceptible to DAH when chemotherapy-induced thrombocytopenia is combined with diffuse alveolar damage from other causes. Viral infections, sepsis, radiation, chemotherapy agents with pulmonary toxicity, and leukostasis from blast counts exceeding 80,000 cells/mm^3 may all produce diffuse alveolar damage in leukemia.[76] Therapy is directed toward correction of thrombocytopenia and supportive care of lung injury.

Drug-Induced Alveolar Hemorrhage

Hemoptysis owing to drug-induced alveolar hemorrhage is rare and may result from therapeutic medications, illicit drugs, and other agents. Implicated agents include crack cocaine,[77] amiodarone,[78] nitrofurantoin,[79] D-penicillamine,[80] retinoic acid,[81] propylthiouracil,[82] infliximab,[83] inhaled resins containing trimellitic anhydride,[84] and various chemotherapeutic agents.[31,85–89]

Vascular Abnormalities

Almost all blood vessels that course through the thoracic cavity have been associated with fistula formation to an airway with resultant hemoptysis. Often this occurs in the setting of endovascular infection, inflammation, congenital or acquired stenoses, aneurysms of these vessels, or chest surgery. Some of the rare vascular-to-airway fistulas that have been described include (1) carotid artery to trachea in a patient with occult laryngeal cancer[90]; (2) various abdominal arterial supplies to pulmonary sequestrations[91]; (3) syphilitic aneurysms of the ascending aorta and other thoracic arteries to pulmonary parenchyma[92]; (4) coronary artery bypass grafts to pulmonary parenchyma or bronchial artery[93,94]; (5) splenopulmonary shunt in portal hypertension following splenectomy[95]; (6) left ventricular pseudoaneurysms[96] to pulmonary parenchyma; and (7) vena caval–bronchial fistulas.[97] Several of the more common bronchovascular communications deserve comment.

Aortobronchial Fistulas

Dissecting aortic aneurysms are often of subacute or chronic duration with variable degrees of inflammation around the dissection. As an aneurysm enlarges it may cause lung compression, pleural adhesions, and dissection of blood into the pulmonary parenchyma. Particularly in situations in which an aortic graft has been previously placed, aortic graft infection may also be present. The net result is an often stuttering course of hemoptysis marked by sudden large bleeds. Therapy is surgical, although these operations are difficult in the presence of graft infections and prior operations.

Pulmonary Artery Aneurysms

Aneurysms of the pulmonary artery remain rare causes of hemoptysis.[98] Mycotic aneurysms are commonly caused by *Mycobacterium tuberculosis*, syphilis, *S. aureus*, and streptococcal species. Poststenotic dilation may occur in congenital pulmonary artery strictures. Structural vascular abnormalities such as those found in Marfan syndrome can also affect the pulmonary arteries.

Beçhet disease, characterized by oral ulcers, uveitis, arthritis, and cutaneous vasculitis, is the only common large-vessel vasculitis that affects the pulmonary arteries.[99] These multiple aneurysms may resolve with high-dose corticosteroid therapy or cyclophosphamide.[100,101]

An idiopathic syndrome characterized by fatal hemoptysis from pulmonary artery aneurysms, associated with fever and recurrent superficial and deep venous thromboembolism, was originally reported in 1959 by Hughes and Stovin.[102] Although infection and angiodysplasia have been proposed as possible causes of the aneurysms, the current consensus is that vasculitis is the primary process.[103]

Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) present with progressive hypoxemia, paradoxical emboli, or bleeding complications including hemoptysis or hemothorax.[104] Although the majority of these lesions are likely congenital telangiectasias that enlarged over years,[105] acquired AVMs have been noted after chest surgery and trauma and have been associated with actinomycosis, schistosomiasis, cirrhosis, and metastatic carcinoma.[106] The hereditary Osler-Weber-Rendu disease (OWR) is associated with hemorrhagic telangiectasias in many organ systems. Approximately 15% of OWR patients have pulmonary arteriovenous aneurysms,[107] and up to 36% of patients with a single PAVM and 57% of patients with multiple PAVMs have OWR.[108] Bronchial artery telangiectasias with bleeding[109] have also been described, although the pathogenic relationship to pulmonary artery telangiectasias remains speculative. Treatment of PAVMs, particularly if hemoptysis has developed, is to obliterate the lesion with BAE.[110]

Trauma

Hemoptysis following major trauma requires emergent thoracic surgical consultation and management. Although some cases will be simple lung contusions that manifest as a focal radiographic abnormality on chest radiograph with blood-streaked sputum present, some thoracic trauma victims with hemoptysis need early exploration. The majority of cases with hemoptysis need bronchoscopy to localize bleeding and exclude a tracheobronchial rupture, which can be clinically silent for weeks. The most common reason for emergent thoracotomy remains pulmonary hemorrhage. Pneumonorrhaphy (suture repair of the lung) is preferred for minor injuries with lobectomy and pneumonectomy performed for more severe injuries.

Lung laceration is common after penetrating pulmonary injury. However, it can also occur after blunt thoracic trauma in which sheer forces of acceleration or deceleration leave intraparenchymal lacerations involving airways or vasculature. Continued bleeding into the lung can present with rupture into the pleural space (hemothorax), intraparenchymal hematoma formation, or hemoptysis. Thoracic splenosis is a rare and remote event from the time of trauma. In this condition, splenic tissue is transported across the diaphragm after penetrating injury, where it becomes functional and vascularized within the lung. Hemoptysis may thereafter occur spontaneously.

Vascular Monitoring Catheters

Use of pulmonary artery catheters has decreased significantly and complications causing hemoptysis occur rarely. More distal and prolonged inflation of the catheter balloon can cause fatal pulmonary artery dissection, pseudoaneurysm formation, or pulmonary artery rupture.[111,112] Endovascular damage may predispose to thrombus formation and pulmonary infarction. Preventive measures include placement of the catheter at an insertion distance when full inflation is required to obtain an occlusion pressure, slowly inflating the balloon (never inflating against resistance), full inflation of the balloon to prevent the catheter tip from projecting beyond the balloon, and daily monitoring of catheter position with chest radiography.

If hemoptysis occurs with a pulmonary artery catheter in place, rapid diagnosis and treatment are required. Risk factors for pulmonary artery rupture include concomitant anticoagulation, cardiopulmonary bypass, balloon migration, hypothermia, advanced age, and pulmonary hypertension.[112] Surgical resection of the involved lobe or angiographic ablation of the involved pulmonary artery has been successful in decreasing the incidence of recurrent and often fatal hemoptysis. Other successful interventions for acute conditions have included proximal reinflation of the pulmonary artery catheter to stop blood flow to the pulmonary artery segment that is bleeding; high levels (18 mm Hg) of positive end-expiratory pressure to decrease the pulmonary artery to bronchial pressure gradient; resumption of cardiopulmonary bypass for patients in cardiac surgery; and operative banding of the pulmonary artery, which can be unclamped 48 hours later.[112,113]

Invasive Pulmonary Interventions

Increasing use of new invasive diagnostic and therapeutic pulmonary interventions can be associated with iatrogenic complications including hemoptysis. Although the incidence is low, hemoptysis has been reported with percutaneous CT-guided transthoracic lung biopsy, endoscopic lung volume reduction coil treatment, and radiofrequency ablation.[114–117]

Management

The primary principles of managing massive hemoptysis are airway and lung protection, localization of the bleeding source, and control of hemorrhage. Assessments and interventions are frequently performed empirically because the cause of hemoptysis may not be known at the time of presentation. Therapy to control minor and moderate hemoptysis can usually proceed along diagnostic paths. The inability to determine when and whether an individual patient's hemoptysis will worsen suggests that all patients with an estimated blood loss of more than 200 mL should be hospitalized in a unit in which airway support can be rapidly provided if necessary.

Massive hemoptysis should be managed within a framework of expeditious therapy to stabilize and resuscitate the patient. Fig. 44.1 is a suggested algorithm for management. A multidisciplinary collaborative approach involving intensivists, pulmonologists, interventional radiologists, and thoracic surgeons is optimal to improve outcomes.[7] The urgency and aggressiveness of management are influenced by the rate of bleeding. The study by Crocco and colleagues[6] (Table 44.1) demonstrated that the incidence of death was 71% in patients with 600 mL of hemoptysis in less than 4 hours, compared with 22% and 5% mortality rate if 600 mL of hemoptysis occurred in 4 to 16 hours and 16 to 48 hours, respectively. Sputum containers should be placed at the bedside of patients who are not intubated to allow measurement of blood loss and an estimate of the bleeding rate. High bleeding rates, hemodynamic instability, and severe oxygenation failure signal the need for rapid evaluation and treatment. A critical care setting is optimal for patients with massive hemoptysis.

In addition to the management steps outlined later, laboratory studies should be obtained, including complete blood cell count,

TABLE 44.1 Mortality Associated With Rate of Bleeding

	OPERABLE					
	Surgical Management		No Surgery		Nonoperable	
Blood Loss	No. of Patients	Deaths	No. of Patients	Deaths	No. of Patients	Deaths
600 mL in <4 h	11	4 (36%)	6	6 (100%)	11	10 (91%)
600 mL/4–16 h	10	1 (10%)	3	1 (33%)	5	2 (40%)
600 mL/16–48 h	11	1 (9%)	0	0	10	0

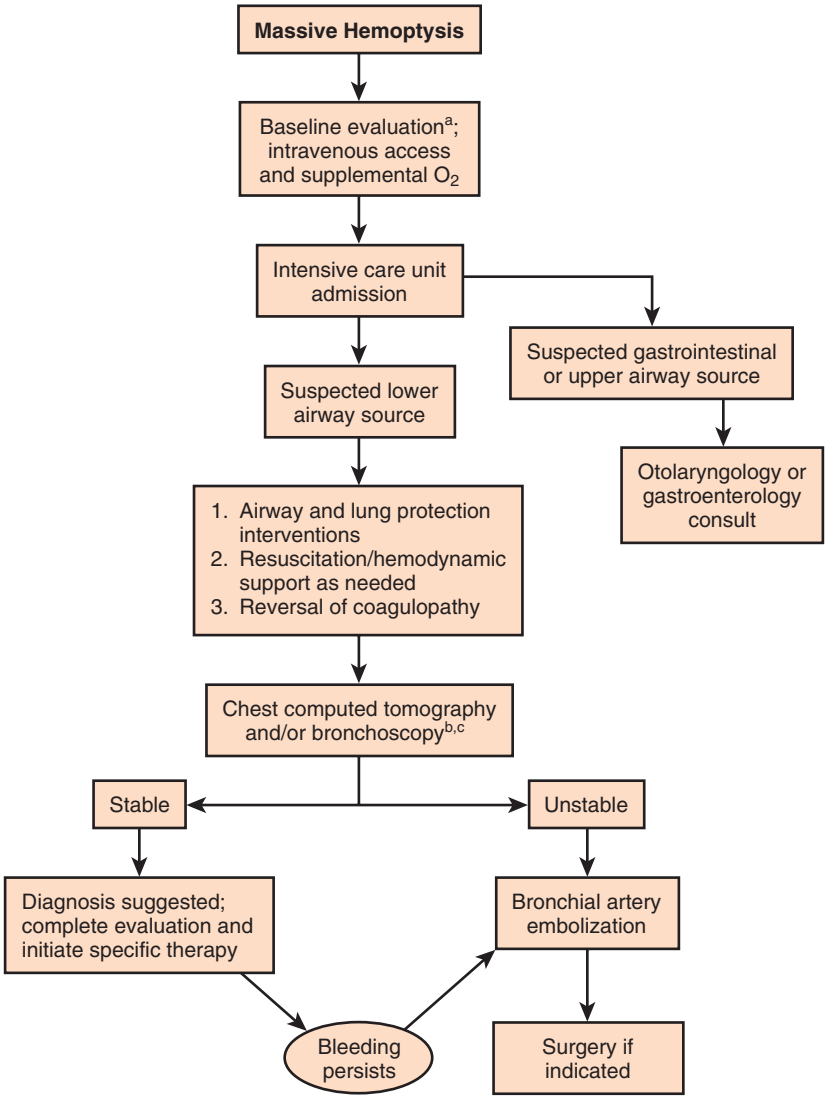

Fig. 44.1 Massive hemoptysis. [a]History and physical examination, complete blood cell count, coagulation studies, type and cross-match, chest radiograph, arterial blood gas levels. [b]Local availability and patient stability should guide choice; computed tomography is preferred in initial evaluation in stable patients. [c]Local measures, including topical vasoconstrictors, bronchial blockers, laser photocoagulation, electrocautery, and hemostatic agents, can be used endobronchially. *O_2,* Oxygen.

coagulation studies, and type and cross-match for possible blood transfusion. An arterial blood gas measurement may be needed to assess ventilation and acid-base status, although pulse oximetry is usually adequate to assess oxygenation. Additional studies may be needed to investigate possible causes of hemoptysis such as infection or vasculitis. The hemodynamic status of the patient should be evaluated and fluids or blood administered for hypotension or evidence of impaired oxygen delivery. Antibiotics may be indicated if there is suspicion of active infection.

Airway and Lung Protection

Patency of the airway and the ability to protect the airway should be assessed as soon as hemoptysis is noted. All patients should be provided with supplemental oxygen as needed to maintain adequate oxyhemoglobin saturation. Patients with mild to moderate amounts of hemoptysis usually do not require intubation, but intubation in massive hemoptysis is usually needed to facilitate diagnostic and therapeutic interventions as well as to provide support for oxygenation and ventilation. Additional steps may be needed to prevent contamination of the unaffected lung from blood and to preserve respiratory function.

Patient Positioning

If the source of bleeding is localized to one lung, the patient with massive bleeding should be positioned with the bleeding side down to keep bleeding contained to one lung. Once the airway is secured, the optimal patient position is more controversial. Clotting of blood in a dependent lung has the potential to tamponade the bleeding, yet clotted blood in the proximal airway can result

in lung collapse and atelectasis. Furthermore, if the pulmonary circulation is bleeding, it can be influenced by gravity by placing the bleeding segment higher than other areas of the chest. By converting that segment to a zone 1 condition in which alveolar pressure is higher than pulmonary artery pressure, bleeding may be decreased.

Endotracheal Intubation

Endotracheal intubation is often difficult in patients with active bleeding. Orotracheal intubation is preferred to allow use of a larger endotracheal tube (preferably 8 mm inner diameter or larger) to facilitate suctioning, ventilation, and bronchoscopy. The orotracheal route also allows for selective mainstem bronchial intubation if needed.

If the patient's physical examination, chest radiograph, and other imaging studies readily identify the bleeding lung, specific interventions to protect the airway to the normal lung can be attempted. Mechanisms to localize ventilation to one lung using a single-lumen endotracheal tube include selective intubation of one of the mainstem bronchi and selective endobronchial tamponade with a bronchial blocker (see later discussion).

Selective bronchial intubation is easiest in a patient with a bleeding left lung. Because of the leftward displacement of the carina in most individuals, an endotracheal tube advanced blindly will almost always intubate the right main bronchus. Unfortunately, the right upper lobe bronchus is so close to the carina that a right mainstem intubation may also cause right upper lobe atelectasis. The ability to ventilate and oxygenate a patient with the right lower and right middle lobes alone depends on the underlying cardiopulmonary reserve. Intubation of the left main bronchus is facilitated by placing the patient in a right lateral decubitus position to shift the mediastinum rightward. Angulation of the endotracheal tube curvature toward the left and progression of the tube over a coudé catheter may be helpful. Selective mainstem intubations can be facilitated by a bronchoscope.

Double-Lumen Endotracheal Tubes

Devices used for single-lung ventilation have also been applied to the management of hemoptysis.[118] A double-lumen endotracheal tube is an alternative to a single-lumen endotracheal tube for airway management in massive hemoptysis. Successful placement of this type of endotracheal tube requires training and experience.[119] The independent isolation of each mainstem bronchus allows for single-lung ventilation and isolation of the unaffected lung from blood contamination when bleeding is localized to one lung. The smaller suction ports of each independent lumen can cause difficulty in suctioning blood. Endobronchial evaluation requires a pediatric bronchoscope or double-lumen tube removal once bleeding has been controlled. Proximal airway masses may preclude placement of a double-lumen endotracheal tube.

Localization of Bleeding

Localization of bleeding facilitates diagnostic and therapeutic efforts regardless of the amount of hemoptysis. Because blood in the mouth can originate from the gastrointestinal tract or from diverse sites in the sinuses, nasal airway, or upper airway proximal to the larynx, an initial evaluation is needed to confirm that bleeding is from the lung. The characteristics of the expectorated blood and clinical presentation of the patient often help in differentiating hemoptysis from upper airway or gastrointestinal sources (Table 44.2). A pH assessment of the blood (low pH expected in gastric hemorrhage) and observation of expectorated sputum can be performed at the bedside.

TABLE 44.2 Features of Hemoptysis and Patient Presentation

Hemoptysis Feature	Clinical Presentation
Blood usually bright red	Often dyspneic
Portion of blood usually frothy Alkaline pH	Hypoxemia
Blood usually mixed with sputum	Preceding cough common
Alveolar macrophages may be present in sputum smear	Anemia and melena uncommon

Chest Radiograph

All patients with hemoptysis need a baseline evaluation that consists of a physical examination and chest radiograph. The chest radiograph may suggest specific diagnoses and help in localization of bleeding. However, blood filling the alveoli can obscure an underlying pathologic condition and present with bilateral infiltrates, making localization of the bleeding site problematic.

Chest Computed Tomography

The importance of chest CT in the diagnosis of acute hemoptysis and localization of bleeding has increased with advances in technology. In a series of 80 patients with massive hemoptysis, emergency high-resolution CT was not only equivalent to bronchoscopy in localizing bleeding (70% vs. 73%), but it was more efficient than bronchoscopy for identifying the cause of bleeding (77% vs. 8%).[120] High-resolution CT also allows the adequate prediction of nonbronchial systemic arterial supply, which can be the cause of bleeding in massive hemoptysis and a significant cause of recurrent bleeding after successful BAE.[121] Contrast enhancement increases the yield by identifying vascular abnormalities (i.e., thoracic aneurysm or AVMs) that would allow for more timely surgical referral.

The use of multidetector CT angiography to visualize the bronchial and nonbronchial systemic vasculature has been found to increase the number of pulmonary artery vaso-occlusions and reduce the number of urgent surgical resections compared with single-detector helical CT.[122] Multidetector CT angiography before BAE is helpful in identifying bronchial and nonbronchial systemic arteries causing hemoptysis and in determining the feasibility of BAE.[123–125]

CT modalities including multiplanar reconstruction and endobronchial simulation (i.e., virtual bronchoscopy) will likely increase the diagnostic yield of chest CT even further as these techniques become more available. Chest CT (preferably multidetector CT angiography), except in unstable patients, should therefore be performed in patients before bronchoscopy and BAE to efficiently guide management.

Bronchoscopy

Although the diagnostic yield of bronchoscopy remains low in hemoptysis owing to causes other than endobronchial carcinoma, it remains a vital tool in the management of acute massive hemoptysis in unstable patients. Localization of bleeding

can facilitate immediate interventions for hemorrhage control, including appropriate patient positioning, selective intubation, endobronchial tamponade, endobronchial infusions, laser photocoagulation, and guidance for BAE or surgical resection. However, patients with lateralizing radiography and known causation who are candidates for BAE usually do not need prior bronchoscopy unless bronchoscopic airway management is necessary.[20,126,127] This strategy can avoid delays in definitive therapy, reduce cost, and avoid the risk of airway compromise from sedation associated with bronchoscopy.

During massive hemoptysis the rigid bronchoscope has some advantages over flexible fiberoptic instruments. Ventilation is secured through the bronchoscope lumen, suctioning is not impeded, and visualization is less likely to be significantly impaired. The flexible instrument has advantages of subsegmental localization of bleeding and visualization of the upper lobes. Because the two bronchoscopes have complementary properties, they are often used together. The rigid bronchoscope is used to secure ventilation and localize the bleeding lung; the flexible scope passed through the rigid scope allows for further definition of the bleeding site and diagnosis.

Hemorrhage Control

Expectant Therapy

Cough suppression has been recommended for the majority of patients with massive hemoptysis; moderate doses of codeine are most commonly used. Although no prospective study has evaluated the efficacy of cough suppression on patient outcome, the large swings in intrathoracic pressure that occur with coughing are likely to be detrimental.

The additional factor that must be considered in cough suppression is the necessary removal of blood clots that can cause endobronchial obstruction. Particularly when a central airway lesion is responsible for bleeding, the suctioning necessary to remove blood clots may be associated with rebleeding and perpetuation of a vicious cycle. Blood clots left unsuctioned, however, may cause atelectasis, which is detrimental to patient weaning from the ventilator. Airway stabilization can usually be attained with serial bronchoscopies and suctioning. Additional techniques may be provided by interventional pulmonologists.

Endobronchial Tamponade

Acute lung bleeding may be amenable to control by endobronchial tamponade with balloon-tipped devices known as bronchial blockers.[129–132] Several types of devices are available: Fogarty vascular embolectomy catheter, a single-lumen endotracheal tube with an enclosed movable bronchial blocker, and a wire-guided bronchial blocker.[133] Regardless of the selected device, experience is required for successful placement and safe utilization.[119] The blocker is directed to the bleeding bronchus under guidance of fiberoptic bronchoscopy. By advancing the blocker to the smallest subsegment to which bleeding can be visualized, bleeding can be contained and diagnostic and a therapeutic workup can continue. Other balloon catheters can also be used for this purpose,[134] although they must be carried to the bleeding site on the outside of the bronchoscope by the bronchoscopic shuttle technique.[133] Multiple catheters can be placed if hemoptysis is multifocal and catheters can be left in place for 24 to 48 hours until bleeding is controlled.[132]

Bronchial occlusion in massive hemoptysis has also been achieved with endoscopic placement of silicone spigots.[136,137] The spigots are left in place for several days while more definitive interventions are instituted to control bleeding.

Endobronchial Agents

Although a variety of agents have been infused into the airway through the bronchoscope to control bleeding, no studies directly compare the agents with each other or with other modalities of therapy. Nevertheless, the potential advantage of these agents is their administration during bronchoscopy for the localization of bleeding. Thrombin and fibrinogen-thrombin mixtures have been used in some sites to provide a hemostatic clot in the area of bleeding, with good success.[138] Oxidized regenerated cellulose mesh, a biodegradable cellulose fabric, is an alternative procoagulant used in patients with massive hemoptysis and showed a 98% success rate in a series of 57 patients.[139] Once deployed in the area of hemorrhage, the mesh absorbs blood, swelling into a gelatinous mass that promotes tamponade and coagulation. Endobronchial sealing with *n*-butyl cyanoacrylate, a biocompatible glue with prothrombotic properties, has also been used with success in small case series.[140]

Topical vasoconstrictors, including iced saline solution, epinephrine,[141] and vasopressin or vasopressin derivatives,[142,143] have also been used effectively for airway bleeding in anecdotal reports. The likely mechanism is vasoconstriction of bronchial arteries. These may be safe, effective alternatives in patients without access to BAE or surgery, or in unstable patients in need of a temporizing intervention until definitive therapy is available.

Endobronchial use of agents affecting coagulation and fibrinolysis has also been reported. Bronchoscopically instilled factor VII has been used successfully in hemoptysis owing to DAH.[144] Tranexemic acid has been used by bronchoscopic instillation and nebulization to control bleeing.[145,146] A dry powder formulation of tranexamic acid has recently been developed.[147]

Laser Photocoagulation

The neodymium:yttrium aluminum garnet or argon plasma laser has been used successfully for airway carcinoma with persistent hemoptysis. Recognizing that carcinomatous bleeding is usually progressive and can be life threatening, aggressive photocoagulation of the endobronchial site may provide the only possibility for palliation after chemotherapy and radiation have been exhausted. Appropriate training, however, is imperative to ensure appropriate patient selection and to avoid catastrophic complications such as tracheal fire or vessel perforation.[148]

Bronchial Artery Embolization

BAE was first described in 1974 to control massive hemoptysis in the nonsurgical patient.[149] Subsequent studies on safety and efficacy have confirmed immediate, safe control of hemoptysis in 79% to 100% of a variety of patients, resulting in early use of BAE in the management strategy.[150–157] The technique for BAE localizes the bronchial arteries supplying the lobe that is bleeding. A bronchial arteriogram is performed to ensure that there is no communication to the anterior spinal artery, to determine whether a vascular pathologic condition is present, and to ensure that the bleeding area of lung parenchyma is served by the vessel. Only rarely will vascular extravasation indicative of bleeding be observed, usually in patients with massive bleeding. Angiographic signs that suggest a source of bleeding include hypertrophied/enlarged/tortuous bronchial arteries with parenchymal hypervascularity, bronchial artery aneurysms, and bronchial artery to pulmonary vein or pulmonary artery shunting.[158] The angiographic technique usually

begins with the injection of a contrast agent in the descending aorta just below the left subclavian artery to identify bronchial arteries supplying the majority of the lung and phrenic arteries supplying the lung bases. Identification of anomalous origins of the bronchial arteries may require a full arch aortogram in some patients.[159] For pathologic conditions of the lower lung, a selective phrenic artery injection is used if the entire lung is not visualized by bronchial injections. Rarely, these lower injections may demonstrate a pulmonary sequestration. For pathologic conditions of the upper lung zone, a unilateral subclavian artery injection is done to exclude nonbronchial systemic collateral arteries.

No studies have evaluated the optimal embolization material for control of hemoptysis. Gelatin sponge particles, polyvinyl alcohol particles, or liquid polymers (e.g., *n*-butyl cyanoacrylate) with a predetermined polymerization time have all been used with success.[160] Velour, polyurethane particles of varying size, metal coils, protein macroaggregates, and fibrinogen-thrombin mixtures[161] have also been instilled. Combinations of materials are used in a significant number of patients.[156,162] Liquid sclerosants, such as absolute alcohol or Gelfoam Powder (Pharmacia and Upjohn Company/Pfizer, Kalamazoo, MI), should be used with caution because they may pass into the smallest vessels at the bronchial surface, producing bronchial necrosis.[163]

Significant complications of BAE are rare when the appropriate technique is used. Chest pain, dysphagia, and fever are the most common complications. Myocardial infarction, bronchial wall necrosis, and esophageal necrosis may also rarely occur. The most devastating complication is spinal cord infarction resulting from embolization of the anterior spinal artery, which arises from the bronchial artery circulation in approximately 5% of normal patients. However, with proliferation of the bronchial artery circulation, as occurs in CF, communication to the anterior spinal artery may be found in up to 55% of cases.[164] By performing high-quality bronchial arteriograms to define vascular anatomy and avoiding the anterior spinal artery by wedging the angiography catheter distal to its takeoff (or by avoiding the vessel altogether), a safe procedure can almost always be ensured. The recent introduction of microcatheter technology (i.e., "superselective" catheterization) allows achievement of a more distal, safe catheter position and has greatly reduced the number of aborted procedures and complications arising from anterior spinal artery embolization.

Recurrent hemoptysis is common after BAE and can occur immediately, in the first several weeks to months (early), or after several years (late). Immediate recurrence of hemoptysis in the first few days after BAE may occur in approximately 10% of patients[151] and may be due to several causes. For the patient who continues to bleed during the procedure, the appropriate blood vessel usually has not been embolized. Other common causes include bleeding from nonbronchial systemic or pulmonary vessels, particularly if not evaluated initially, and lysis of the hemostatic plug in the embolized bronchial artery. Recurrence of hemoptysis in the first several months after BAE may be related to incomplete embolization, although later recurrence at 1 to 2 years may be related to neovascularization or recanalization related to inflammation or disease progression.[165] Reporting of outcomes varies considerably in BAE studies but early recurrence of bleeding may occur in 3.5% to 26% of patients.[152,154,156,166] Late recurrence of bleeding may occur in 10% to 40% of patients.[150,152,153,156,166] The incidence of recurrence is not uniform in all lung diseases, and higher recurrence rates are noted in *Aspergillus* fungus balls, bronchiectasis, tuberculosis, cavitary lung disease, and lung cancers.[9,150,155,156,165,167,168] The use of superselective embolization, which provides less of a stimulus for neovascularization, may improve recurrence rates.[169] BAE can be considered a palliative intervention for the acute cessation of massive hemoptysis that allows for a more controlled evaluation of the patient for potentially curative interventions.

Surgery

A significant question in control of massive hemoptysis is whether conservative management techniques including endobronchial tamponade and BAE are better than emergent surgery in improving outcomes. Given the high success rates of BAE and low associated morbidity and mortality rates, more conservative techniques are now considered first-line therapy over emergent surgery. The proportion of patients with massive hemoptysis who undergo emergent or urgent surgery often is not reported, but some studies found 12% to 14% of patients required surgical intervention.[157,170] Although perioperative and hospital mortality rates were high in past experience, more recent studies report a mortality rate of less than 15%.[170–174] The outcome of surgery is significantly influenced by the cause and severity of hemoptysis, patient comorbidities, extent of lung resection, and experience of the surgical team. Absolute indications for surgery do not exist, but patients with vascular disruptions (e.g., leaking aortic aneurysm, AVMs, pulmonary artery rupture, chest trauma); focal fungal disease, tuberculosis, or bronchiectasis; or failed BAE or early recurrence of bleeding after BAE should be considered for urgent surgery in the setting of massive hemoptysis.[155,168] Mycetomas, active tuberculosis, and bronchiectasis represent a large majority of the causes of hemoptysis in surgical reports.

Important issues in the assessment of a patient for thoracic surgery include the underlying cardiopulmonary reserve, precise localization of bleeding, and the focality of the patient's disease. Formal testing of lung function is not practical in the setting of massive hemoptysis, so a clinical assessment is often obtained on the basis of premorbid exercise tolerance.

Patients with fibrosis and adhesions between the lung and chest wall, commonly seen in tuberculosis, fungal disease, and bronchiectasis, have significant surgical risks because they often require pneumonectomy. Video-assisted thoracoscopic procedures may be successful in some patients.[175]

The decision regarding surgery for massive hemoptysis is a difficult one that often must be made rapidly, without all desired clinical information available. The availability of BAE and endobronchial tamponade may provide time for a reasoned decision to be made regarding surgery in all but the most rapidly bleeding patients.

Other Therapies

As new devices and interventions are developed for the management of other pulmonary and nonpulmonary conditions, some may be adapted to treat massive hemoptysis. Covered self-expanding stents have been used to occlude a bleeding site in a patient not treatable by BAE or surgery.[176,177] Recombinant activated factor VII has been used systemically to control hemoptysis in DAH[70,71,178] and focal bleeding associated with community-acquired pneumonia,[179] thoracic trauma,[180] and CF.[181] Recombinant activated factor VII is not approved for use in hemoptysis and can be associated with increased thrombosis. A pilot study of systemic tranexamic acid found a nonsignificant decrease in the severity of hemoptysis, but a recent review found insufficient evidence to determine if systemic tranexamic acid use is warranted.[182,183]

Key Points

- The adverse clinical effects of hemoptysis, such as impaired gas exchange, airway obstruction, and hypotension, are relevant for defining a life-threatening condition.
- Bleeding from the higher-pressure bronchial circulation (rather than the pulmonary circulation) causes almost 90% of the cases of massive hemoptysis.
- Massive hemoptysis is more common with bronchiectasis, tuberculosis or its sequelae, lung cancer, and aspergilloma than with chronic bronchitis, pneumonia, and pulmonary emboli.
- DAH should be considered a potential cause of hemoptysis in the presence of diffuse infiltrates on chest radiograph, systemic manifestations of vasculitis, hypoxemic respiratory failure, and anemia.
- The primary principles of managing massive hemoptysis are airway and lung protection, localization of the bleeding source, and control of hemorrhage.
- A multidisciplinary collaborative and organized approach to managing massive hemoptysis is needed to improve outcomes.
- Orotracheal intubation with a larger endotracheal tube (preferably 8-mm inner diameter or larger) is preferred for airway protection in massive hemoptysis to facilitate suctioning, ventilation, and bronchoscopy.
- Chest CT (preferably multidetector CT angiography), except in unstable patients, should be performed in many patients before bronchoscopy and BAE to efficiently guide management.
- BAE is a safe and effective technique to control bleeding in massive hemoptysis and should be used as the initial therapeutic modality in most patients.
- Patients with vascular disease; focal fungal disease, tuberculosis, or bronchiectasis; or failed BAE or early recurrence of bleeding after BAE should be considered for urgent surgery of massive hemoptysis if they have sufficient cardiopulmonary reserve.

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Review Questions

1. Which of the following patients with recurrent massive hemoptysis after bronchial artery embolization would be the best candidate for surgical intervention?
   - **a.** A 68-year-old with chronic obstructive lung disease and hemoptysis owing to squamous cell lung cancer
   - **b.** A 21-year-old with severe cystic fibrosis and hemoptysis owing to bronchiectasis
   - **c.** A 65-year-old with chronic lymphocytic leukemia and hemoptysis owing to right upper lobe aspergilloma
   - **d.** 35-year-old bone marrow transplant patient with hemoptysis owing to diffuse alveolar hemorrhage

   Answer: c. Surgical intervention for massive hemoptysis is usually considered when bleeding recurs after bronchial artery embolization. Important issues in considering whether a patient is a candidate for surgery include the underlying cardiopulmonary reserve, precise localization of bleeding, and the focality of the patient's disease. Patient c is the best candidate for surgery owing to the focality of the disease causing hemoptysis. Patient a is unlikely to have sufficient pulmonary reserve to survive lung resection as is patient b with diffuse fibrotic and bronchiectatic lung disease. Patient d is not a good candidate owing to the diffuse nature of the hemorrhage.
2. A 54-year-old patient with prior treated tuberculosis presents with massive hemoptysis and is admitted to the intensive care unit (ICU) for management. Vital signs on admission are heart rate 110 beats/min, respiratory rate 28 breaths/min, blood pressure 108/54 mm Hg, and oxygen saturation by pulse oximetry is 90% on room air. The patient is intubated on arrival to the ICU. The chest radiograph shows a cavitary lesion in the right upper lobe and fibrotic changes of the right upper lobe. High-resolution computed tomography (CT) scan confirms the same findings. Which of the following is the next best intervention?
   - **a.** Bronchial artery embolization
   - **b.** Flexible fiberoptic bronchoscopy with iced saline solution lavage
   - **c.** Flexible fiberoptic bronchoscopy with placement of a bronchial blocker
   - **d.** Replace endotracheal tube with a double-lumen endotracheal tube

   Answer: a. This patient has only mild hemodynamic abnormalities and a focus for bleeding identified on CT scan which allows for immediate bronchial artery embolization (BAE). BAE is safe and effective and offers rapid control of bleeding. Bronchoscopy may delay definitive therapy if undertaken in this type of patient. Bronchoscopic interventions, such as iced saline solution lavage and placement of a bronchial blocker, are only temporizing measures and the patient would still require more definitive intervention to stop the hemorrhage. Similarly, placement of a double-lumen tube may allow for isolation of the bleeding lung but would not control bleeding.
3. Which of the following is the most common complication of bronchial artery embolization?
   - **a.** Myocardial ischemia
   - **b.** Spinal cord infarction
   - **c.** Bronchial wall necrosis
   - **d.** Fever

   Answer: d. Chest pain, dysphagia, and fever are the most common complications following bronchial artery embolization. Myocardial ischemia, bronchial wall necrosis, or esophageal necrosis is rare. The most devastating complication is spinal cord infarction owing to embolization of the anterior spinal artery, but high-quality bronchial arteriograms and superselective techniques make this complication rare today.

45

Pneumothorax and Barotrauma

ROBERT C. HYZY AND ROMMEL SAGANA

CHAPTER OUTLINE

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Complications Related to Management

Definition and History

Pneumothorax is defined as air in the pleural space because of a break in the visceral or parietal pleura. The term *pneumothorax* was used for the first time in 1803.[1] Laennec[2] gave the first clinical description of pneumothorax in 1819; however, the first chest radiograph demonstrating this entity was not published until 1901.[3] Definitive therapy became available with the advent of tube thoracostomy in 1876.[4] It was thought to be always associated with tuberculosis until 1932 when "spontaneous pneumothorax in the apparently healthy" was first described.[5]

Spontaneous pneumothorax can be classified as primary or secondary. Primary spontaneous pneumothorax (PSP) occurs in patients with no apparent underlying lung disease. Secondary spontaneous pneumothorax (SSP) occurs in association with a known underlying lung disease such as chronic obstructive pulmonary disease (COPD).[6] Nonspontaneous causes of pneumothorax include traumatic and iatrogenic (Table 45.1).

Incidence

The incidence of PSP in men varies geographically from 7.4 per 100,000 population per year in the United States to 37 per 100,000 population per year in the United Kingdom. In women, the incidence is substantially less, ranging from 1.2 per 100,000 population per year in the United States to 15.4 per 100,000 population per year in the United Kingdom.[7] The reason for these differences is not known. In a study that evaluated 1199 patients with pneumothorax that included 865 male patients and 334 female patients, 60.3% of the pneumothoraces were spontaneous, 33.6% were traumatic, and 6.1% were iatrogenic.[8]

The estimates of the incidence of recurrent PSP range from 20% to more than 50% with most recurrences within the first year.[9]

Pathophysiology

Emphysema-Like Changes

PSP occurs in patients with no previously known lung disease. It is important to note, however, that this does not mean there is no underlying pathologic process. A finding of abnormal pleura is very common in PSP if looked for carefully.[10] Abnormalities seen in PSP are summarized in Table 45.2 and include blebs and bullae, which are otherwise known as emphysema-like changes (ELCs). These areas of weakness of the visceral pleura are prone to rupture, allowing air to leak into the pleural space. Abnormalities can be visualized radiographically with high-resolution computed tomography (CT) scans and macroscopically at thoracoscopy.[10,11] High-resolution CT imaging reveals these defects in approximately 80% of PSP with PSP. The literature is mixed as to whether the presence of or extent of ELCs is directly related to the risk of recurrence. Some case series suggest that there is no association,[12,13] although others suggest the presence of contralateral blebs/bullae is a risk factor for future pneumothorax.[14,15] The only clear conclusion that can be drawn is that there is a direct association between the presence of ELCs and the occurrence (but not necessarily recurrence) of a pneumothorax (Table 45.2 and Fig. 45.1).

TABLE 45.1 Classification of Pneumothorax

Type	Etiology
Primary spontaneous pneumothorax	No underlying lung disease (but blebs/bullae commonly present)
Secondary spontaneous pneumothorax	Associated with underlying lung disease (e.g., chronic obstructive pulmonary disease, cystic fibrosis, AIDS with emphysema)
Traumatic iatrogenic pneumothorax	Related to trauma to the thorax Secondary to transthoracic or transbronchial lung biopsy (10% risk), central venous catheterization, supraclavicular nerve block

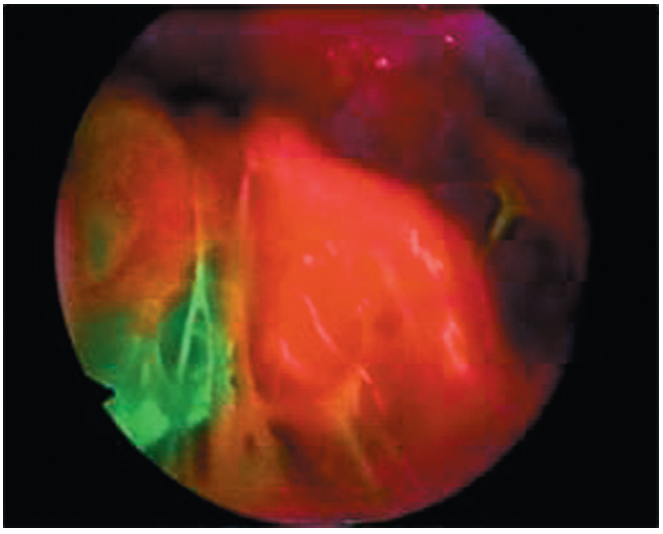
From Grundy S, Bentley A, Tschopp JM. Primary spontaneous pneumothorax: a diffuse disease of the pleura. *Respiration.* 2012;83:185–189.

TABLE 45.2 Pathologic Changes Associated With Primary Spontaneous Pneumothorax

Pathologic Abnormality	Description
ELCs (i.e., blebs/bullae)	Macroscopically visible areas of weakness on visceral pleura Occasionally seen to be the site of air leak Present in approximately 80% of cases Often bilateral
Fluorescein enhancement	Represents areas of pleural/subpleural abnormality not visible with white light autofluorescence Often present at sites distinct from ELC in lungs of patients with PSP and not in those of control subjects Provides evidence of diffuse pleural porosity
Distal airway inflammation	Inflammatory infiltration with lymphocytes and macrophages within walls of bronchioles Associated fibrotic changes and compensatory emphysema

ELCs, Emphysema-like changes; *PSP,* primary spontaneous pneumothorax.
From Grundy S, Bentley A, Tschopp JM. Primary spontaneous pneumothorax: a diffuse disease of the pleura. *Respiration.* 2012;83:185–189.

• **Fig. 45.1** Large bulla at the apex of the left lung in a 12-year-old boy with recurrent primary spontaneous pneumothorax. (From Noppen M, De Keukelieire T. Pneumothorax. *Respiration.* 2008;76:121–127.)



• **Fig. 45.2** Air leak identified by fluorescein-enhanced autofluorescence thoracoscopy in a 27-year-old man with recurrent primary spontaneous pneumothorax. The air leak was situated at the base of a highly vascularized, severe malformation of the apex of the lung. (From Noppen M, De Keukelieire T. Pneumothorax. *Respiration.* 2008;76:121–127.)

Pleural Porosity

ELCs are not the sole cause of PSP. Air leak has been described in areas where no ELCs are seen, leading to the concept known as "pleural porosity."[16,17] When evaluated with fluorescein-enhanced autofluorescence, areas of high-grade abnormality in the visceral pleura were frequently visualized separate from any area of abnormality seen with white light at thoracoscopy in patients with PSP. High-grade abnormalities were not seen in control patients.[18] Areas of fluorescein leak (i.e., areas of potential air leak) were visualized in only a small proportion of PSP, but these areas were noted to be distinct from areas of ELC. When studied with electron microscopy, the linings of some resected areas of ELC have been shown to be almost completely absent of mesothelial cells and have abnormal pores present[19] (Fig. 45.2).

Distal Airway Inflammation

Pathologic findings suggest an inflammatory cause to the formation of ELCs. Chronic distal airway inflammation with lymphocyte and macrophage infiltration alongside fibrotic changes and compensatory emphysema can be seen microscopically in areas of lung tissue from patients with PSP.[20] In a different study, the presence of respiratory bronchiolitis (RB) was seen in close to 90% of patients with PSP who underwent surgical resection in a different study.[21] However, all these patients in this study were smokers, and smoking is a recognized cause of RB. It has been proposed

that distal airway inflammation associated with PSP leads to obstructive gas trapping and consequent increases in distal airway pressure, which possibly causes air leak into the pleural space.[22]

Smoking

Cigarette smoking is a significant risk factor for PSP. It is thought to be due to the consequences of airway inflammation leading to airway obstruction with a check valve phenomenon, causing air trapping and development of pneumothorax.[22] The lifetime risk is 12% in smokers compared with 0.1% in nonsmokers. Risk is also directly related to the amount of cigarette smoking. Compared with nonsmokers, the relative risk of PSP in men was seven times higher in light smokers (1–12 cigarettes per day), 21 times higher in moderate smokers (13–22 cigarettes per day), and 102 times higher in heavy smokers (>22 cigarettes per day). For women, the relative risk was 4, 14, and 68 times higher in light, moderate, and heavy smokers, respectively.[23] Cessation of smoking appears to reduce the risk of recurrence,[9] and continued smoking increases the risk of recurrence.[24]

RB, a form of airway inflammation associated with cigarette smoking, may contribute to the development and recurrence of PSP. In a study with 115 patients with PSP who underwent video-assisted thoracoscopic surgery (VATS), pneumothorax recurrence rates were higher in patients with extensive rather than nonextensive RB for both nonoperative and postoperative pneumothorax.[25]

Genetics

Familial inheritance of pneumothorax describing the clustering of PSP in certain families has been published. Autosomal dominant, autosomal recessive, polygenic, and X-linked recessive inheritance mechanisms have been proposed.[26–28] Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant cancer disorder that predisposes patients to benign skin tumors and renal cancer. It is associated with pleuropulmonary blebs and cysts that lead to PSP.[29] In one study of 198 patients with this syndrome, 48 patients (24%) had a history of pneumothorax.[30] The gene responsible for this familial cancer syndrome *(FLCN)* has been mapped to chromosome 17p11.2.[31,32] Other mutations of *FLCN* have been associated with spontaneous pneumothorax and bullous lung disease in the absence of Birt-Hogg-Dubé syndrome.[33]

Patients with Marfan syndrome are tall, and pneumothorax is a common pulmonary complication. Marfan syndrome is caused by the mutation in *FBN1* gene on chromosome 15. This gene is responsible for the formation of 10- to 12-nm microfibrils in the extracellular matrix of connective tissue. It is hypothesized that familial spontaneous pneumothorax is caused by a connective tissue disorder that exhibits mendelian inheritance and *FBN1* has been postulated as the causative gene.[34]

Classification

Spontaneous Pneumothorax

Primary Spontaneous Pneumothorax

PSP is classically seen in previously healthy young men with an asthenic body habitus. The incidence of PSP rises with increasing height among adults of both sexes, more so in men. For those 76 inches or taller, the rate was 200 per 100,000 person-years.[35] It is hypothesized that individuals with tall stature and low body mass index combined with smoking are predisposed to develop ELCs owing to the pressure gradient between the lung base and the apex, resulting in increased alveolar distending pressures at the apex.[36] Smoking, as previously described, greatly increases the risk of PSP. Smoking increases the relative risk of developing spontaneous pneumothorax about 9-fold in women and 22-fold in men, and there is a statistically significant dose-response relationship between smoking and spontaneous pneumothorax.[37]

• BOX 45.1 Frequent and/or Typical Causes of Primary Spontaneous Pneumothorax

- Airway disease
  - Emphysema
  - Cystic fibrosis
  - Severe asthma
- Infectious lung disease
  - *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia
  - Tuberculosis
  - Necrotizing pneumonia
- Interstitial lung disease
  - Idiopathic pulmonary fibrosis
  - Sarcoidosis
  - Histiocytosis X (Langerhans cell histiocytosis)
  - Lymphangioleiomyomatosis
- Connective tissue disease
  - Rheumatoid arthritis, scleroderma, ankylosing spondylitis
  - Marfan syndrome
  - Ehlers-Danlos syndrome
- Malignant disease
  - Lung cancer
  - Sarcoma

From Noppen M, De Keukelieire T. Pneumothorax. Respiration. *2008;76:121–127.*

Secondary Spontaneous Pneumothorax

SSP has been described in a large variety of diseases, including COPD with emphysema, cystic fibrosis (CF), tuberculosis, lung cancer, human immunodeficiency virus (HIV)-associated *Pneumocystis jiroveci* pneumonia, followed by more rare but "typical" disorders such as lymphangioleiomyomatosis and histiocytosis X (Box 45.1). Because lung function in these patients is already compromised, SSP often presents as a potentially life-threatening disease requiring immediate action, as opposed to PSP, which is more of a nuisance than a dangerous condition. The general incidence is almost similar to that of PSP.[38]

Chronic Obstructive Pulmonary Disease

COPD is the most common cause of SSP, with nearly 70% of SSP attributed to COPD.[39] The peak incidence of SSP from COPD typically occurs later in life, averaging 60 to 65 years of age.[40] The clinical presentation of pneumothorax in COPD is often atypical—pain may be absent, anxiety and breathlessness may predominate and be out of proportion to the collapsed lung, and the classic sign of hyperresonance may not be helpful because of the underlying emphysema. The air leak in these patients is usually large, and the tissues are slow to heal, so it is weeks before the tubes can be removed.[41]

Pneumothorax in Drug Abusers

When the peripheral veins of chronic abusers of drugs become obliterated because of a sclerotic or infectious process, the individual

may attempt to use larger veins in the groin or neck. Attempted subclavian or supraclavicular ("pocket shot") injection of drugs in the street setting has led to unilateral or bilateral pneumothoraces.[42–44] Douglas and Levison[45] found that the incidence of pneumothoraces is equal in both sexes and that it is less of a problem in teenagers and in addicts older than 40 years of age. It was also noted that although most drug users describe using small (21- or 22-gauge) needles, a large, complete, or tension pneumothorax usually develops.

Pneumothorax in HIV-Infected Patients

Pneumothorax is an uncommon but potentially fatal complication of HIV infection. The first report of spontaneous pneumothorax in patients with AIDS was in 1984.[46] With the diagnosis of AIDS, a patient's risk of sustaining a nontraumatic pneumothorax increases to 450 times that of the general population.[47] It has since been described in a generalized HIV-infected population.[48,49] Pneumothorax complicated 1.2% of all hospital admissions in a cohort of 599 HIV-infected patients with follow-up over 3 years in a prospective observational study. There was also an associated increase in in-hospital mortality rate (31% vs. 6%) for patients without pneumothorax.[48]

A high incidence (2%–9%) of pneumothorax has been reported in patients with AIDS and *Pneumocystis carinii* pneumonia (PCP).[50–52] *P. carinii,* which was thought to be a protozoan, has been renamed as *Pneumocystis jiroveci* and is now classified as an archiascomycetous fungus.[53] Causes of pneumothorax in HIV-infected individuals include *P. jiroveci*[54–57] along with other infectious agents such as *Mycobacterium tuberculosis, Mycobacterium avium intracellulare,* pulmonary cytomegalovirus, *Pneumococcus* organisms,[54] or pulmonary toxoplasmosis.[54] Pneumothorax has also been described in HIV-infected individuals from Kaposi sarcoma.[58]

The cause of pneumothorax in patients with PCP is unclear. Several investigators believe that extensive tissue invasion within the alveolar interstitium in severe PCP is an important factor in causing necrosis and subsequent pneumothorax. Several observations highlight this point. The most common sites of tissue invasion with PCP are the alveolar septa, pleurae, and vasculature.[59] Tissue invasion could cause necrosis as a result of direct tissue injury by toxins from *Pneumocystis,*[59] infarction from vascular compromise,[60,61] or as a result of the host inflammatory response.[62]

The administration of aerosolized pentamidine has been implicated in the pathogenesis of cavitation, cyst formation, and pneumothorax,[50,63,64] but the biologic basis for this relationship is unknown. No direct toxic action of pentamidine on the lungs has been described, so an indirect effect may be present. Cavitation owing to PCP may occur primarily in the upper lobes and periphery because aerosolized pentamidine is preferentially delivered to the proximal parenchyma of the lower lobes. Inadequate deposition of pentamidine in the periphery of the lung could allow a chronic, low-grade infection with *Pneumocystis* to persist, leading to peripheral lung destruction and pneumatocele formation. Increased survival time of patients with AIDS owing to prophylaxis could allow for development of these lesions.[50]

Several other risk factors for AIDS-related pneumothorax have been identified. In addition to previous or active infection of *P. jiroveci* and aerosolized pentamidine, cigarette smoking and the presence of pneumatoceles on chest radiograph are risk factors.[65] The association between cigarette smoking and AIDS-related pneumothorax could be explained by subclinical obstructive disease preventing adequate deposition of aerosolized pentamidine in the lung periphery, resulting in subpleural *Pneumocystis* infection.[65] Pulmonary tuberculosis also appears to increase the risk of pneumothorax in AIDS.[66]

Catamenial Pneumothorax

In most cases, catamenial pneumothorax is related to pelvic or thoracic endometriosis.[67,68] Catamenial pneumothorax occurs typically within 24 to 72 hours after onset of menstruation. It is often recurrent and more common than previously thought. Two mechanisms have been described for pneumothorax related to endometriosis. The most common is the movement of endometrial implants to the diaphragm, preferentially to the right side because of the recognized peritoneal circulation up from the pelvis to the right side. These implants then create channels or "holes" through the diaphragm that allow the implants or air to move into the chest. The second and much less frequent cause of endometrial implants causing pneumothorax in the chest is through the venous implants that lodge into the lung itself.[69] Clinical manifestations of thoracic endometriosis include chest pain, dyspnea, and hemoptysis. Treatment for the prevention of recurrence is indicated after a first episode of catamenial pneumothorax because recurrences are frequent.[38]

Cystic Fibrosis

SSP occurs in approximately 6% of all patients with CF and this number increases to 16% to 20% among those who survive to 18 years of age.[70,71] SSP from CF is usually due to rupture of apical subpleural cysts. The risk of pneumothorax is inversely proportional to the forced expiratory volume in 1 second (FEV_1). Other factors associated with an increased risk of pneumothorax include infection with *Pseudomonas aeruginosa, Burkholderia cepacia* complex, or *Aspergillus* spp. A previous history of massive hemoptysis also increases risk.

Nonspontaneous Pneumothorax

Traumatic Pneumothorax

Pneumothorax ranks second to rib fractures as the most common sign of chest trauma. It occurs in up to 50% of chest trauma victims.[72] Most pneumothoraces are caused by a penetrating injury, but closed chest trauma causing alveolar rupture from thoracic compression, fracture of a bronchus, and esophageal rupture have also been reported.[73,74] Traumatic pneumothorax can be classified as open, closed, tension, or hemopneumothorax. A tension pneumothorax should be managed immediately by decompression with a large-bore needle, usually in the second anterior interspace in the midclavicular line. Open pneumothorax should have a moist sterile gauze pack placed over the open wound, followed by a chest tube. Hemopneumothorax (20% of trauma patients) requires insertion of a large-bore (28F–36F) chest tube.[38]

Occult pneumothorax may be present in half of patients with blunt abdominal trauma, and in many patients the pneumothorax is undetected by chest radiograph.[75–79] CT of the chest should therefore always be performed in these patients. Most surgeons and emergency physicians will place a chest tube in occult and nonoccult pneumothoraces. Studies suggest, however, that clinically stable patients and those who do not have an enlarging pneumothorax may be treated conservatively, ultimately requiring chest tube placement in about 10% of cases.[80]

Traumatic Iatrogenic Pneumothorax

Iatrogenic pneumothorax occurs most often after transthoracic needle biopsy (24%), subclavian vein catheterization (22%),

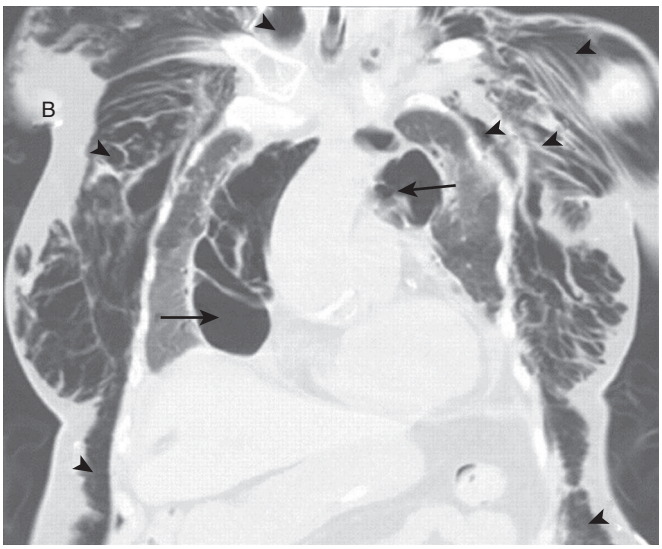
thoracentesis (20%), transbronchial lung biopsy (10%), pleural biopsy (8%), and positive-pressure ventilation (7%).[81] Diagnosis of iatrogenic pneumothorax is often delayed. Small and asymptomatic iatrogenic pneumothoraces, however, often do not need any treatment and resolve spontaneously. In larger or symptomatic pneumothoraces, simple manual aspiration or placement of a small catheter or chest tube attached to a Heimlich valve is usually sufficient.[82] Larger tubes may be necessary in patients with emphysema or when mechanical ventilation begins.

Pulmonary Barotrauma During Mechanical Ventilation

Pulmonary barotrauma (PBT) refers to alveolar rupture owing to elevated transalveolar pressure (the alveolar pressure minus the pressure in the adjacent interstitial space). PBT was previously estimated to range between 3.8% and 41.7% of patients undergoing mechanical ventilation.[83] The rate in actuality may be lower because low tidal volume ventilation is becoming more common. Consequences of barotrauma include pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema.

Positive-pressure ventilation increases transalveolar pressure, which can cause alveolar rupture.[84] Alveolar rupture allows air from the alveolus to enter the pulmonary interstitium where it can dissect along the perivascular sheaths toward the mediastinum. This can lead to pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema[85,86] (Fig. 45.3). Bronchopleural fistula, tension pneumothorax, tension lung cyst, and subpleural air cyst have also been reported but are less common.[87]

In a multicenter prospective cohort study of 5183 mechanically ventilated patients, the incidence of PBT was 3%.[88] Asthma, chronic interstitial lung disease, and acute respiratory distress syndrome (ARDS) were identified as independent risk factors for barotrauma. Other studies have also demonstrated that acute lung injury and ARDS are independent risk factors for PBT.[89,90] Elevated peak and plateau pressures have been identified as risk factors.[91,92]



• **Fig. 45.3** Chest computed tomography revealing extensive subcutaneous emphysema *(arrowheads)* from the lower neck to the upper abdomen and pneumomediastinum *(arrows).* (From Lai JI, Po-Chou L, Wang WS, et al. Barotrauma related extensive pneumothorax, pneumomediastinum, and subcutaneous emphysema in a patient with acute respiratory distress syndrome with low tidal volume. *Postgrad Med J.* 2010;86:567–568.)

Neither open lung strategies using high levels of positive end-expiratory pressure (PEEP) nor recruitment maneuvers have been shown to increase the risk of barotrauma.[93,94]

Clinical Presentation

The clinical presentation of PBT can vary. With pneumothorax, patients may complain of dyspnea or chest pain. Physical findings can include tachycardia, tachypnea, hypertension, or oxyhemoglobin saturation accompanied by unilateral reduction of breath sounds. If a tension pneumothorax develops, there may be hypotension and tracheal deviation. As a general rule, in young male patients with a history of asthma, drug use, forceful cough, or intense physical activity who present with dyspnea, chest pain, and/or subcutaneous cervical emphysema, a high suspicion of spontaneous pneumomediastinum should be entertained until proved otherwise.[95] Patients with pneumomediastinum may complain of dyspnea and chest or neck pain. Other findings include tachycardia, tachypnea, and hypertension. A crunching sound may be heard during auscultation. Rarely, hypotension from decreased venous return and cardiac output may occur if tension pneumomediastinum develops.[96] Pneumoperitoneum may manifest itself as abdominal pain. Other physical findings include abdominal distention, tenderness, and tympany. Rarely, abdominal compartment syndrome may develop if the pneumoperitoneum progresses to a tension pneumoperitoneum.[97] Subcutaneous emphysema generally presents as painless soft tissue swelling. It typically appears in the upper chest, neck, and face. Compression of the affected areas can reveal crepitus. A rare consequence of severe subcutaneous emphysema is compartment syndrome.[98]

Diagnosis

The diagnosis of pneumothorax is suspected when a patient presents with the symptoms and signs described earlier and then confirmed with a portable chest radiograph. An upright chest radiograph has the highest diagnostic yield for pneumothorax, although diagnosis in the intensive care unit (ICU) may be difficult as most patients are semirecumbent or supine.[99] The difficulty in detection of a pneumothorax in a supine position in the ICU or after trauma is due to several factors. There are limitations in patient mobilization and positioning owing to overlying support apparatus and patient body habitus. Limitations in technique with portable chest x-rays often cause underexposed or overexposed images. The distribution of free air in the pleural space is highly variable and dependent on the patient's position, anatomy, and associated pathology in the lung parenchyma and pleural space. The imaging findings of pneumothorax in the supine position are frequently subtle, requiring expertise and a heightened degree of suspicion.[100]

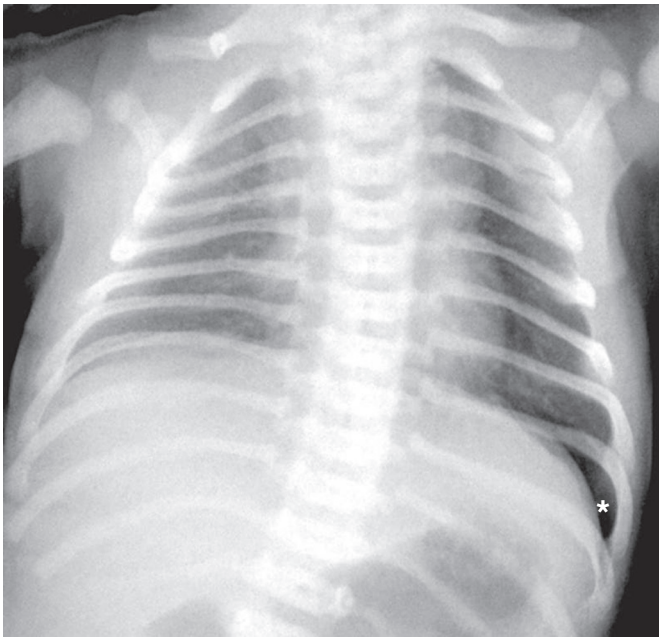
In a fully upright chest radiograph, a pneumothorax appears as a radiolucent collection between the visceral and parietal pleurae in the superior portion of the chest. In contrast, when a patient is supine, free air collects in the anterior chest, displacing the costophrenic angle inferiorly, often creating a "deep sulcus" sign. The deep sulcus sign refers to a unilateral increase in the apparent size of the costophrenic angle (Fig. 45.4).

Bedside ultrasound is being used more readily in the ICU to rapidly diagnose pneumothorax. Using the M-mode, the absence of "lung sliding" is indicative of the presence of a pneumothorax.[101]

Meta-analysis of studies using ultrasound to diagnose pneumothoraces has shown that the sensitivity and specificity of ultrasound in detecting pneumothorax are approximately 88% to 91% and 98% to 99%, respectively. These studies evaluated the use of ultrasound in diagnosing pneumothorax in critically ill and trauma patients.[102]

Tension pneumothorax is diagnosed clinically when a patient presents with unilateral absence of breath sounds, a shift of the trachea in the direction away from the absent breath sounds, and hemodynamic compromise in the appropriate setting. Immediate intervention is indicated as there is seldom time for a radiographic evaluation. Rapid clinical improvement after empiric aspiration of a suspected tension pneumothorax is diagnostically definitive. Subsequently, a tube thoracostomy is placed for ongoing management.

Pneumomediastinum frequently coexists with pneumothorax. It is usually diagnosed with a portable chest radiograph. It typically appears as radiolucent streaks in the mediastinum (Fig. 45.5).



• **Fig. 45.4** Supine chest radiograph of a neonate illustrates the deep sulcus sign with abnormal deepening and lucency of the left lateral costophrenic angle *(asterisk)*. (From Kong A. The deep sulcus sign. *Radiology.* 2003;228:415–416.)

Pneumoperitoneum is diagnosed with a chest radiograph less than one-third of the time. A suspected pneumoperitoneum is best evaluated by chest CT.[103] The patient should remain in position for 5 to 10 minutes before the radiograph is taken. This allows time for air to collect in a sufficient volume to be detected radiographically. Pneumoperitoneum may be identified on a supine abdominal radiograph (see Fig. 45.5). Free air accumulates anteriorly when the patient is supine and on a chest or abdominal radiograph may present in several ways. Gas appearing on both sides of the bowel wall is referred to as Rigler sign. Gas outlining the peritoneal cavity is known as the football sign. Gas outlining the medial umbilical folds is called an inverted V sign. Gas may also outline the falciform ligament or localize in the right upper quadrant.[104]

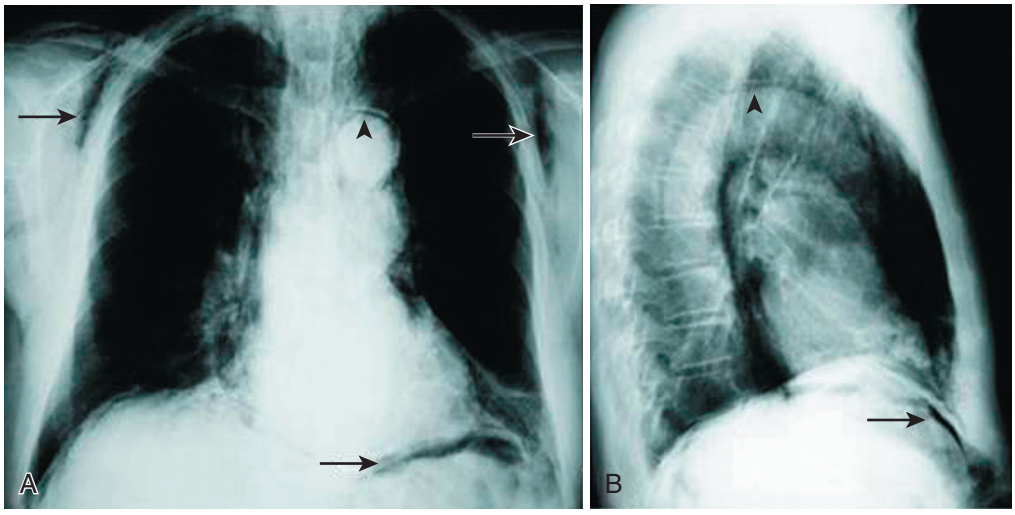
Subcutaneous emphysema is often found by identifying crepitus during physical examination. On chest radiograph of areas of tissue swelling, it can appear as radiolucent streaks throughout the subcutaneous tissue and muscle (see Fig. 45.5).

Prevention

To prevent barotrauma, it is generally recommended that plateau airway pressure be maintained at or below 35 cm H_2O. Plateau pressure is the most indicative of the alveolar pressure and therefore is the measure of greatest concern for the prevention of PBT. Lower plateau airway pressures have been associated with a lower incidence of PBT. A threshold pressure appears to exist at 35 cm H_2O, above which there is a higher incidence of barotrauma. A meta-analysis of 14 clinical trials demonstrated a strong relationship between PBT and a plateau airway pressure greater than 35 cm H_2O or a static compliance less than 30 mL per cm H_2O.[105] There have not been direct comparisons between management targeting a plateau airway pressure or peak airway pressure. Peak airway pressure is likely a less reliable predictor of PBT given the conflicting data.[106–112]

Management

The best treatment for PBT is early recognition, and immediate attempts should be made to reduce plateau airway pressure.[83] This may require lowering the tidal volume or PEEP, as well as increasing sedation, administering neuromuscular blockade, or advancing



• **Fig. 45.5** Chest radiographs revealing the presence of subcutaneous emphysema, pneumomediastinum, and pneumoperitoneum *(arrows)*. (From Alexiou K, Sakellaridis T, Sikalias N, et al. Subcutaneous emphysema, pneumomediastinum and pneumoperitoneum after unsuccessful ERCP: a case report. *Cases J.* 2009;2:120.)

treatment of the underlying condition. In cases of pneumothorax when patients are supported by a mechanical ventilator, there is no high-quality evidence that supports routine insertion of chest tubes for all patients. However, more than 30% of pneumothoraces in mechanically ventilated patients progress to tension pneumothoraces, indicating that these patients must be monitored closely. Treatment for mechanically ventilated patients in whom pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema develops is generally supportive unless there is evidence of tension pneumomediastinum or compartment syndrome from pneumoperitoneum or subcutaneous emphysema.[96]

Prognosis

PBT appears to be associated with increased mortality rate, even though barotrauma is not a direct cause of death in most patients. In a multicenter prospective cohort study, patients with barotrauma had a significantly higher mortality rate (51% vs. 39%), a longer length of ICU stay (median 9 vs. 7 days), and a longer duration of mechanical ventilation (median 6 vs. 4 days) than patients without barotrauma.[88] Mortality rate may be related to the severity of the PBT. In one retrospective cohort study of 1700 mechanically ventilated patients, the mortality rate approached 100% when PBT caused a large (>500 mL per breath) bronchopleural fistula.[112] High-frequency jet ventilation is approved by the U.S. Food and Drug Administration (FDA) for the management of large bronchopleural fistulas, but this may be outweighed in some patients by increased plateau airway pressure (alveolar pressure), decreased oxygenation, or worse hypercapnia.[113]

Pneumothorax After Fiberoptic Bronchoscopy and Needle Biopsy of the Lung

Multiple literature reviews have documented the relative safety of fiberoptic bronchoscopy (FOB) with transbronchial biopsy. One review of more than 9000 such procedures found that the rate of pneumothorax was 1.9%.[114] An immediate postbronchoscopic chest radiograph rarely provides clinically useful information, and in FOB without transbronchial biopsy an immediate postbronchoscopy radiograph is not necessary.[115,116] Another study in 2006 concluded that in asymptomatic patients, routine radiograph after transbronchial biopsy is not necessary.[117] It was determined that certain patient populations should have routine radiographs performed after FOB with transbronchial biopsy: comatose or mentally retarded patients, patients receiving positive-pressure ventilation, patients with severe respiratory compromise as a result of disease or surgery, patients with bullous disease, patients who complain of chest pain, and outpatients. Pneumothorax after bronchoalveolar lavage without biopsy is extremely rare. The complication of pneumothorax after transbronchial needle aspiration is also low.[118]

Pneumothorax is the most common complication of needle aspiration or biopsy of the lung. It has been reported to occur in 17% to 26.6% of patients.[119–122] The chest tube insertion rate is much lower, ranging from 1% to 14.2%.[119–122] Risk factors for the development of biopsy-related pneumothorax include the presence of COPD, the absence of a history of ipsilateral surgery, small lesion size, a long needle path, and repeated pleural puncture.[119–124] Enlarging or symptomatic pneumothorax can be managed by manual aspiration or placement of a small-caliber chest tube.[123]

Delayed pneumothorax after percutaneous fine-needle aspiration has been reported. A study by Choi and colleagues[125] reported on their series of 458 patients who had undergone transthoracic needle biopsy. A follow-up chest radiograph was obtained immediately and at 3, 8, and 24 hours after the biopsy procedure. A pneumothorax that developed after 3 hours was defined as delayed pneumothorax. Pneumothorax developed in 100 of the 458 patients (21.8%), and delayed pneumothorax developed in 15 patients (3.3%). Female gender and absence of emphysematous changes correlated with an increased rate of delayed pneumothorax.

Pneumothorax After Thoracentesis

According to a 1998 National Center for Health Statistics study,[126] physicians perform an estimated 173,000 thoracenteses annually in the United States. Iatrogenic pneumothoraces resulting from thoracentesis increase the morbidity rate, mortality rate, and length of hospitalization. Previous reports indicated chest tube insertion may be required in up to 50% of cases with a mean duration of placement of approximately 4 days.[127,128] Gordon and colleagues[129] performed a systematic review and meta-analysis of 24 studies reporting pneumothorax rates after thoracentesis involving 6605 thoracenteses. The overall pneumothorax rate was 6%. In cases in which pneumothorax developed, 34.1% required chest tube placement. Statistically significant risk factors for developing thoracentesis included performing thoracentesis as a therapeutic procedure as opposed to as a diagnostic procedure; the presence of cough, dyspnea, or chest pain during the procedure; and witnessing the aspiration of air during the procedure.[129] Although not statistically significant, other possible predictors included the need for two or more needle insertions and concurrent mechanical ventilation.[129] Ultrasonography guidance,[130–132] more experienced operators,[133] and fewer needle passes conferred lower complication rates,[134] which paralleled findings from central venous catheter insertion studies. Various mechanisms may explain the pneumothoraces that occur after thoracentesis; the lung may be punctured at the time of needle entry or after the fluid has been withdrawn, or a small amount of air may be drawn into the chest during aspiration or along the needle track if high negative intrapleural pressure develops.[135]

Pneumothorax Resulting From Nasogastric Feeding Tubes

Small-bore Silastic (Dow Corning, Midland, MI) feeding tubes are being used with increasing frequency for short- and long-term enteral hyperalimentation. The first reported case of pneumothorax as a complication of passing a narrow-bore feeding tube was in 1978.[136] This once rare complication has now become more common.[137–139] Narrow-bore feeding tubes are particularly likely to give rise to pneumothorax because of the tube's small diameter (2.7 mm), self-lubricating properties, and wire stylet. These factors allow undetected entry of the tube into the tracheobronchial tree, perforation of pulmonary tissue, and lodging in the pleural cavity.[140] Other factors that increase the risk of a misplaced feeding tube include the presence of an endotracheal or tracheostomy tube (these may increase pulmonary passage of the tube by preventing glottis closure and perhaps by inhibiting swallowing), altered mental status, denervation of airways, esophageal stricture, enlargement of the heart, and neuromuscular weakness.[141] The clinical signs commonly used to determine correct placement of the feeding tube may be misleading. Normally, to confirm the correct placement of a feeding tube in the stomach, a small amount of air is injected. This produces a characteristic gurgle in the left upper quadrant of the abdomen, but a "pseudoconfirmatory gurgle" with a feeding tube in the chest has been reported.[142] Aspiration of large amounts of fluid through the tube is also taken to be a test of correct placement into the stomach, but delayed aspiration of a large

quantity of undigested feeding solution from the pleural space, mistaken for gastric contents, has been reported.[143]

Pneumothorax After Percutaneous Dilational Tracheostomy

Percutaneous dilational tracheostomy was first described in 1985 by Ciaglia and colleagues.[144] A case series described subcutaneous emphysema and pneumothorax as complications after percutaneous tracheostomy in a series of 326 cases.[145] Their review of the literature showed that the incidence of subcutaneous emphysema was 1.4% and that of pneumothorax was 0.8%. Findings associated with pneumothorax included difficult percutaneous dilational tracheostomy and the use of a fenestrated cannula.

Special Situations

Pneumothorax Ex Vacuo

Pneumothorax after partial resolution of total bronchial obstruction,[146] as a complication of lobar collapse,[147] and after therapeutic thoracentesis for malignant effusions[148] has been described. Acute lobar collapse results in a sudden increase in negative pleural pressure surrounding the collapsed lobe. Although the parietal and visceral pleural surfaces remain intact, the gas originating from the ambient tissues and blood is drawn into the pleural space, producing a pneumothorax called *pneumothorax ex vacuo*. Recognition of this type of pneumothorax is crucial because managing it requires relieving the bronchial obstruction rather than inserting a chest tube. The diagnosis of trapped lung requires documentation of chronicity and absence of pleural inflammation, pleural malignancy, or endobronchial lesion. The pathognomonic radiographic sign of a trapped lung is the pneumothorax ex vacuo, characterized as a small to moderate-sized air collection after evacuation of effusion.[149]

Sport-Related Pneumothorax

Pneumothorax as a result of blunt trauma from contact sports is a recognized but underreported event. Several cases of pneumothorax or pneumomediastinum sustained during a contact sport have been described in the literature.[150,151] In a large case series, Kizer and MacQuarrie[152] identified 20 patients who had sustained a spontaneous or traumatic air leak while engaged in an outdoor sport.

Barotrauma Unrelated to Mechanical Ventilation

Although the term *barotrauma* has traditionally been used to describe the development of extraalveolar air during mechanical ventilation, in other instances it may be due to increased intraalveolar pressure, causing air to leak out of the alveoli. PBT of ascent is a well-known complication of compressed air diving. Pulmonary edema and hemorrhage occur when lung volume decreases below residual volume. As a diver ascends and transalveolar pressure exceeds 20 to 80 mm Hg, overexpansion injury in the form of alveolar rupture can occur.[153–155] Divers who hold their breath as they ascend and those with obstructive airway diseases, such as asthma or COPD, are at increased risk.[156]

Pneumothorax is a relatively uncommon complication in divers, developing in only approximately 10% of those with evidence of barotrauma. Patients with a history of spontaneous pneumothorax, bullae, or cystic lung disease are at increased risk of pneumothorax and should be cautioned against diving.[157]

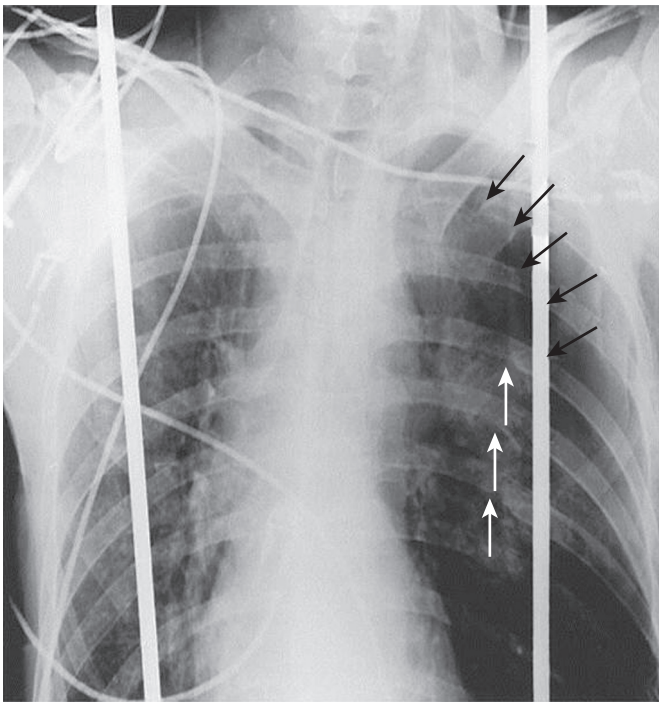
Pneumothorax develops when gas ruptures from the lung parenchyma into the pleural space. If this occurs at a significant depth, the pleural gas expands as the diver ascends (as described by Boyle's law) and can result in a tension pneumothorax. Manifestations include dyspnea, chest pain, tachycardia, hypotension, cyanosis, distended neck veins, tracheal deviation, hyperresonance to percussion, unilateral decrease in breath sounds, and accompanying subcutaneous emphysema in approximately 25% of cases.

If a pneumothorax results in severe hypoxemia or hemodynamic compromise, immediate pleural decompression is required. This is usually accomplished by inserting a large-bore needle into the second intercostal space in the midclavicular line of the affected hemithorax, followed by tube thoracostomy.

Tension Pneumothorax

With a tension pneumothorax, the pleural pressure in the affected hemithorax exceeds atmospheric pressure, specifically during expiration. This is usually the result of a check valve mechanism that facilitates the ingress of gas into the pleural space during inspiration but blocks the escape of gas from the pleural space during expiration. The results are the accumulation of gas leading to a buildup of pressure within the pleural space. There is eventual respiratory failure from compression of the contralateral normal lung followed by circulatory collapse with hypotension and subsequent traumatic arrest with pulseless electrical activity (PEA) due to obstruction of venous return to the heart.

The classic signs of a tension pneumothorax are deviation of the trachea away from the side with the tension, an increased percussion note, and a hyperexpanded chest that moves little with respiration. Radiographically, tension pneumothorax shows a distinct shift of the mediastinum to the contralateral side and flattening or inversion of the ipsilateral hemidiaphragm (Fig. 45.6). Clinically unstable patients should undergo immediate needle decompression



• **Fig. 45.6** Chest radiograph showing the collapsed visceral pleural line of left tension pneumothorax *(black arrows)* in a trauma patient. Note the mediastinal shift to the right, widened rib spacing, and posterior rib fractures on the left *(white arrows)*. A flattening of the left hemidiaphragm is also present (not shown). (From Barton E. Tension pneumothorax. *Curr Opin Pulm Med.* 1999;5:269–274.)

followed by chest tube insertion. Decompression is performed by advancing a standard 14- or 16-gauge intravenous catheter into the pleural space at the junction of the midclavicular line and the second or third intercostal space. The needle is advanced until air can be aspirated into a syringe connected to the needle. The needle is withdrawn and the cannula is left open to air. An immediate rush of air out of the chest indicates the presence of a tension pneumothorax. The maneuver essentially converts a tension pneumothorax into a simple pneumothorax. A chest tube can then be placed.

Clinical Features

PSP usually occurs when the patient is at rest.[158] Patients are typically in their early 20s when presenting with PSP, which is rare after age 40. Chest pain and dyspnea are the two main symptoms associated with the development of pneumothorax. One series evaluated 39 patients who presented with one of the two symptoms and 64% of them had both.[159] The pain is generally reported as ipsilateral, which usually resolves spontaneously within 24 hours.[40] The degree of dyspnea depends on the size of the pneumothorax and the condition of the underlying lung. Cough, malaise, orthopnea, and hemoptysis may also be presenting symptoms.

Physical examination can be normal in small pneumothoraces. Possible physical findings when a large pneumothorax is present include decreased chest excursion on the affected side, diminished breath sounds, and hyperresonant percussion. There may also be subcutaneous emphysema. Labored breathing accompanied by hemodynamic compromise (tachycardia or hypotension) suggests a possible tension pneumothorax, which necessitates emergency decompression. Tension pneumothorax occurs owing to the presence of a ball-valve mechanism; air enters the pleural cavity but cannot escape. As a result, positive pressure builds up. As the tension continues to increase, the diaphragm is flattened, the mediastinum is shifted to the opposite side, and ultimately cardiopulmonary collapse results.

Hypoxemia is common because collapsed and poorly ventilated portions of lung continue to receive significant perfusion. However, hypercapnia is unusual because underlying lung function is relatively normal and adequate alveolar ventilation can be maintained by the contralateral lung.[160] Acute respiratory alkalosis may be present if pain, anxiety, or hypoxia is substantial.

In certain situations, the symptoms of pneumothorax may have an atypical presentation and therefore require a high index of suspicion. During a transbronchial biopsy, a patient may complain of pleuritic chest pain followed by dyspnea. A pneumothorax after a subclavian vein catheterization may present with progressive dyspnea and an alteration of vital signs. In a mechanically ventilated patient, the initial presentation may include hypotension, new-onset respiratory distress, unilateral decrease in breath sounds, a decrease in static and dynamic compliance, and worsening oxygenation.[41,161,162]

Simultaneous bilateral pneumothoraces is a rare condition because, in humans, the left and right pleural spaces are completely separated. Patients can develop a persistent pleuro-pleuro channel after undergoing a median sternotomy, mediastinal surgery, or heart or heart-lung transplant surgery. This condition has been dubbed "iatrogenic buffalo chest" because the North American buffalo is one of few mammals that have communicating pleural spaces.[163] A unilateral thoracic procedure in this situation has been described to cause bilateral pneumothoraces[164,165] and "shifting pneumothorax."[166] Simultaneous bilateral spontaneous pneumothorax (SBSP) has been described in a case series with 12 patients.[167] Of the 12 patients, 5 had no underlying lung disease. In 7 patients, simultaneous bilateral spontaneous pneumothorax was secondary to pulmonary metastases, histiocytosis, undefined interstitial pulmonary disease, tuberculosis, pneumonia, and COPD.

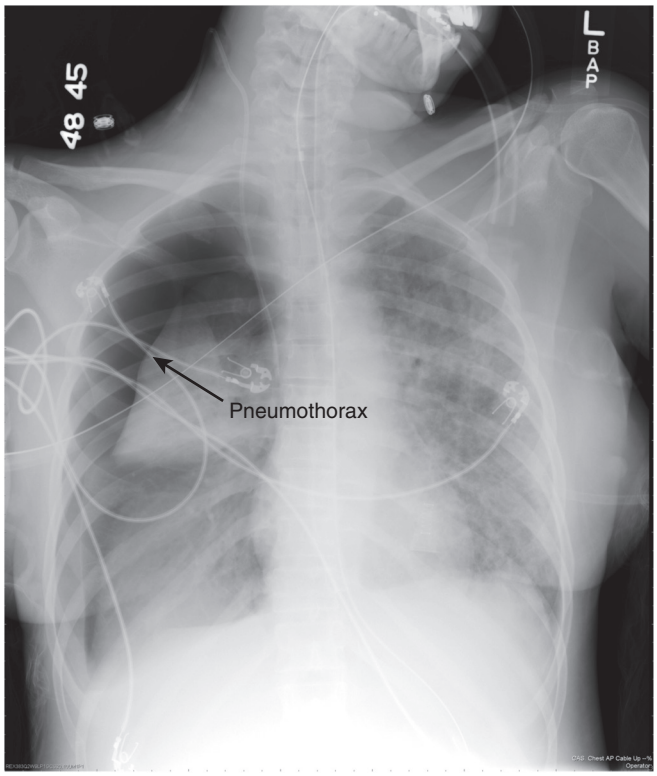
Electrocardiographic Features

The presence of a pneumothorax may lead to distinct electrocardiographic changes, which can be mistaken for myocardial ischemia or infarction. Most findings have been described for left-sided pneumothorax. Poor R-wave progression in the anterior precordial leads with a decrease in R wave from V_4 to V_5, rightward shift of frontal axis, diminution of precordial R voltage, decrease in QRS amplitude, and precordial T-wave inversion have all been described.[168–170] The absence of ST-segment elevation and a significant Q wave and reversal of electrocardiographic changes in the sitting position suggest pneumothorax. In right-sided pneumothorax, there is a loss of S wave in lead V_2 and prominent R-wave voltage, which may mimic posterior wall myocardial infarction.[171]

Diagnostic Imaging Modalities

Radiographic Signs

Chest radiography and CT are the first-line imaging modalities used to identify a pneumothorax. The main feature of a pneumothorax on a chest radiograph is a white visceral pleural line. This line separates the visceral pleura from the parietal pleura by a collection of gas (Fig. 45.7). A pneumothorax may be identified using an upright, supine, or lateral decubitus chest radiograph.



• **Fig. 45.7** Radiograph of right lung pneumothorax. The *arrow* points to the collapsed lung.

The lateral decubitus view is the most sensitive, and the supine view is the least sensitive.

Upright Chest Radiograph

In an upright patient with a pneumothorax, most pleural gas accumulates in an apicolateral location. The visceral pleural line appears either straight or convex toward the chest wall. As little as 50 mL of pleural gas may be seen on a chest radiograph.[172] Although there is generally a loss of lung volume with a pneumothorax, the collapsed lung preserves its translucency because hypoxic vasoconstriction diminishes the blood flow to the collapsed lung. The value of obtaining an expiratory chest radiograph has been overstated. Inspiratory and expiratory upright chest radiographs detected pneumothorax with equal sensitivity.[173]

Supine Chest Radiograph

In a supine patient with a pneumothorax, most pleural gas accumulates in a subpulmonary location. A deep sulcus sign occurs when gas outlines the anterior pleural reflection, the costophrenic sulcus, and the anterolateral border of the mediastinum (see Fig. 45.4). Rarely, pleural gas can accumulate in the phrenicovertebral sulcus. The visceral pleural line may be seen at the lung base and has a concave contour. Around 500 mL of pleural gas is needed to definitively diagnose pneumothorax on a supine chest radiograph.[172]

Lateral Decubitus Chest Radiograph

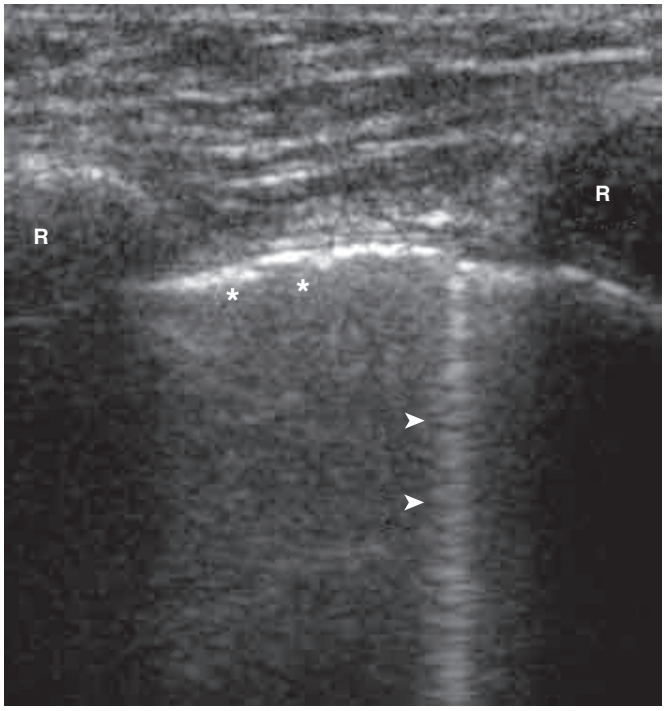
A pneumothorax is most easily detected with a lateral decubitus view. Most pleural gas in this position accumulates in the nondependent lateral location. The visceral pleural line appears as a straight or convex line toward the chest wall. As little as 5 mL of pleural gas may be visible on a lateral decubitus view.[172]

Computed Tomography

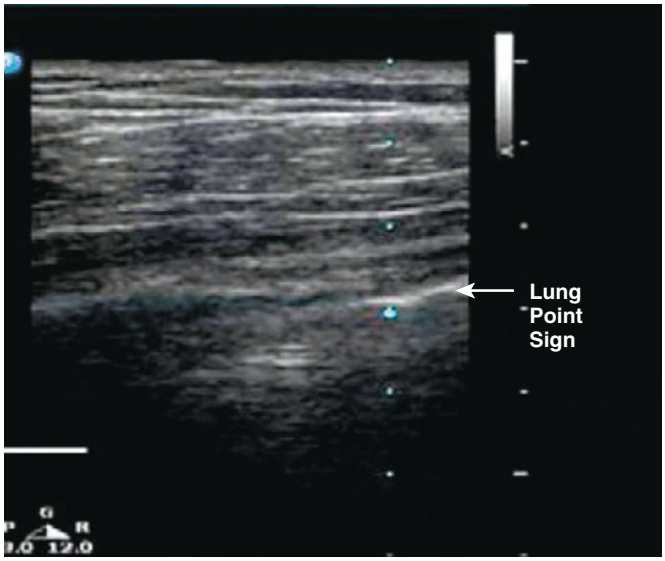
CT scanning is the most accurate imaging modality for the detection of pneumothorax although it is generally not the initial option. This method can identify small amounts of intrapleural gas, atypical collections of pleural gas, and loculated pneumothoraces. Complex pleural disease such as pleural effusion and cystic lung disease is optimally displayed by CT scanning.[174]

Pulmonary Ultrasonography

Ultrasound was first used to detect pneumothorax in a horse in 1986 and then in humans shortly thereafter.[175] In a normal lung, the visceral and parietal pleurae are adjacent, and ultrasound shows shimmering or sliding at the pleural interface during respiration.[176] The absence of lung sliding indicates a pneumothorax. Comet tails are an ultrasound artifact that arises when ultrasound encounters a small air-fluid interface (Fig. 45.8). The presence of sliding lung and comet tail artifacts appear to reliably rule out pneumothorax. The presence of a "lung point" sign is nearly 100% specific for the detection of pneumothorax. Here the visceral pleura is seen to be intermittently coming into contact with the chest wall during inspiration. The lung point sign may also be helpful in determining the actual size of the pneumothorax (Fig. 45.9). A review of four prospective studies found the sensitivity and specificity of ultrasound for pneumothorax to range from 86% to 98%, which was superior to supine chest radiography (sensitivity 28%–75%).[177] A small pneumothorax may be missed with ultrasound, and patients with blebs or scarring may have a false-positive finding.[178]



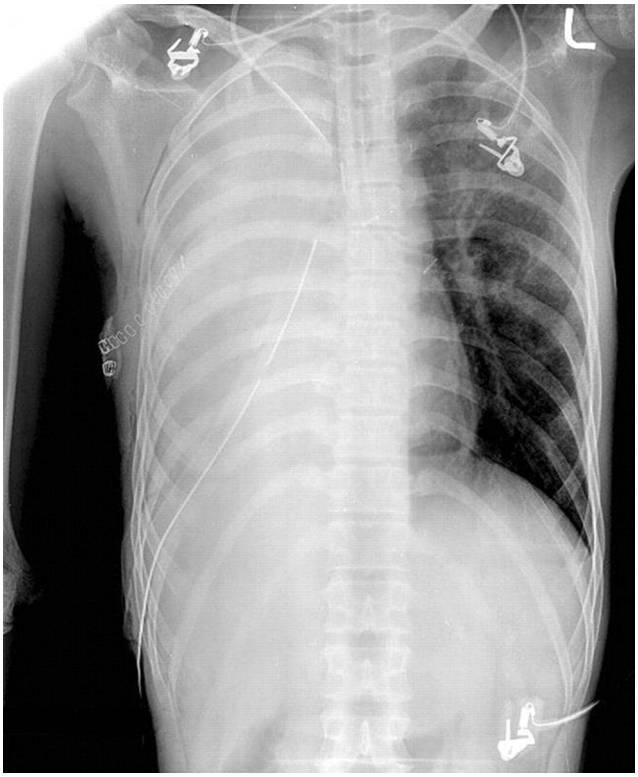
• **Fig. 45.8** Rib shadows *(R)* are visible as bright reflectors with distal shadow. The pleura *(double asterisks)* is a bright echogenic line beneath the ribs. Comet tail artifacts *(arrowheads)* arise from normal pleura reflecting sound waves. (From Mt. Sinai Emergency Ultrasound Division Tutorials. Pneumothorax. Available at http://sinaiem.us/tutorials/pneumothorax.)



• **Fig. 45.9** Lung point sign. B-mode depicting the lung point: sliding lung touching the chest wall. (From Husain LF, Hagopian L, Waymen D, et al. Sonographic diagnosis of pneumothorax. *J Emerg Trauma Shock.* 2012;5:76–81.)

Differential Diagnosis: Conditions Mimicking Pneumothorax

Large subpleural bullae can mimic a loculated pneumothorax. Bullae can be distinguished from pneumothorax owing to the fact that only bullae typically have a medial border that is concave to



• **Fig. 45.10** Reexpansion pulmonary edema. (From Tung YW, Lin F, Yang MS, et al. Bilateral developing reexpansion pulmonary edema treated with extracorporeal membrane oxygenation. *Ann Thorac Surg.* 2010;89:1268–1271.)

the chest wall.[179] Exceptions to this distinction occur with subpulmonary collections of gas, loculated collections of gas, and pleural adhesions. In trauma cases, the stomach can herniate into the chest after rupture of the left hemidiaphragm, and a gas-filled stomach may be mistaken for a loculated pneumothorax. This can be disastrous if drainage with a thoracostomy tube is attempted. A skinfold can generally be distinguished from a pneumothorax by careful evaluation of the radiograph. Skinfolds generally extend beyond the rib cage, stop short of the ribs, and gradually increase in opacity with an abrupt dropoff at the edge of the image. Blood vessels often extend beyond the skinfold.[180]

Management

Fig. 45.10 represents an algorithmic approach to the management of pneumothorax.

Management of the First Episode of Pneumothorax

Initial management is directed at removing air from the pleural space followed by preventing recurrence. Approaches for the management of the initial episode include observation, supplemental oxygen, simple aspiration of the pneumothorax, and tube thoracostomy. The choice of therapy in a given patient depends on various factors such as the size of the pneumothorax, whether the pneumothorax is primary or secondary, the condition of the lungs, the clinical stability of the patient, the outcome of the patient, and whether the pneumothorax has occurred in a special setting. Various guidelines for managing pneumothorax have been published.[181,182]

Estimating the Size of a Pneumothorax

Determining the size of a pneumothorax is difficult. The average interpleural distance approximates the size of a pneumothorax from a frontal chest radiograph by taking the sum of the distances in millimeters between the ribs and the visceral pleura at the apical, midthoracic, and basal levels and then dividing the sum by 3. Another method is called the Light index. It uses the following calculation to estimate the size of a pneumothorax:

$$\%\ \text{Pneumothorax} = 100 - (D_L{}^3 / D_H{}^3 \times 100),$$

where D_L is diameter of the collapsed lung cubed, and D_H is diameter of hemithorax on the collapsed side cubed. Both methods express the size of the pneumothorax as a percentage, although the Light method better correlates with the amount of pneumothorax gas removed by suction.[183,184]

These methods are difficult to apply and tend to underestimate the size of a pneumothorax. As a result, some clinicians tend to describe a pneumothorax as large or small rather than use percentages. The American College of Chest Physicians guidelines defines a small pneumothorax as less than 3 cm in apex-to-cupola distance.[181] British Thoracic Society guidelines define a pneumothorax as small if the distance from the chest wall to the visceral pleural line is less than 2 cm. They define a large pneumothorax if the distance from the chest wall to the visceral pleural line is 2 cm or greater.[182] There is an ongoing trial comparing conservative versus invasive therapy in patients presenting with their first large (≥32%) PSP. Conservative management involves a period of observation before discharge, with intervention for worsening symptoms or physiologic instability.[185]

Treatment Options

Supplemental Oxygen

The choice of treatment depends on patient characteristics and clinical circumstances. Patients who are clinically stable who are having their first PSP can be observed with administration of supplemental oxygen if their pneumothorax is small (≤2–3 cm between the lung and chest wall on a chest radiograph).[186] Supplemental oxygen is used to facilitate reabsorption of pleural air, and its importance should not be underestimated. The absorption of gas depends in part on the gradient between the partial pressure in the capillaries and that in the pleural space. On room air, the net gradient is only 54 mm Hg, whereas it exceeds 550 mm Hg when the patient is receiving 100% oxygen.[183] A normal rate of reabsorption is 1.25% of the volume of the hemithorax per 24 hours.[7] The rate of reabsorption increases sixfold if humidified 100% oxygen is administered.[187] Therefore hospitalized patients with any type of pneumothorax who are not subjected to aspiration of air or tube thoracostomy should be treated with supplemental oxygen at high concentrations.[188]

Removal of Air From Pleural Space

In a patient whose pneumothorax is large (>20%–25%), progressive, tension type, or symptomatic or who has an underlying chronic lung disease, is supported by a ventilator, or has a recurrent pneumothorax, the pleural space air should be removed. Several therapies have been developed for this purpose.

Aspiration

Simple aspiration is most easily accomplished by using a commercially available thoracentesis kit. An 18-guage needle with an 8F to 9F catheter is inserted in the second intercostal space in the midclavicular line. Once the catheter is inserted into the pleural space, the catheter is threaded deeper into the pleural space, and then the needle is withdrawn. Air is manually withdrawn through the indwelling catheter until no more can be aspirated. If the lung has not expanded after 4 L has been aspirated, then it is assumed there is a persistent air leak. Thoracoscopy should then be performed. A chest tube should be inserted if thoracoscopy is not readily available.

Once no further air can be aspirated, one of two methods may be approached.[189] A closed stopcock can be attached and the indwelling catheter secured to the chest wall. After 4 hours, a chest radiograph should be obtained and if there is adequate lung expansion, the catheter can be removed. After another 2 hours of observation, another chest radiograph should be performed. If the lung remains expanded on this chest radiograph, the patient can be discharged.[190] Alternatively, the catheter can be left in place and attached to a Heimlich (i.e., one-way) valve. The patient can then be discharged with follow-up within 2 days.[181,191] One advantage of aspiration over tube thoracostomy is that the patient need not be hospitalized whether the catheter is removed after aspiration or left attached to the Heimlich valve. There is a lower morbidity rate compared with tube thoracostomy and the procedure is better tolerated. Outcomes have been found to be similar between thoracostomy and aspiration. In a meta-analysis of three randomized controlled trials (194 patients) that compared aspiration versus tube thoracostomy, aspiration resulted in shorter hospitalization stays and similar clinical outcomes.[192] In another randomized trial, 137 patients who had a first episode of PSP were assigned to receive manual aspiration versus tube thoracostomy. The groups had similar rates of immediate (62% vs. 68%) and 1-week success (89% vs. 88%). Aspiration was associated with a shorter hospital stay (1.8 vs. 4 days).[193]

Tube Thoracostomy

If necessary, most patients with PSP can be managed with a small chest tube (≤22F) or chest catheter (≤14F).[194,195] In the absence of trauma and with good aseptic technique, prophylactic antibiotics are not recommended.[196] The preferred location for insertion of the chest tube is via an incision at the fourth or fifth intercostal space in the anterior or midaxillary line.[197–199] In men, this corresponds to the nipple line and in women, to the inframammary crease. It is important to direct the tube anteriorly because the tube tends to track between the lobes in patients who have complete fissures. If this happens, the tube may get walled off by the lung and cease functioning. A more recent study found the position of a chest tube in the pleural cavity categorized as upper, middle, or lower third of the pleural cavity did not significantly influence chest tube duration.[200] The second intercostal space in the midclavicular line has been suggested as an alternative site for tubes, but this requires placement through the pectoralis muscle. This chest tube site is more painful for the patient and the tube is more difficult to dress and manage. Once an insertion site is identified, the tube is inserted using blunt dissection and secured in place.

The chest tube can then be connected to a water seal device, with or without suction, and left in position until the pneumothorax resolves. Once the air leak has resolved, the lung has fully expanded, and the pleural air removed, then the chest tube can be removed in a sequential fashion. The chest tube can generally be removed if there is no visible air leak present and air does not accumulate when suction is removed. If there is any question as to whether an air leak has resolved, a "clamp trial" can be performed. This involves clamping the chest tube and performing a chest radiograph repeated at intervals (e.g., 2, 6, and then 12 hours). If air does not reaccumulate, the tube can be removed.

Percutaneous Pneumothorax Catheters and Thoracic Vents

Alternatives to tube thoracotomy involve using small-lumen catheters or thoracic vents (one-way valve feature). Small catheter tubes have the advantages of ease of insertion, good response, and low incidence of complications. Liu and colleagues reported that in their study using pigtail catheters in 50 patients versus traditional chest tubes in 52 patients that the pigtail drainage was no less effective than the traditional chest tube.[201] Complications can include catheter failure from kinking, malposition, inadvertent removal by the patient, and occlusion of the tube or valve by pleural fluid. A thoracic vent can also be used to manage a simple pneumothorax.[202,203] It is inserted in the second intercostal space in the midclavicular line. This device has the advantages of a urethane tube that does not kink, a self-contained one-way valve, and a unique signal diaphragm that reflects pleural pressure. This device is not suitable for use in patients who are expected to have large-volume or protracted air leaks.

Thoracoscopy

VATS is an effective treatment of PSP.[204–206] Pleurodesis is created by pleural abrasion or a partial parietal pleurectomy. When necessary, an endoscopic stapler can be used to resect bullae.[207–210]

Persistent Air Leak and Bronchopleural Fistula

If a lung is at least 90% inflated but an air leak is present after 3 days, more aggressive treatment may be warranted. The simplest approach is to attach the chest tube to a unidirectional flutter valve such as a Heimlich valve. This allows rapid discharge of the patient with subsequent outpatient follow-up. An alternative approach is to perform an autologous blood patch.[211,212] This involves withdrawing blood from the patient's peripheral vein and aseptically infusing the blood into the pleural space through the chest tube. The ideal amount of blood to infuse is not known. The range in different series has been 24 to 200 mL. After infusion of the blood, the tubing from the chest tube is draped over a hook approximately 60 cm above the patient's head and then down to a water seal device on the floor. The chest tube is then removed 24 hours after cessation of the air leak. The most serious side effect is empyema, which occurred in 9% of patients in one series.[213]

An air leak persisting for more than 7 days is termed a *bronchopleural fistula* (BPF) and can occur in up to a third of pneumothorax cases.[214] The term refers to the presence of a connection between the tracheobronchial tree and the pleural space. It most commonly occurs as a complication of pulmonary resection, but may develop after spontaneous pneumothorax, mechanical ventilation, chest trauma, or lung infection, particularly where an abscess ruptures onto the pleural surface.[215]

After 7 days of a persistent air leak, tube thoracostomy is deemed to have failed and more definitive treatment can be planned. Currently, the first-line treatment of patients with BPF or persistent

air leak is considered to be thoracic surgical intervention (VATS) unless there is a contraindication for surgery. Bronchoscopic techniques can be considered a complementary rather than a competing intervention.

The first step in management of a persistent air leak is localization of the source. CT scanning is a noninvasive technique that offers the potential of identifying the bronchial segment or subsegment. Flexible bronchoscopy offers two different methods of identifying the site of a BPF or persistent air leak. A central BPF, located in a main, lobar, or segmental bronchus, may be directly visible, either as a defect within the mucosa or after the installation of saline solution via the bronchoscope when bubbling at the site of a bronchial resection margin may be visible.[215] When the origin of the air leak is located more distally in the bronchial tree or within the lung parenchyma, the technique of sequential balloon occlusion of bronchi can be used.[216]

Various techniques have been described to achieve bronchial occlusion. There have been no randomized controlled trials comparing the efficacy between these techniques. The techniques that have been used to occlude bronchi include insertion of a mechanical device,[217] use of stents,[218] instillation of a liquid material that subsequently solidifies,[219] submucosal injection of a filler or sclerosant,[220] use of thermal energy via laser or argon plasma coagulation to seal a visible defect,[221] or endobronchial valves.[222]

Recurrence Prevention

Once the initial episode of pneumothorax has resolved, the decision to prevent future pneumothoraces must be made. Different recurrence rates have been reported in the literature: from 20% to 52% after the first PSP.[223–225] In the following groups of patients, further management against recurrence is recommended: recurrent pneumothorax, patients with chronic air leak, patients with large bullae, patients who live in remote areas, and patients in which a recurrence could be a hazard (e.g., airline personnel or divers). The following are established risk factors for recurrence: more than one previous episode, COPD, air leak for more than 48 hours after first episode, and large cysts seen on radiograph. The following are possible risk factors for recurrence: nonoperative management of first episode (vs. tube drainage) and tube drainage for only 24 hours during first episode (vs. 3–4 days). Further management in these high-risk groups is aimed at preventing recurrence. Therapies to prevent recurrence include chemical pleurodesis, VATS, or surgical thoracotomy.

Chemical Pleurodesis

In patients who are unable or unwilling to undergo VATS, pleurodesis (adhesion of visceral and parietal pleura) can be done by introducing the sclerotic agent via the chest tube. Tetracycline had been used for pleurodesis,[226] but sterile tetracycline is no longer available. As a result, intrapleural instillation of doxycycline has been used as an alternative for pleurodesis.[227] Intrapleural doxycycline can be painful, so it is recommended that patients be premedicated with analgesics or anxiolytics. Talc slurry, which is composed of finely powdered magnesium silicate, can also be used for pleurodesis.[228–230] Recurrence rates after treatment vary between 5% and 8%. Controversy exists whether talc should be used as a sclerosant in young, otherwise healthy individuals owing to safety concerns and fear of long-term complications. Intrapleural injection of talc for malignant pleural effusions has been associated with development of ARDS in 1% to 2% of patients.[231] Extensive pleural thickening and calcifications were reported in another patient years after treatment.[232] However, several studies support the safety of talc pleurodesis for prevention of recurrent pneumothorax.[228,233,234]

Video-Assisted Thoracoscopic Surgery Pleurodesis

VATS is effective not only in the treatment of spontaneous pneumothorax but also in the prevention of recurrent pneumothorax.[235,236] The rate of recurrence is less than 5% after VATS with bleb/bullae resection and pleurodesis. Mechanical pleurodesis with dry gauze, chemical pleurodesis with talc, and laser ablation of the parietal pleura are among the techniques used.

Surgical Thoracotomy

Surgical management for the first episode of spontaneous pneumothorax is indicated under the following circumstances: 3% to 4% of patients have a persistent leak resulting from a large fistula that needs to be closed surgically; about 5% of patients have frank hemothorax and surgical intervention is required to control the bleeding; and a trapped lung that fails to reexpand may require decortication.

The indications for open thoracotomy are the same as those for VATS. Thoracoscopy has virtually replaced open thoracotomy in the management of spontaneous pneumothorax owing to shorter hospitalizations and less postoperative pain.[237,238] Thoracotomy is recommended only if thoracoscopy is unavailable or has failed.

Management Under Special Circumstances

Secondary Spontaneous Pneumothorax

Patients with SSP should be hospitalized owing to their diminished pulmonary reserve from their underlying lung disease. Patients with a small pneumothorax (≤2 cm between the lung and chest wall on a chest radiograph) who are clinically stable may be observed. Patients with a large pneumothorax or who are clinically unstable should have a chest tube placed. Tube thoracotomy is generally preferred over needle aspiration because it is more likely to be successful. In one trial, tube thoracostomy was more likely to have the pleural air completely evacuated than with needle aspiration (93% vs. 67%).[239] About 80% of patients with SSP will have lung expansion and cessation of their air leak within 7 days after tube thoracostomy.[240,241] Patients who are supported by mechanical ventilation or who are at risk for a large air leak should be managed with a 24F to 28F chest tube. A smaller chest tube (16F–22F) is preferred for most other patients. The chest tube should be connected to a water seal device with or without suction. In general, the chest tube should remain in place until a procedure is performed to prevent a recurrent pneumothorax. Patients who decline preventive interventions can have their chest tube clamped 12 hours after the last evidence of an air leak. A chest radiograph should be done 24 hours after the last evidence of an air leak, and if the pneumothorax has not recurred, the chest tube can be removed.

Pneumothorax in Patients With HIV Infection

Because the majority of pneumothoraces in HIV-infected patients occur in association with *P. jiroveci,* all patients with HIF infection who present with a pneumothorax should undergo a diagnostic evaluation for *P. jiroveci* infection. *P. jiroveci* pneumonia–related pneumothorax is complicated by a virulent form of necrotizing subpleural lesions with resultant diffuse air leaks refractory to standard treatment.[242] Asymptomatic patients with a small pneumothorax (<15%–20%) may be observed. Symptomatic patients and those with a larger pneumothorax will need chest tube

thoracostomy, and those with a persistent air leak will likely need additional therapy with VATS for stapling and pleurodesis. Patients who are poor operative candidates may benefit from bedside pleurodesis.

Pneumothorax in Cystic Fibrosis

Pleurodesis as an initial step in the management of pneumothorax in CF is considered contraindicated because it results in extensive pleural adhesions that jeopardize subsequent lung transplantation.[243] If initial tube thoracostomy does not bring resolution of air leak within 5 days, blebectomy should be performed. If blebectomy is unsuccessful, a definitive pleural ablative procedure should be considered.

Catamenial Pneumothorax and Pneumothorax Complicating Pregnancy

The initial episode is managed in the usual manner. Recurrences, which occur 72 hours before or after menstrual flow, are managed by pleurodesis or hormonal treatment.[244] Therapeutic options include oral contraceptive pills, danazol, progestational agents, and gonadotropin-releasing hormone analogs.[69] Thoracotomy should be considered if the patient is unable to take ovulation-suppressing drugs, has a recurrent pneumothorax while taking drugs, or wants to become pregnant. Pneumothorax complicating pregnancy is managed in the usual way, but because of the high rate of recurrence during parturition, thoracotomy with resection of blebs if present should be considered.[245]

Pneumothorax in Air Travelers

The volume of gas is inversely proportional to the pressure at which it is exposed. As barometric pressure falls in the aircraft cabin during ascent, trapped air in any noncommunicating body cavity, such as in a lung bleb or bulla, will expand. Regulatory government agencies, such as the Federal Aviation Administration, have requirements specifying that commercial aircraft cabins be pressurized to simulate an altitude (so-called cabin altitude) of approximately 8000 ft (2438 m). It is estimated that the volume of air in a noncommunicating body cavity will increase by approximately 38% upon ascent from sea level to the maximum "cabin altitude" of 8000 feet (2438 m).[246] For patients who develop signs and symptoms of a pneumothorax in-flight, administration of supplemental oxygen is the most important intervention. For patients in respiratory distress, emergency landing at the nearest airport will allow prompt evaluation and insertion of a chest tube, if needed. The optimal length of time to wait after resolution of a pneumothorax is unknown.[247] For patients with a prior pneumothorax, the decision regarding air travel must be made on an individual basis. One must take into consideration the likelihood of recurrence and how well the patient would tolerate a subsequent pneumothorax. A patient with relatively normal lung parenchyma could be permitted to fly 2 weeks after resolution of an iatrogenic pneumothorax. In a patient with severe bullous emphysema, limited cardiopulmonary reserve, and a prior spontaneous pneumothorax, air travel may be contraindicated.

Pneumothorax in Lymphangioleiomyomatosis

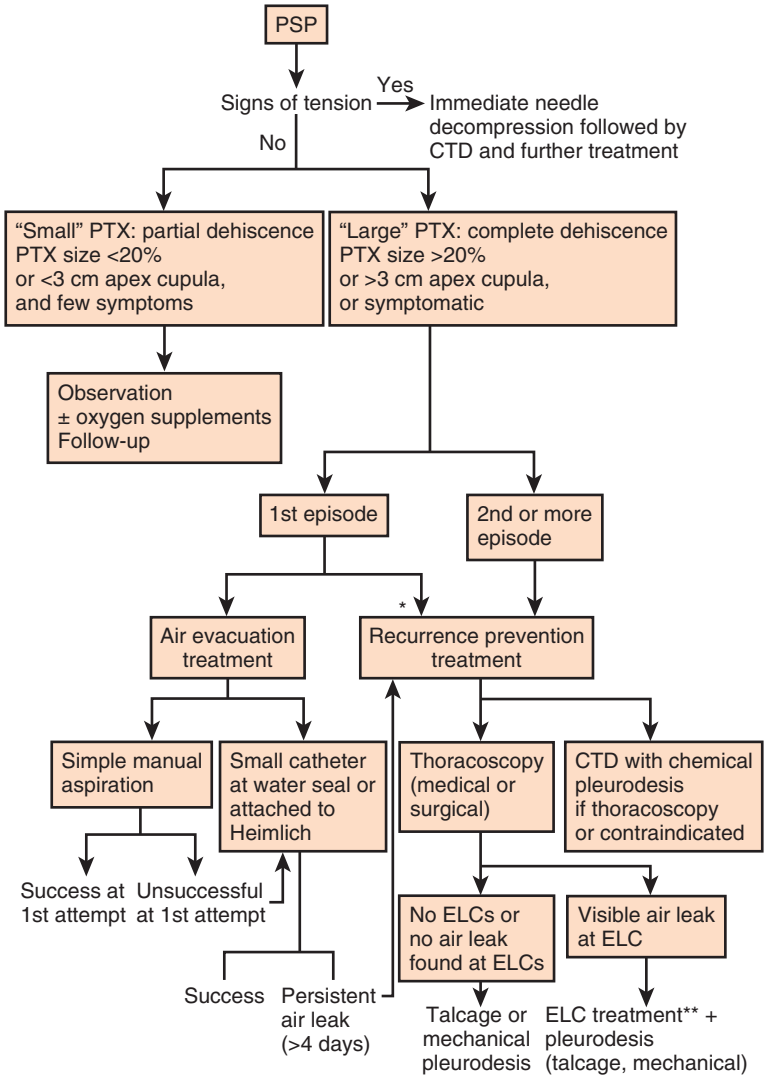
Lymphangioleiomyomatosis is a rare and often fatal disease that affects predominantly women of childbearing age. The normal architecture of the lung is distorted by multiple small cysts, ranging from 0.1 cm to several centimeters in diameter, with progressive decline in lung function. Spontaneous pneumothorax occurs in 50% of cases. It is often recurrent, can be bilateral, and may necessitate pleurodesis.[248,249] Because of the morbidity and cost associated with multiple recurrences, recommendations include definitive intervention at the time of the initial pneumothorax. Pleurodesis in these cases does not preclude successful transplantation.[250]

Complications Related to Management

Reexpansion pulmonary edema may occur after rapid reexpansion of a collapsed lung in patients with a pneumothorax. It is typically unilateral[251] (Fig. 45.11). The pathophysiologic mechanism is unknown. The incidence of reexpansion pulmonary edema initially appeared to be related to the rapidity of lung reexpansion and to the severity and duration of lung collapse. However, a study examining development of reexpansion pulmonary edema after thoracentesis found that it was independent of the volume of fluid removed and pleural pressures, and recommended that even large pleural effusions be drained completely as long as chest pain or end-expiratory pleural pressure less than −20 cm H_2O does not develop.[252] Patients typically present soon after the inciting event, although presentation can be delayed for up to 24 hours in some cases. The clinical course varies from isolated radiographic changes to complete cardiopulmonary collapse. Mortality rates as high as 20% have been described.[253] Treatment is generally supportive. Supplemental oxygen is administered and, if necessary, mechanical ventilation is used. The disease is usually self-limited.

Key Points

- PSP occurs primarily in tall, thin, previously healthy young men, most of whom are smokers. The chest radiograph often shows apical subpleural blebs or bullae. Rupture of these bullae is *not* related to physical activity but may be related to changes in atmospheric pressure. COPD is the most common cause of secondary pneumothorax. Presentation of pneumothorax in COPD is often atypical and causes excessive morbidity and mortality rates.
- A high incidence of pneumothorax occurs in HIV-infected patients, related to PCP and the mechanical ventilation and bronchoscopy that are commonly required in these patients. In this group of patients, pneumothorax is frequently bilateral, recurrent, and unresponsive to conservative therapy.
- Traumatic pneumothorax, which occurs as a result of a penetrating injury, may occur with closed chest trauma.
- Pneumothorax is a common complication of mechanical ventilation. Interstitial emphysema is a harbinger of this complication. High peak and mean airway pressures, PEEP, use of volume-cycled ventilators, intubation of right mainstem bronchus, chronic airway obstruction, and aspiration pneumonia increase the incidence.
- Simultaneous bilateral pneumothoraces and "shifting pneumothoraces" are rare but interesting conditions that may develop



• **Fig. 45.11** An algorithmic approach to the treatment of primary spontaneous pneumothorax *(PSP)*.*After informed consent or in certain patient groups (aircraft personnel, divers).** Staple bleb/bullectomy, electrocoagulation, ligation. *CTD,* Chest tube drainage; *ELCs,* emphysema-like changes; *PTX,* pneumothorax. (From Noppen M, De Keukelieire T. Pneumothorax. *Respiration.* 2008;76:121–127.)

because of persistent pleuropleural communication called *iatrogenic buffalo chest.*

- An immediate postbronchoscopy chest radiograph is rarely useful but should be done in certain groups of patients (e.g., comatose, mentally retarded, ventilated, or with respiratory compromise).
- Pneumothorax induced by a misplaced small-bore feeding tube is not uncommon. Clinical signs may be misleading.
- A visceral pleural line with absence of lung markings peripherally is the classic radiographic sign of pneumothorax. When the chest radiograph is obtained in the supine position, the signs are very different.
- Pulmonary ultrasonography is a promising technique for detection and exclusion of pneumothorax, especially in critically ill patients.
- PBT refers to alveolar rupture owing to elevated transalveolar pressure. The clinical presentation can vary, ranging from absent symptoms with subtle radiographic findings to respiratory distress or cardiac arrest owing to a large tension pneumothorax. Prevention is critical and limiting plateau pressures to less than 30 cm H_2O may be an effective approach.
- The approach to management of a pneumothorax is dictated by the clinical condition rather than merely the size of the pneumothorax, which is best estimated by CT scan of the chest. Expectant therapy is recommended for a small PSP in a stable patient. Reabsorption of air is hastened by 100% oxygen.
- Air can be removed by simple aspiration, a small-lumen catheter, or tube thoracostomy. Unstable patients with a large secondary pneumothorax must be managed with tube thoracostomy.
- Tension pneumothorax is a medical emergency and requires a high clinical suspicion followed by prompt thoracostomy if the patient is clinically stable. However, in an unstable patient, needle decompression followed by chest tube placement may be required.
- Definitive management of recurrent pneumothorax or persistent leak can be done by open thoracotomy or video-assisted

thoracoscopy associated with pleurodesis, pleural abrasion, parietal pleurectomy, or bullectomy. In patients unsuitable for or unwilling to undergo surgery, chemical pleurodesis via a chest tube may be done.

- Pneumothorax tends to recur in patients with CF. Blebectomy, without stripping the pleura, is recommended in these patients so that they may remain transplant candidates. Pleurodesis should not be done in these cases because adhesion development jeopardizes subsequent lung transplantation.
- Pneumothorax in pregnancy is managed in the usual manner initially. In view of the high recurrence rates during parturition, thoracotomy with resection of blebs should be considered.

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Review Questions

1. A 58-year-old man with a history of COPD presents to the emergency department with dyspnea. A chest x-ray confirms the presence of a pneumothorax. Which of the following increased his risk for developing a spontaneous secondary pneumothorax?
   a. COPD
   b. Body mass index (BMI) of 28
   c. Previous history of tobacco use
   d. Previous history of intravenous drug use
   Answer: a. COPD is a known risk factor for developing a pneumothorax. Current, not previous, intravenous drug abuse is a risk factor related to attempted subclavian or supraclavicular injection attempts. A previous history of tobacco use or a BMI of 28 are not risk factors.
2. Pulmonary barotrauma (PBT) refers to alveolar rupture as the result of elevated transalveolar pressure (the alveolar pressure minus the pressure in the adjacent interstitial space). Which of the following has been identified as an independent risk factor for PBT?
   a. BMI greater than 30
   b. Plateau pressure less than 30 cm H_2O
   c. Acute respiratory distress syndrome (ARDS)
   d. Pneumonia
   Answer: c. ARDS has been identified as an independent risk factor for developing PBT. BMI greater than 30 and pneumonia have not been identified as risk factors. Plateau pressure less than 30 cm H_2O will help prevent PBT.
3. A 45-year-old woman with a history of asthma is intubated urgently in the intensive care unit (ICU) because of a severe asthma exacerbation. Three hours after intubation, despite heavy sedation, her peak and plateau pressures on the ventilator continue to increase. Her systolic blood pressure has decreased from 150 mm Hg to 84 mm Hg. Physical examination reveals decreased/absent breath sounds over the right lung. Her trachea is deviated to the left. Which of the following is the most correct next step?
   a. Obtain a chest x-ray
   b. Initiate paralytics
   c. Insert an 18-gauge needle in the second intercostal space for midclavicular line followed by aspiration of air
   d. Disconnect from ventilator and perform bag-mask ventilation
   Answer: c. The patient has signs of a tension pneumothorax involving the right lung with hemodynamic compromise. The correct answer is to aspirate the air as described.
4. A 60-year-old man presents to his pulmonologist after being discharged from the hospital after experiencing a pneumothorax. The patient is asking if he is at risk for a recurrent pneumothorax. Which of the following are established risk factors for recurrence of a pneumothorax?
   a. Age greater than 50
   b. COPD
   c. More than one episode of pneumothorax
   d. b and c
   Answer: d. Explanation: Both COPD and a prior episode of a pneumothorax are established risk factors for developing a subsequent pneumothorax.
5. A 21-year-old man presents to the local emergency department (ED) with sudden onset of chest pain. A chest x-ray confirms the presence of a 2-cm left pneumothorax. While in the ED the patient's chest pain resolves. His vital signs are stable on room air. Which of the following is the correct next step?
   a. Simple aspiration with an 18-gauge needle followed by a chest x-ray
   b. Chest x-ray in the ED to confirm stability of the pneumothorax. Once confirmed, discharge from the ED with follow-up with his primary care physician in 24 to 48 hours and a repeat chest x-ray.
   c. High-flow oxygen with inpatient admission
   d. Tube thoracostomy followed by admission to the hospital
   Answer: b. Based on a study evaluating outcomes of patients presenting to an ED with a primary spontaneous pneumothorax, patients who are clinically stable with a small (<2–3 cm) pneumothorax may be observed. A large pneumothorax (>25% of the pleural space) or a symptomatic patient may require more invasive treatment.

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Toxic Gas, Fume, and Smoke Inhalation

JOHN F. FRASER, DIRK M. MAYBAUER, AND MARC O. MAYBAUER

CHAPTER OUTLINE

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- History

Pathogenesis of Inhalation Injury
- Toxic Smoke Compounds
- Heat
- Systemic Toxins
- Airway Injury
- Pulmonary Parenchymal Injury

Diagnostics and Treatment
- Initial Prehospital Rescue
- Airway Management
- Monitoring and Investigations
- Fluid Resuscitation
- Treatment of Carbon Monoxide Intoxication
- Treatment of Cyanide Intoxication
- Bronchoscopy
- Mechanical Ventilation
- Nebulization Treatments
- Nonventilatory Pulmonary Treatments
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Epidemiology

The global burden of disease represented by inhalation injuries continues to grow. Industrialization of developing nations results in increased morbidity and mortality. Inhalation injury can be defined as "an injury due to the inhalation of thermal and/or chemical irritants" and consists of both acute and chronic exposures.

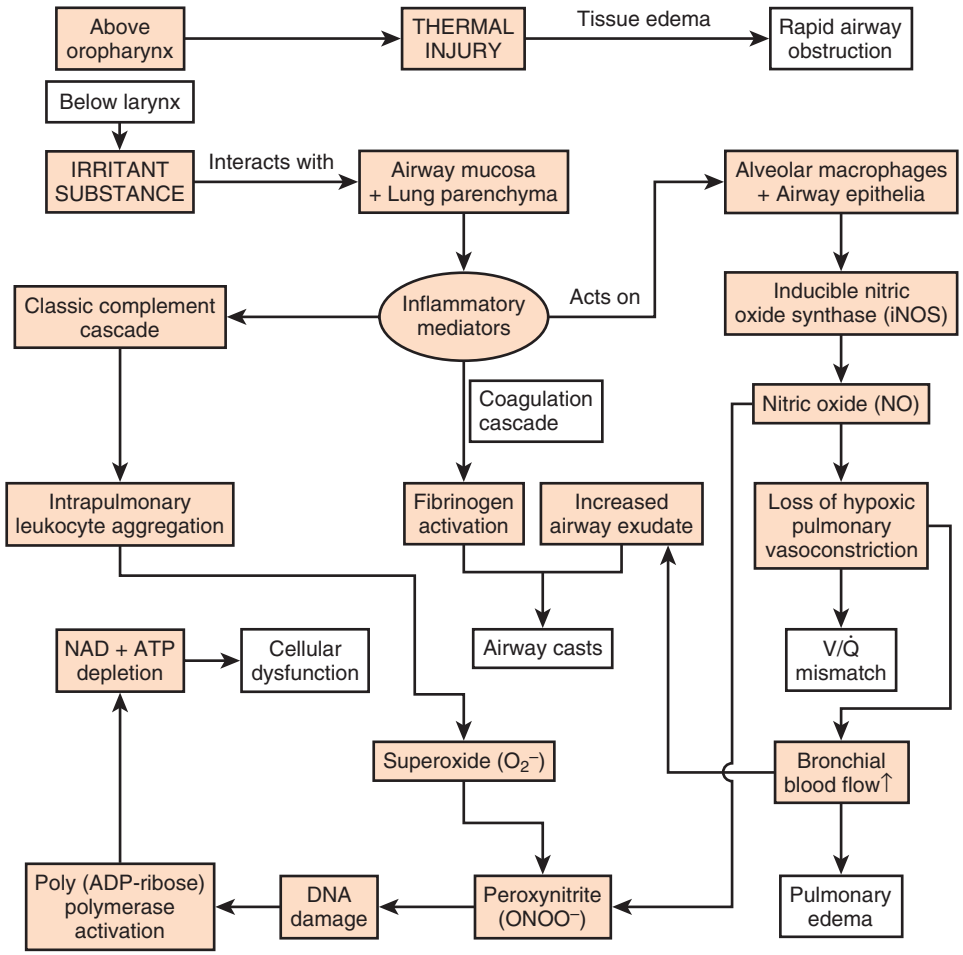
Chronic exposure to inhalation of atmospheric pollution may damage the lung over decades, predisposing to infection, pulmonary fibrosis, or cancer.[1] The World Health Organization estimates that more than a billion people, mainly in developing countries, develop airway and pulmonary inflammation resulting from inhaled smoke from indoor cooking fires, forest fires, and burning of crops.[2] In the industrial world, chronic inhalation injury may be due to cigarette smoking or occupational exposure (e.g., asbestos). This aspect of inhalation injury is not further discussed in this textbook, and readers are referred to other resources.[3]

Acute smoke inhalation results in approximately 23,000 injuries and 5000 to 10,000 deaths per year in the United States alone. Among industrial countries, the United States has one of the highest incidences of smoke inhalation injuries.[4] The ensuing pulmonary derangements, which follow burn and smoke inhalation injuries, are major contributors to morbidity and mortality in fire victims. The pathophysiology of the injury is multifaceted and induces distant organ dysfunction (Fig. 46.1). The consequences of the profound airway inflammation are heightened by pulmonary shunting and augmented microvascular pressure gradient, resulting in hypoxemic respiratory failure.[5] Although survival from burn injury continues to improve, this is not mirrored in inhalation management. The acute lung injury (ALI) caused by smoke inhalation and pneumonia has a major negative impact on mortality figures in patients with burn injuries. Inhalation injury alone increases mortality in burn victims by approximately 20% and pneumonia increases the rate by approximately 40%, with a maximal increase of approximately 60% when both are present.[6] However, age and burn surface area are risk factors of mortality, whereas the impact of patient- and center-level variables and treatments on survival is unknown. In a recent study of burn and nonburn centers at 68 U.S. academic medical centers, it was shown that in addition to older age and major surface burns, mortality in smoke inhalation–related ALI is predicted by initial vasopressor use, higher diagnostic-related group–based risk-of-mortality assignment, and care at centers with fewer than 500 beds, but not by initial antibiotic therapy.[7] Inhalation injuries are considered an independent risk factor for acute respiratory distress syndrome (ARDS).[8] The mainstay of treatment of the person with smoke inhalation remains optimal respiratory support with airway toilet, adequate fluid resuscitation, early and aggressive surgical interventions, and precise antimicrobial interventions. Continued research into this systemic process is needed to stop smoke inhalation injury from being the major cause of death in fire victims.[9]

History

Inhalation injuries resulting from both toxins and smoke have been recorded in the history books for several thousand years and have been used with enmity from the outset. Thucydides records the Spartans burning pitch, naphtha, and sulfur to produce sulfur dioxide while attacking Athenian cities in 423 BC.[10] The fifteenth century brought incendiary devices filled with sulfa and belladonna.[11]

The history of toxic gases other than smoke tends to run hand in hand with military conflict, and it was not until the First World War, during which at least 14 different toxic respiratory agents were used, that the increased usage sparked off once more. The years 1914 and 1915 marked the modern nascence of inhalation warfare when France released chloroacetone and Germany released thousands of liters of chlorine gas in Belgium, at Ypres. More than



• **Fig. 46.1** Pathophysiology of acute smoke inhalation injury. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *NAD,* nicotinamide adenine dinucleotide; *V̇/Q̇,* ventilation-perfusion.

1 million casualties were attributed to the use of chemical agents during that war, with sulfur gas being anointed as the "king of battle gases."[12]

The 1925 Geneva Protocol signed by many countries pledged never to use gas warfare again.[11] Sadly, this has not been adhered to, with Italy being accused of using mustard gas against Abyssinia in Ethiopia. The Chinese suffered gas inhalation at the hands of the Japanese during the Second World War, and the Kurds were victim to similar agents during the attacks by Iraq through the 1980s.[13] Sarin gas poisoning was used in Japan in the mid-1990s. In 1994 and 1995, inhaled biochemical weapons were used for terrorism acts like the sarin gas attacks in Japan.[14] More recently, it is believed that gas inhalation has been used extensively by the Assad regime in Syria.[15] Cyanide (CN) may be considered one of the most likely agents of chemical terrorism, as it is capable of causing mass incapacitation and casualties and can cause mass confusion, panic, and social disruption. In addition, CN possesses all attributes of an ideal terrorist weapon: it is plentiful, readily available, and easily obtainable because of its widespread use in industry and laboratories.[16] Although military interest in biochemical warfare diminished after World War II, there was an understanding of the devastation possible with nuclear weapons; terrorist organizations understand the fear, panic, and collapse of infrastructure that could be realized through the release of such a substance in a busy city. It seems likely that there are many areas of the world where such agents are, or can be, manufactured in great quantities.[11]

Equally, smoke inhalation has a long record in history, with the first recording by Pliny in the first century AD. He described the execution of prisoners over greenwood smoke, and it seems he may have died through toxic smoke inhalation himself during the eruption of Mount Vesuvius in 79 AD. More recently, two much more industrial occurrences highlighted the problems of smoke inhalation. The Cocoanut Grove fire of 1942 resulted in the deaths of 491 people who were trapped in a burning building. The number of patients who sustained burns was minimal, and it was then that the realization hit that smoke alone could kill as easily, if not more so, than cutaneous burns.[17] More than 2000 burn/smoke casualties resulted after the chain of fires and explosions that rippled through refineries and factories in Texas City, Texas, in the 1940s.[18] The understanding of smoke and carbon monoxide (CO) inhalation in enclosed spaces was further highlighted in the fire at the MGM Grand Hotel in Las Vegas in 1980 and the Stardust Nightclub fire in Dublin in 1981. Again, the small number of burn injuries was dwarfed by the deaths resulting from smoke and CO.[19] CN's independent role became clear in the 1980s, particularly after the aircraft fire at Manchester International Airport, Manchester, UK, in 1985 in which the majority (87%) of the 54 individuals who died had potentially lethal levels of CN in their blood, as opposed to only 21% of the victims with carboxyhemoglobin (COHb) levels

exceeding 50%. This event highlighted that different combustants produce different inhalants, and depending on the environment, these may be more lethal than CO, which had been regarded as the primary toxic threat.[4] Hence, the determinants of inhalants are both environment and material being combusted. It is therefore a mixed toxicology after smoke inhalation.

The terrorism attacks on September 11, 2001, on the World Trade Center in New York were associated with a high incidence of inhalation injuries. Among the 790 injured survivors, 49% incurred inhalation injury caused by toxic compounds in the smoke and dust.[20,21] Industrial catastrophes, biochemical warfare, and terrorism will continue to occur. This chapter's aim is to help physicians diagnose and then manage patients with inhalation injuries.

Pathogenesis of Inhalation Injury

Toxic Smoke Compounds

Smoke is a heterogeneous compound. Each fire produces different toxic features relating to the material combusted and the environment in which the fire occurs, specifically oxygen content. Hence, each patient with smoke inhalation may represent a new condition with a possibility of many different inhalants.[22] The components of smoke that cause damage are as follows:

- Heat.
- Particulates, deposited in the airways according to their size, with substances smaller than 1 μm in diameter able to reach the alveolar zone suspended in air. At that site, these chemically laden particles increase airway resistance and cause cell lysis and irritation while diminishing pulmonary surfactant production and efficacy.[22]
- Systemic toxins, such as CO and CN, that adversely affect oxygen transport by erythrocytes and utilization by mitochondria.[23]
- Respiratory irritants are implicated in the high mortality rates. Water-soluble gases such as ammonia and hydrogen chloride react with water contained in mucous membranes and produce strong alkalis and acids, which elicit profound inflammatory reactions, which rapidly induce systemic changes via the dense alveolar-capillary interphase. Lipid-soluble irritants (e.g., oxides of nitrogen, phosgene, and aldehydes) exert their effects more slowly as they dissolve into the cellular membrane.[24]

Heat

Burns to the nasal and oropharyngeal mucosa are common in fire-exposed victims, but it is rare to encounter thermal injury below the vocal cords. This is because the oropharynx acts as an effective "heat sink," with the thermal energy of the heated air dissipating into the cells they pass by, causing rapid cell injury, necrosis, and swelling of the upper airway (Fig. 46.2). This can result in upper airway obstruction, which can be fatal before the sequelae of pulmonary burn become apparent. Superheated steam is an exception, where the oropharynx cannot absorb all the thermal energy, and hence airway burn occurs in this situation.[25]

Systemic Toxins

Systemic toxins are products of incomplete combustion and include CO and hydrogen cyanide. CO intoxication, together with heat incapacitation and a hypoxic environment, is the most common immediate cause of death from fire.[23] CO is an odorless, colorless gas that binds to erythrocyte hemoglobin with about 250 times the affinity of oxygen. The resulting COHb molecule is unable to transport oxygen, thus impairing oxygen delivery to the tissue and shifting the oxygen-dissociation curve to the left.[26] Furthermore, at the tissue level, CO competes with, and inhibits, oxygen binding to the cytochrome oxidase system of enzymes, inhibiting the aerobic metabolism chain and thus incapacitating cellular respiration.[24] Hence, CO paralyzes oxygen carriage in the blood and subsequent utilization in the tissue (see Table 46.1). Thermal decomposition of nitrogen-containing polymers in oxygen-poor environments produces smoke containing hydrogen cyanide, inhibiting electron transport and cellular respiration.[22] Therefore inhalation of oxygen-deficient gas can cause hypoxic brain injury, which is treated like any anoxic brain injury; the neurologic outcome of treatment is variable.[27]

• **Fig. 46.2** Swollen hyperemic epiglottis and narrowed laryngeal opening.

Airway Injury

Although the inhaled gases as described earlier can cause significant and fatal alterations in physiology, the chief mediator of the pathophysiology of smoke inhalation is particulate matter. Carbonaceous particles (soot) impregnated with a multitude of toxins reach the alveolar level suspended in air.[28] The chemicals associated with these particles vary depending on the products combusted but commonly include aldehydes from cellulose-based materials such as wood and paper; nitrogen oxides from fabric combustion; halogen acids and sulfur dioxide from rubber; ammonia from wool, silk, and polyurethane; and phosgene from polyvinyl chloride.[25] Water-soluble compounds are readily soluble in airway mucus and interact freely with tissue at more proximal levels of the respiratory system. Less water-soluble compounds (such as phosgene) penetrate the airway mucosa deeply and may cause severe delayed damage through late interaction with distal airway tissues, up to 48 hours after exposure. This is an important consideration when treating patients who initially present with apparently mild clinical effects after smoke inhalation.[25]

Pulmonary Parenchymal Injury

Although thermal injury is mostly adsorbed in the upper airway, the other components of smoke—particulate materials, systemic

toxins, and respiratory irritants—descend to the lung and trigger a cascade of events, resulting in pulmonary edema, bronchiolar obstruction, cell death, and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch.[22]

Of paramount importance is the cascade of inflammatory mediators activated by the interaction of irritant substances with the airway mucosa and lung parenchyma. The main inflammatory mediators involved are tumor necrosis factor α, interleukin [IL]-8, IL-6, IL-1β, and nuclear factor κβ.[29] Intrapulmonary leukocyte aggregation after activation of the classic complement cascade releases even more chemokines and cytokines, leading to the production of free radicals of oxygen and nitrogen[30] from nitric oxide synthase (NOS)-triggered nitric oxide (NO) and peroxynitrite ($ONOO^-$) production. The vasodilation induced by NO rapidly increases bronchial blood flow and decreases the degree of the protective hypoxic pulmonary vasoconstriction in poorly ventilated areas of the lung, resulting in $\dot{V}/\dot{Q}$ mismatch.[31] This also intensifies the spread of irritants from the pulmonary to systemic circulation. NO also combines with superoxide (O_2^-) produced in large quantities by activated neutrophils to form $ONOO^-$. This reactive nitrogen species leads to DNA damage and subsequent activation of poly (adenosine diphosphate ribose [ADP-ribose]) polymerase, an enzyme important in DNA repair. This activation and subsequent action requires a large amount of chemical energy in the form of adenosine triphosphate and nicotinamide adenine dinucleotide (NAD), the depletion of which causes necrotic cell death of deprived energy-dependent tissues.[30] The combination of these effects contributes to tissue injury and increased pulmonary vascular permeability, leading to decreased diffusion, edema, and $\dot{V}/\dot{Q}$ mismatch. Furthermore, neutrophils are sequestered from the systemic circulation to the intrapulmonary compartment and are activated, and fibrinogen release by inflammatory mediators causes airway cast formation and widespread plugging. These casts obstruct a number of the smaller airways, and subsequent efforts to mechanically ventilate this inhomogeneous lung can induce ventilator-induced barotrauma as normal lung is overdistended, whereas other regions collapse and atelectasis occurs. The further tissue injury is heightened with biotrauma of ventilation, and the production of chemokines leads to a potent accumulation of damage.[24]

Much of the study of smoke inhalation injuries in animal models has focused on aspects of this pathophysiologic sequence. Attempts to manipulate and alter the chain of effects experimentally have reinforced these theories and suggested exciting treatment targets. Nevertheless, experimental treatments have yet to deliver specific therapeutic modalities that improve the course of smoke inhalation injury.[5]

Diagnostics and Treatment

Initial Prehospital Rescue

The first priority at the injury scene is rescue of the victim from the source of fire to minimize the exposure time. This is usually the responsibility of firefighters.[4] The patient must be assessed as a trauma patient and not merely as the victim of an isolated burn or smoke inhalation injury. Standard early management of severe trauma protocols must be observed, including stabilization of the neck. After the immediate administration of a high flow of O_2 to reduce COHb levels (Table 46.1), a primary survey must then follow to assess accompanying injuries, such as burns or trauma with simultaneous estimation of the extent of smoke inhalation. In addition, it is important to determine whether the victim has been exposed to an explosion and to assess the possibility of blast injury to the lung. If possible, information about comorbidities should be obtained. Standard cardiopulmonary monitoring (electrocardiogram, pulse oximetry, and noninvasive blood pressure) and intravenous access should be established.[32] CO poisoning can result in an erroneously high arterial oxygen saturation (SaO_2) reading owing to the light absorption of the classic "cherry red" hemoglobin in smoke inhalation. After these basic measures, the safety of the airway must be assessed. The risk of rapidly developing airway edema has to be taken into account even if no dyspnea is present, but it must be balanced by the real risks faced by endotracheal intubation itself in an unstable, potentially hypoxic patient with possible neck injuries. In the authors' opinion, endotracheal intubation that is entirely prophylactic is ill advised. Nevertheless, the airway with early edema is likely to worsen, particularly if significant fluid resuscitation is required for burn injury, and hence repeated and thorough assessment of the airway is mandatory.

Patients with evidence of stridor or heat and smoke inhalation injury combined with extensive face or neck burns may mandate early intubation. In the case of oral burn without inhalation injury, an airway secured early represents the safest approach. However, victims with smoke inhalation injury but no facial or neck burns can be carefully observed and can be intubated later, if necessary.[33] The patient's head should be elevated to 45 degrees to minimize facial and airway edema. In the field, fluid resuscitation can be minimized to reduce the risk of airway compromise if the necessary skills or equipment are not readily available for intubation. Nebulized adrenaline or corticosteroids may be used in the hope of minimizing upper airway edema, although there is no conclusive evidence for the efficacy of these treatment strategies.[34] Bronchospasm is frequently observed, and the nebulized administration of bronchodilators, such as β_2-agonists, will reduce this effect while improving respiratory mechanics by decreasing airflow resistance and peak airway pressures in ventilated patients. This results in improved dynamic compliance. In addition, β_2-agonists provide antiinflammatory properties, represented by a decrease in inflammatory mediators, such as histamine, leukotrienes, and tumor

TABLE 46.1 Carboxyhemoglobin Concentration and Related Symptoms

COHb (%)	Symptoms
<20	Slight headache and dilation of peripheral blood vessels
21–40	Severe headache and pulsating in temporal blood vessels, vertigo, dizziness, nausea and vomiting, circulatory collapse
41–60	Symptoms as above, syncope, tachycardia, hyperventilation, intermittent seizures, cyanosis, coma, shock, Cheyne-Stokes respiration
61–80	Coma, intermittent seizures, impaired heart and lung function, weak pulses, slow breathing, death within hours
>81	Death occurs within minutes

COHb, Carboxyhemoglobin.

necrosis factor α. Finally, β_2-agonists are associated with improved airspace fluid clearance and stimulation of mucosal repair.[35–37]

After initial stabilization of the patient, information about the type of fire and combustible materials involved, whether the fire occurred in an enclosed space, and the estimated duration of exposure should be sought. In cases of presumed specific intoxication, appropriate therapies should begin.[24] Diagnosis of such intoxications is impossible in the field, but a high degree of suspicion must be maintained if the combustion materials and enclosed space lead the treating practitioner to assume risk of CO or CN. All patients should be immediately administered 100% O_2 from a high-flow face mask to reduce the CO binding to hemoglobin. Specific therapies exist to treat the toxicity of CO and CN, which aim to reduce the serum levels of these substances (discussion to follow,[38] Table 46.2). Depending on the Glasgow Coma Scale score, the severity of injury, and the symptoms, the patient's condition may mandate intubation and mechanical ventilation with a fraction of inspired oxygen (FIO_2) of 1.

TABLE 46.2 Treatment Strategies for Acute Smoke Inhalation

Current	Under Investigation
Rescue victim from source	Activated protein C
High-flow 100% oxygen	Antiinflammatory drugs Methylprednisolone Phenytoin
Body check	Nitric oxide synthase inhibitors
Intravenous access	Antioxidants γ-Tocopherol 21-Aminosteroid
± Intubation	Endothelin-1–receptor antagonist tezosentan
If upper airway edema: Nebulized adrenaline Nebulized corticosteroids	P-selectin blockade
If bronchospasm: Nebulized α_2-agonists	Nebulized deferoxamine-pentastarch complex
If elevated COHb: High-flow 100% oxygen Hyperbaric oxygen	Mechanical ventilation: High-frequency percussive ventilation Airway pressure release ventilation Volumetric diffuse ventilator
If cyanide intoxication: Amyl nitrate Sodium thiosulfate Hydroxocobalamin Cyanokit	Extracorporeal membrane oxygenation
Mechanical ventilation Low tidal volume	Arteriovenous carbon dioxide removal
Nebulized heparin	Pulmonary decontamination with nebulized amphoteric chelating agents
Nebulized N-acetylcysteine	

COHb, Carboxyhemoglobin

Airway Management

Clinical suspicion of inhalation injury of the upper airway is aroused by the presence of certain risk factors such as history of exposure to fire and smoke in an enclosed space or a period of unconsciousness at the accident scene, burns including the face and neck, singed facial or nasal hair, altered voice, dysphagia, oral or nasal soot deposits, or carbonaceous sputum. The most immediate threat from inhalation injury is upper airway obstruction resulting from edema (see Fig. 46.2). Early intubation is recommended when this complication threatens and the patient was not intubated on scene.[39] However, exposure to smoke does not always lead to severe injury, and in the absence of overt evidence of respiratory distress or failure it may be difficult to identify patients who will experience progressive inflammation and ultimately require intubation of the trachea. When intubation occurs in the field, the optimal technique to secure a difficult airway is a contentious issue. Experienced operators may attempt to preserve spontaneous breathing, which allows patients to maintain their own reflexes even when intubation is not possible. Others may elect to perform a rapid-sequence induction, which provides better intubating conditions but oblates all of the patient's own airway reflexes. Attention should be given to gastric residuals during enteric feeding after admission to the burn intensive care unit (ICU). In addition, the development of sepsis can slow gastric emptying, which can result in retained fluids in the stomach and risk of aspiration.[32]

The condition of a patient with a compromised airway has evolved to maintenance of the airway at all costs. This primitive survival instinct is neutralized if paralyzing agents or heavy sedation is administered and the safe airway can rapidly become unsalvageable. Intubation of a spontaneously breathing patient, though more technically challenging, is safer as the patient will continue breathing at all costs. In terms of anesthetic airway management, the most profound and clinically significant effect of burn injuries on drug response relates to muscle relaxants. Burn injuries influence responses to both succinylcholine and the nondepolarizing muscle relaxants. In burned patients, sensitization to the muscle relaxant effects of succinylcholine can produce exaggerated hyperkalemic responses severe enough to induce cardiac arrest, although this tends to occur 24 to 48 hours after injury rather than immediately.[40] However, recommendations regarding the safe use of succinylcholine after burn injury cannot be given. Various authors recommend avoidance of succinylcholine at intervals ranging from 24 hours to 21 days after burn injury,[41] but it seems clear that the hyperkalemic response associated with burn does not occur in the first day and hence the drug can be used with standard precautions at this stage.

An increase in the numbers of acetylcholine receptors and the proliferation of these receptors away from the neuromuscular junction have been suggested as common mechanisms explaining both reduced sensitivity to nondepolarizing relaxants and the exaggerated hyperkalemia that may follow succinylcholine administration in burned patients. Resistance is apparent by 7 days after injury and peaks by approximately 40 days. Sensitivity returns to normal after approximately 70 days. In contrast to other nondepolarizing neuromuscular blockers, mivacurium dosage requirements in pediatric patients appear to be unchanged by burn injury.[42]

Preoxygenation may be more difficult in victims of smoke inhalation, and relative loss of mandibular mobility may impair airway manipulation, making bag-mask ventilation difficult. The swelling and distortion of the mouth and mandibular aspect of the airway may make preoxygenation and direct laryngoscopy difficult or impossible. Preoxygenation with small aliquots of

anxiolysis and analgesics (such as 0.5- to 1-mg increments of midazolam and 25- to 50-μg boluses of intravenous fentanyl) with sequential direct spraying of lignocaine to the oropharynx and then subsequently under direct vision of the larynx/epiglottic area is technically difficult but safe in experienced hands. Fiberoptic intubation with nebulized or directly sprayed lignocaine spray while maintaining spontaneous ventilation is equally safe but requires a substantial level of skill with the bronchoscope. However, pediatric patients are unable to cooperate and must be adequately sedated. Because deep sedation and full anesthesia cause collapse of pharyngeal tissues and airway obstruction, they are unsuitable for fiberoptic intubation in patients whose airway would be difficult to manage with a mask.[43]

Agents that may prove useful to facilitate fiberoptic intubation include the ultrashort-acting remifentanil. The novel α_2-adrenergic agonist dexmedetomidine, which provides sedation, anxiolysis, and analgesia with much less respiratory depression than other sedatives,[44] may be considered, although further data are required until its widespread use is adopted. Ketamine remains a very useful drug, as it provides some analgesia and facilitates a degree of spontaneous breathing while allowing dissociative anesthesia; however, airway secretions may be copious and the clinician must always be aware of this.

Securing an endotracheal tube in a patient with facial burns presents a variety of problems. Tape or ties across damaged or grafted skin can worsen tissue loss or induce graft failure. A useful technique to avoid these problems involves the use of a nasal septal tie.

The use of a laryngeal mask airway has also been successful for airway management during burn surgery for children.[45] In the acute phase or in the ICU, the laryngeal mask airway serves as a rescue device when endotracheal intubation fails, but it must be replaced with a definitive airway as soon as is practically possible, as gastroparesis is common in the burn patient.

Monitoring and Investigations

Damages to the airway and lung from inhalation injury often develop with a latency of several hours and are affected by other injuries and degree of fluid resuscitation required. Nevertheless, airway management and the oxygenation status of the patient, regardless of intubation status, need to be frequently reevaluated; such is the dynamic nature of smoke inhalation injury.[25] After stabilization of cardiopulmonary hemodynamics and pulmonary gas exchange, the assumed diagnosis of smoke inhalation injury needs to be verified. However, as no uniform criteria are available, the diagnosis of smoke inhalation injury has a subjective component based on history, physical examination with supporting imaging, and blood gas assays. Bronchoscopic examination of the airway represents the gold standard to detect a pathognomonic mucosal hyperemia with soot staining below the larynx being diagnosed (Fig. 46.3). Although chest radiographs are mandatory and may reveal injuries consistent with trauma—that is, fractured ribs, pneumothorax, and pulmonary contusion—they provide little information acutely as to the degree of smoke inhalation. Specific changes that may be seen related to the smoke inhalation include signs of diffuse atelectasis, pulmonary edema, or bronchopneumonia.[46] It has been shown that airflow narrowing owing to airway wall thickening is related to the development of pneumonia and the number of mechanical ventilation days and represents an important factor of respiratory deterioration in smoke inhalation injury. The utility of computed tomography scanning on admission can reveal airway wall thickening and can be predictive for pulmonary deterioration.[47]

• **Fig. 46.3** Soot staining in the hyperemic trachea.

A uniform algorithm for assessing inhalation injury or a reliable indicator of progressive respiratory failure in patients with smoke inhalation injury has not yet been established. This failure is largely explained by the extreme heterogeneity of the clinical presentation. In addition, the delay in the manifestation and development of ALI as a consequence of systemic inflammatory response syndrome, initiated by accompanying burns or trauma, complicates the evaluation of the isolated effects of smoke inhalation. Frequent blood gas and sputum analyses are useful to monitor patients with smoke inhalation injury.[33] In addition, inexplicably high lactate levels, despite adequate fluid resuscitation, are helpful for the diagnosis of CN poisoning. In a study by Pham and colleagues,[48] CN poisoning in the canine model showed two phases of injury. The first (compensated) phase had a mechanism consistent with a traditional global oxygen consumption defect. The second (decompensated) phase had a mechanism consistent with heart failure. This heart failure was due to bradycardia. The systolic blood pressure remained relatively constant, whereas diastolic blood pressure decreased by 19%. Cardiac output, heart rate, and oxygen delvery (DO_2) increased to a maximum of 6%, 10%, and 10%, respectively, at 40 minutes, after which they declined to a low of 32%, 28%, and 30% below baseline, respectively. Stroke volume remained constant. Oxygen consumption initially increased by 5% and then decreased to 24% below baseline. The oxygen extraction ratio initially declined to 35% below baseline and then increased throughout the rest of the study. In clinical practice, serial venous blood gases may unmask cytopathic hypoxia, by insufficient O_2 extraction, that may be seen as increased central venous ($ScvO_2$) or mixed venous (SvO_2) oxygen saturations.

Fluid Resuscitation

Optimal fluid management is critical to the survival of the victim of a major thermal injury, with additional or isolated inhalation injury, and when septic complications occur. Modern fluid resuscitation formulas originate from experimental studies in the pathophysiology of burn shock. Fluid resuscitation in the patient with thermal injury has been recognized as an essential aspect of the care since the first studies were published in 1905.[49] The

improvement in outcome with cutaneous burns can be related to the development of a protocol based on providing adequate fluid resuscitation to allow optimal organ function while minimizing the physiologic cost associated with overresuscitation.

Burn shock is both hypovolemic shock and cellular shock and is characterized by specific hemodynamic changes, including decreased cardiac output, extracellular fluid, plasma volume, and oliguria. As in the treatment of other shock forms, the primary goal is to restore and preserve tissue perfusion to avoid ischemia. However, in burn shock, resuscitation is complicated by obligatory burn edema, and the voluminous transvascular fluid shifts that results from a major burn are unique to thermal trauma.[50] Blalock may have been the first to postulate the mechanism, where he induced burn to one side of mongrel dogs and assessed the weight changes in both burned and unburned tissue, demonstrating that burn tissue edema correlated to the drop in blood pressure and was similar in composition to plasma.[51] Although the exact pathophysiology of the postburn vascular changes and fluid shifts is still unclear, major components of burn shock are the increase in total body vascular permeability and the changes in microcirculation. Fluid resuscitation is aimed to support the patient throughout the initial 24-hour to 48-hour period of hypovolemia and has existed since the early 1950s.

Cope, in his seminal paper after the Cocoanut Grove disaster, was the first to report the increased fluid requirement seen in patients with smoke inhalation injury.[52] This observation has been confirmed by multiple other papers, despite the lack of thermal injury below the larynx; hence fluid loss seems unlikely. One theory, which concurs with much of the known pathophysiology, relates to inflammatory excess seen after smoke inhalation. Approximately 28% of all neutrophils reside in the human lungs, and this percentage increases after inhalation insult. As described earlier, it is well recognized that the particulate and chemical nature of inhalation injury induces neutrophil activation and the release of numerous cytokines, proteases, and free radicals. This further recruits neutrophils from the systemic circulation, and the local inflammatory state rapidly becomes systemic owing to the vast alveolocapillary interphase transporting these mediators and modulators of vasodilatation to distant organs. The upregulation is not only in number but also in responsiveness to endotoxin.[24,53] Regardless of mechanism, numerous authors have reported that smoke inhalation per se increased the fluid requirement substantially.[54–56]

Although underresuscitation in thermal and smoke inhalation injury is known to induce organ failure and death, there are growing concerns with overresuscitation, where the "fluid creep" can induce increased extravascular water content, resulting in compartment syndrome in extremities or in the abdomen.[57] Even after thousands of patients have been saved by fluid resuscitation, resuscitation formulas are still controversially discussed, depending on advantages and disadvantages for the individual patient. Crystalloid solutions, such as lactated Ringer solution (sodium concentration 130 mEq/L), are the most popular resuscitation fluids currently used. Crystalloid formulas are the Parkland formula (which recommends 4 mL/kg per percent total body surface area [TBSA] burn in the first 24 hours, with half of the amount administered in the first 8 hours) and the modified Brooke formula (which recommends 2 mL/kg per percent TBSA burn). Colloid formulas, the dextran formula, and hypertonic saline solution formulas are also in use.[50,58–60]

Concerns with colloid administration in the resuscitation of early burns began with the work of Goodwin and colleagues in the 1980s,[61] who suggested that there was a lack of benefit over crystalloid and potential pulmonary harm, and research grew substantially in the late 1990s, but more recent work suggests that concerns of increased capillary leak, particularly in the lungs, are overplayed, and the pendulum seems to be swinging back toward the judicious use of colloid to minimize the risk of abdominal compartment syndrome (ACS). A randomized controlled trial (RCT) by O'Mara and colleagues compared plasma with crystalloid in burn resuscitation and showed that colloid resulted in less abdominal compartment syndrome but no demonstrable improvement in outcome.[62]

Early studies in fluid resuscitation post smoke inhalation suggest a mean fluid requirement of 5.8 mL/kg per percent TBSA burn for optimal outcomes, but more recent studies suggest the figure may be lower than originally expected.[55]

Hypertonic salt (HTS) solutions have been known for many years for effectiveness in the treatment of burn shock by fluid-sparing effects and a reduction of volume load in the early phase of injury.[63] Rapid infusion leads to serum hyperosmolarity and hypernatremia, reducing the shift of fluids from intravascular to interstitial areas, which may prevent edema formation and the need for escharotomy.[64,65] The use of HTS, however, is controversial because although there may be beneficial effects, other studies have demonstrated an increase in mortality with HTS treatment of major burns.[66]

Part of the dubiety regarding the exact volume required relates to the lack of consensus of scoring severity of inhalation injury. The extent of cutaneous burn can be readily assessed. Such a scoring system for inhalation injury is lacking, and inhalation can be mild to moderate or severe. In a 3-year retrospective review by Endorf and Gamelli, numerous demographic and injury-related factors, including bronchoscopic scoring, failed to determine which patients with inhalation injury required increased fluid resuscitation. From its 80-patient cohort, the authors postulated that a PaO_2/FIO_2 ratio of less than 350 may be the best early determinant of which patients would require excess fluid resuscitation.[67]

In addition to hypovolemia, the risk of infection in smoke inhalation patients is extraordinarily high. Shirani and coworkers[6] have shown that inhalation injury alone increased the mortality of burn patients by a maximum of 20%, and pneumonia by a maximum of 40%, with a maximum increase of approximately 60% when both are present. These data indicate that inhalation injury with additional septic complications such as pneumonia has significant, independent, additive effects on burn mortality and that these effects vary with age and burn size. The presence of inhalation injury and sepsis increases the fluid requirements for resuscitation from burn shock after thermal injury.[54] Chen and coworkers[68] have demonstrated that HTS confers beneficial effects on burn shock, reduces bacterial translocation, and enhances host defenses by several mechanisms in the treatment of burn shock and sepsis. It is of high interest to further investigate HTS in animal models and later in humans. Future studies with HTS alone and in combination with already established resuscitation formulas are needed to find a risk/benefit ratio for such a treatment. HTS may have the potential to improve resuscitation strategies and outcome in burn care, but it cannot be recommended at the present time because of a lack of evidence.[69]

Despite the treatment of septic complications after inhalation injury, the gradual shift toward less fluid in both burn and smoke inhalation may relate to the changes in the ICU modalities of care—including point-of-care devices to assess oxygenation, less injurious ventilation, and more rapid debridement of burn tissue.[70]

Debates and ongoing research on fluid resuscitation may last for decades, but they are needed to improve outcomes in this patient population. However, in the authors' experience

it is worthwhile to start fluid resuscitation using the modified Brooke formula (which recommends 2 mL/kg per percent TBSA burn) to closely monitor urine output (0.5–1 mL/kg per hour recommended) and to increase fluid administration up to a rate that will maintain the recommended urine output. This strategy may prevent initial overresuscitation in many patients, decreasing edema formation, and will suit the increased needs of patients with inhalation injury who may need up to 6 to 8 mL/kg per hour to maintain adequate organ perfusion. Excessive fluid administration beyond a urine output of 1 mL/kg per hour is ill advised.

Although protocols should not be abandoned, a routine and recurrent assessment of the patient with inhalation injury would be essential to minimize physiologic injury as a result of fluid resuscitation, whether too little or too much.

Treatment of Carbon Monoxide Intoxication

Current treatment recommendations of CO poisoning begin with cessation of exposure, immediate administration of 100% oxygen, and supportive care.[71] The rationale of hyperbaric oxygenation therapy (HBOT) is based on its ability to rapidly displace CO from hemoglobin, thus reducing the duration of the hypoxemic state. Administration of 100% oxygen at 3 atmospheres reduces the CO half-life from 250 minutes in room air to 30 minutes.[33] Besides this efficiency, its use remains controversial owing to the questioned correlation between COHb levels and outcomes. This may also be explained by limited access to the patient during HBOT, which has a major impact on the treatment quality of combined burn injuries.[33] A Cochrane database review of six RCTs did not reveal a beneficial effect of HBOT compared to standard treatment in respect to neurologic sequelae.[72] However, the results should be interpreted with care, as concerns have been raised regarding the design and analyses in all the included trials. In summary, all patients with CO intoxication should be immediately treated with 100% oxygen. Although data do not support its routine use, HBOT may be considered in stable patients with severe neurologic symptoms and high COHb concentrations (>50%), but no major burns or severe pulmonary injury.[53]

Treatment of Cyanide Intoxication

Hydrogen cyanide in fire smoke is an underappreciated threat and one of the most common poisonings in patients who incur smoke inhalation.[73] Its lipophilicity and lack of dissociation allow it to penetrate through mucous membranes with ease, resulting in a myriad of symptoms within minutes, and possible death if the dose is large enough.[74] Patients may describe a burning, dry throat with inexplicable feelings of anxiety. Clinical signs range from a patient presenting with tachypnea, confusion (and the classic almond breath fetor) to unconsciousness, cardiovascular collapse, and death, generally from respiratory arrest (Table 46.3).[23] The key for the receiving clinician is to have a high index of suspicion in such a patient, as there is no immediately available laboratory test. Blood gas analysis may reveal an inexplicably high lactate level in the absence of CO poisoning or other trauma. However, CN poisoning frequently coexists with significant CO poisoning, and hence may be overlooked.[4,75] For adequate treatment of CN poisoning after smoke inhalation injury, several antidotes are available: The "CN antidote kit" includes amyl nitrite, thiosulfate, and sodium nitrite.[76] Because these substances are methemoglobin generators, which may additionally impair oxygen transport, they should be used only in the case of proven diagnosis (increased plasma levels of CN) and under continuous monitoring in the ICU, particularly in episodes of poisoning with CO simultaneously.[33] Methemoglobin chelates CN to form cyanmethemoglobin. As cyanmethemoglobin dissociates, free CN is converted to thiocyanate by liver mitochondrial enzymes (rhodanese) using thiosulfate as a substrate. Thiocyanate is then excreted into the urine.[77] In contrast to these antidotes, hydroxocobalamin, a vitamin B_{12} derivative, actively binds CN by forming cyanocobalamin, which will be directly excreted by the kidneys.[38] Data are growing regarding the safety and efficacy of hydroxocobalamin. Prospective observational studies reveal that empiric administration of hydroxocobalamin was associated with survival among 67% of patients who were confirmed after administration to have had CN poisoning. An RCT in pigs assessed the efficacy of hydroxocobalamin versus sodium thiosulfate in the treatment of acute CN toxicity. The study indicated that in severe poisoning (CN administered to hypotension to 50% of baseline blood pressure), hydroxocobalamin was safe, efficacious, and resulted in much improved survival. Worryingly, sodium thiosulfate failed to reverse CN-induced shock. The authors concluded that only hydroxocobalamin was effective.[78] In case of intoxication with cyanide the recommended initial dose is 70 mg/kg IV infusion over 15 minutes.[79] Because of the avoidance of methemoglobin production, hydroxocobalamin can be used safely in the preclinical setting. Accordingly, hydroxocobalamin represents the active compound of the Cyanokit (Meridian Medical Technologies, Inc., Columbia, MD), which is used in the prehospital management of smoke inhalation injury in Europe with a reported improvement in mortality.[38]

Aggressive restoration of cardiopulmonary function augments the hepatic clearance of CN via the enzyme rhodanese and has been reported to be successful in severe CN poisoning (blood levels 5.6–9 mg/L) as well as after ingestion or smoke inhalation, even without the use of antidotes.[80–82] Hydroxocobalamin has been used safely and successfully by emergency personnel in out-of-hospital settings and may represent a new option in cases of suspected or confirmed CN poisoning in the field.[83] Therefore the standard care of CN poisoning should combine the aggressive supportive therapy with current data supporting the use of hydroxocobalamin as the optimal specific therapy.[53]

TABLE 46.3 Hydrogen Cyanide Concentration in Air and Related Symptoms

Hydrogen Cyanide (ppm)	Symptoms
0.2–5	Odor threshold
10	Occupational exposure limit
18–36	Slight symptoms, headache
45–54	Will be tolerated for 30–60 min
100	Death within 1 h
110–135	Death within 30–60 min
181	Death within 10 min
280	Immediate death

Bronchoscopy

Within each burn center, diagnostic as well as treatment options are determined by the availability of resources (such as xenon 133 scans, fiberoptic bronchoscopy, or 24-hour/day anesthesia staff coverage) and local tradition. A clear diagnosis proving smoke inhalation has occurred allows for the planning and delivery of therapeutic interventions.[46] Inhalation injury can be diagnosed with confidence based on clinical presentation and bronchoscopic findings. Changes observed with bronchoscopy include erythema, lesion, erosion, ischemia, or necrosis of the mucous membrane, as well as small to significant edema, blisters, and unidentified damage of the lung parenchyma when the changes in the lower respiratory tract are below the reach of the fiberoptic scope, which can be used for inspection of the upper (oropharynx) and main (trachea and bronchi) respiratory tract[84] (see Figs. 46.2 and 46.3).

Early prediction of which patients are vulnerable to resuscitation stresses, increased pulmonary complications, respiratory failure, and mortality is complex and frequently not possible. Many attempts to identify prognostic indicators for patients with smoke inhalation injuries have been made.[85,86] It has been difficult to identify reliable indicators of progressive respiratory failure in patients with smoke inhalation injury. Most of these studies have involved small numbers of patients and assessed a small number of clinical features. Prognostic estimations will ultimately rely on a system that allows quantification of the severity of inhalation injury.[46] Many observational studies have compared outcomes with various grading systems.[73,84,87,88] These grading systems often combine bronchoscopic findings with a small number of other clinical findings. However, it has been recognized that proximal injury observed by bronchoscopy is frequently greater than the peripheral, parenchymal injury. Masanes and colleagues[89] found that inhalation injury could be diagnosed by fiberoptic bronchoscopy in some burn patients who were otherwise asymptomatic. Liffner and colleagues[88] found that their scoring system for grading the severity of bronchoscopic evidence of inhalation injury did not correlate with the development of ARDS. Similarly, although it is generally recognized that inhalation injury increases fluid resuscitation needs in burn patients, Endorf and Gamelli found no correlation of severity of bronchoscopic findings with fluid resuscitation requirements.[67] In a review article, Woodson concluded that a consensus may be facilitated when a clinical variable or constellation of variables is identified that is reliably related to the development of respiratory failure or other complications in patients who have inhaled smoke.[46] A large multicenter study combining the experience of several institutions is more likely to identify such a correlation. However, consensus in diagnosis and quantification of inhalation injuries may await a theoretic advance with identification of a mediator or marker of cell injury or cell death that reliably and in some concentration-dependent way correlates with pulmonary or systemic complications of inhalation injury.

A widely accepted grading system for inhalation injury severity is presently not available. However, a randomized controlled multicenter trial to validate a standardized scoring system for inhalation injury that can be used to both quantify injury severity and predict mortality after inhalation injury is warranted.[46]

Mechanical Ventilation

Since the advent of positive-pressure ventilation, there has been an understanding that this therapeutic maneuver can paradoxically cause harm as well as save lives. Numerous studies have tried to identify optimal ventilatory strategies, positive end-expiratory pressure (PEEP) levels, and modes. An open lung strategy with low–tidal volume ventilation has been shown to be associated with improved outcome and reduced duration of ventilation.[90] In keeping with the ARDS Network data, low tidal volumes are mandated to minimize ventilator-induced lung injury).[91] An open lung strategy is advised owing to the decrement of surfactant in this population, but no study has shown an improved outcome with higher levels of PEEP. The frequent casts that occur after smoke inhalation result in areas of collapsed alongside open lung, and application of PEEP may result in tidal hyperinflation in areas of the lung, whereas there is an inability to aerate the collapsed area of lung. Hence, frequent airway toilet with mucolytics is essential to minimize ventilator-induced lung injury. Newer modalities such as electrical impedance tomography to assess breath-to-breath changes have demonstrated the rapid changes in ventilatory inhomogeneities seen after smoke inhalation.[92] A number of modalities have been suggested specific to the ventilatory idiosyncrasies associated with smoke inhalation.[93]

High-frequency oscillation (HOV) has been advocated by some as an alternative to the classic ARDS Network low–tidal volume ventilation in patients with smoke inhalation–induced ARDS.[93] However, a randomized trial of the use of HFO as the initial mode of mechanical ventilation in ARDS published in 2013 was stopped early owing to increased mortality in the HOV arm (47%) versus control (35%).[94] It is now recommended that HOV not be used in the initial mechanical ventilation of ARDS.

The volumetric diffusive respirator (VDR) is a pneumatically powered, pressure-limited ventilator that stacks oscillatory breaths to a selected peak airway pressure by means of a sliding venture called a Phasitron (Percussionaire Corporation, Sandpoint, ID), resulting in low tidal volumes. Exhalation is passive and a level of continuous positive airway pressure can be selected. In addition, VDR reestablishes the physiologic diffusive gas exchange, whereas standard ventilation modes induce a convective gas exchange.[95] A prospective clinical analysis revealed an improved gas exchange and a decrease in peak pressures.[96] A retrospective study in 330 patients with inhalation injury even reported a lower mortality rate.[97] Although these studies compared the VDR to high-volume ventilatory strategies, data regarding a comparison with modern low–tidal volume ventilation are still lacking. This may represent one reason why VDR is not universally accepted. Another factor might be that the VDR differs from other ventilators and therefore requires special training. In addition, tidal and minute volumes cannot be monitored, and humidified air and nebulized saline solution are necessary to prevent airway desiccation.[53]

As in conventional long-term ventilation of patients, common complications must be considered. Mosier and associates[98] documented that patients with combined thermal and inhalation injury requiring urgent intubation or prolonged ventilation have a high incidence of bacterial bronchial contamination. Inhalation injury creates a damaged tracheobronchial mucosa, and early intubation provides a portal for bacterial contamination. In patients with smoke inhalation that necessitated urgent intubation, a 50% incidence of ventilator-associated pneumonia has been described.[99]

The use and timing of tracheostomy in burn patients elicit a great deal of passionate discussion but very little solid data. Burn survivors with TBSA greater than 60% are more likely to undergo repeated surgery and have burns to the head and neck region, therefore increasing the requirement for tracheostomy. However, an association has been demonstrated between tracheostomy and the high prevalence of chest infection in patients with inhalation

injury, greater burn size, and prolonged mechanical ventilation.[100] The authors would advise caution in overinterpreting this study, as association does not infer causation, and sicker patients tend to be ventilated for longer periods, resulting in a higher incidence of both tracheostomy and ventilator-associated pneumonia. The tracheostomy allows for less sedation, earlier mobilization, and a more comfortable method of ventilation for a long-term patient.

Nebulization Treatments

As described previously, smoke-inhalation injury causes airway damage by the destruction of the ciliated epithelium that lines the tracheobronchial tree. Casts produced from these cells, polymorphonuclear leukocytes, and mucus can cause upper airway obstruction, contributing to pulmonary failure.[24] In the early 2000s, it was proposed that a combination of aerosolized heparin and a mucolytic agent, N-acetylcysteine, can ameliorate cast formation and reduce pulmonary failure secondary to smoke inhalation. In a study of 90 consecutive pediatric burn patients at the Shriners Hospitals for Children in Galveston, Texas, who had bronchoscopically diagnosed inhalation injury requiring ventilatory support, 5000 units of heparin and 3 mL of a 20% solution of N-acetylcysteine aerosolized every 4 hours the first 7 days after the injury resulted in a significant decrease in reintubation rates, in incidence of atelectasis, and in mortality for patients treated with the regimen when compared with controls, and this practice has ever since been part of the ventilation protocol at this institution.[101] Clinical studies of frequent nebulization therapy have presented conflicting results, suggesting that increasing frequency of nebulization may increase the risk of pneumonia. Although nebulization is used in many centers, this therapy has not been universally adopted.[102]

A recent systematic review on inhaled anticoagulation regimens, in both preclinical and clinical studies, has shown improved survival and decreased morbidity without altering systemic markers of clotting and anticoagulation. In some preclinical and clinical studies, inhaled anticoagulants were associated with a favorable effect on survival. This approach appears sufficiently promising to merit a well-designed prospective study to validate its use in patients with severe smoke inhalation–associated ALI requiring mechanical ventilation.[103]

Nonventilatory Pulmonary Treatments

Extracorporeal membrane oxygenation (ECMO) is used in specialized centers for neonatal, pediatric, and adult respiratory and cardiac failure. It requires a highly skilled team of intensivists and perfusionists, and echocardiographic support is essential for optimal usage of this modality.[104,105] The goal of ECMO is to support gas exchange, allowing the intensity of mechanical ventilation to be reduced and thus decreasing the potentially injurious effects of ventilator-induced lung injury until recovery. Furthermore, ECMO may be considered the definitive rescue therapy for refractory life-threatening hypoxemia, as pulmonary gas exchange is not required. Our group performed a systematic review and meta-analysis of the literature to collect all available clinical data to elucidate the role and present evidence of ECMO on severe hypoxemic respiratory failure resulting from burn and smoke inhalation injury.[106] Only a small number of clinical trials with a limited number of patients were available. The data suggested a higher ECMO therapy survival than nonsurvival rate of burn patients with acute hypoxemic respiratory failure. ECMO run times of less than 200 hours correlate with higher survival compared with 200 hours or more, and scald burns show a tendency of higher survival than flame burns. A case series, which was published after our meta-analysis, suggested a 90-day survival rate of 28% out of 11 burn patients in ARDS requiring ECMO.[107] In contrast, data from the University Hospital of South Manchester show weaning from ECMO in 100% and a 80% survival rate in five patients (personal communication, data submitted January 2017). Most recently, a group from Taiwan reported in a small case series that venoarterial ECMO did not provide benefits for circulatory support in patients with more than 90% TBSA burn resulting from a stun grenade explosion. However, the one patient who sustained "only" 50% TBSA second-degree burns and inhalation injury that resulted in hypoxemia survived using venovenous ECMO.[108] Based on the low number of studies and patients, as well as the low grade of evidence of these studies, there are currently inadequate data to support the use of ECMO in burn or smoke inhalation injury. Even though reports are promising, especially in the pediatric burn population, this review highlighted the lack of evidence for the use of ECMO in this setting. ECMO in adult respiratory failure is controversial, as early randomized trials showed poor outcomes[109–111] and use has been limited to highly specialized centers. Nevertheless, ECMO technology and expertise have improved. Recently the Conventional Ventilation versus ECMO for Severe Adult Respiratory Failure trial[112] and selected case series have shown improved outcomes, with survival of 75% to 85% in refractory respiratory failure.[113,114] Therefore RCTs of patients with burn and smoke inhalation injury are warranted to provide definitive recommendations and to further advance this therapeutic option in patients when other ventilatory modalities have failed. Currently there are large animal studies assessing the efficacy of ECMO in severe smoke inhalation that have shown promising results.[115]

Experimental Treatments

Against the background of the current literature, there has been a remarkable increase in our knowledge about the pathogenesis of smoke inhalation injury. There are several promising therapeutic approaches, including the nebulization of adrenaline, β_2-agonists, antioxidants, anticoagulants, intratracheal instillation of perfluorohexane, as well as the use of different ventilation modes.[116–126] However, as has been highlighted, smoke inhalation may begin as a single-organ injury but rapidly becomes systemic. Hence, although treatment paradigms may focus on smoke inhalation, it is more frequently a mixed insult of smoke and burn, smoke and pneumonia, smoke and toxicology, and smoke and trauma. Even isolated smoke inhalation generally induces distant organ dysfunction rapidly after injury. Hence, it is unlikely that a single "magic bullet" will be found for this condition, and the clinician is best equipped with a comprehensive understanding of the complex pathophysiology and multitudinous clinical presentations of smoke inhalation injury. The treatment can then be patient and inhalation specific, with a systemic rather than organ-specific approach to these patients (see Table 46.2).

Key Points

- Smoke inhalation represents a huge burden of disease in patients with and without burn injury.
- Early signs may be mild, so a high index of suspicion must be maintained, particularly in burn victims from an enclosed environment.
- Prophylactic control of the airway should be considered in patients with worsening symptoms.
- Concomitant poisoning with carbon monoxide or cyanide should be considered when an enclosed smoke inhalation occurs, and definitive treatment should be considered early.
- Bronchoscopy is a more useful tool than chest radiograph to determine severity of inhalation injury.
- Injurious ventilatory parameters can exacerbate the acute and late-phase lung injury.
- Despite a great deal of research, exemplary critical care management is the only process that improves outcome in smoke inhalation management.

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Review Questions

1. What is the most common cause of death in patients with acute smoke inhalation?
- **a.** Carbon monoxide toxicity
- **b.** Cyanide toxicity
- **c.** Thermal injury to the lung parenchymal tissue
- **d.** Inflammatory excess induced by adsorption of toxins and interaction of irritants with mucosa

Answer: d. Carbon monoxide poisoning occurs—mostly in an enclosed space—as the result of an oxygen-deficient environment. Cyanide toxicity is similar but requires a fire substrate high in nitrogenous compounds (e.g., artificial foam, wool). Thermal injury below the cords is unusual unless the patient is deeply comatose or superheated steam is involved. The vast alveolar-capillary interphase in the lung means that there is rapid transfer of inflammatory proteins and irritants rapidly transferred systemically, which result in the majority of late-phase deaths.

2. Initial management of smoke inhalation at the scene of the injury should focus on which of the following?
- **a.** Intubation and ventilation in all smoke inhalation victims
- **b.** Provision with high concentration oxygen, with assessment of airway and cervical spine control
- **c.** Provision of intravenous hydrocortisone to minimize airway swelling
- **d.** Assessment of the size of burn and fluid requirements before determining the degree of airway injury

Answer: b. Smoke inhalations normally occur in association with trauma and must be treated as a potential neck injury until proven otherwise. Intubation can be hazardous in inhalation injury and should be undertaken only when the risk/benefit ratio has been assessed and the cervical spine status is clear. Airway injury will cause death rapidly, whereas any pathologic developments owing to fluid losses take substantially longer to occur. The key is to maximize oxygen administration as this reduces the half-life of the carboxyhemoglobin complex, minimizing the cytopathic hypoxia that results.

3. A 76-year-old female prisoner presents via ambulance after setting fire to her mattress in the local prison. She is normotensive, but despite fluid bolus her blood pressure is 114/66 mm Hg, with a pulse of 88 beats/min, and she has a serum lactate level of 6.8 mmol/L despite only a 10% body surface area (BSA) burn. The patient appears more anxious and agitated than seems normal with such a burn size. The carboxyhemoglobin level is 3.0 g/dL. What is the cause of the elevated lactate level?
- **a.** Burn shock owing to hypoperfusion
- **b.** Low cardiac output state
- **c.** Cytopathic hypoxia
- **d.** Liver failure

Answer: c. Lactate elevation is most likely due to cytopathic hypoxia (blockage of intracellular processing of oxygen) owing to cyanide. An oxygen-deficient environment with burning of a nitrogenous compound (such as furniture) can cause raised levels cyanide. There is no rapid test to define levels, and the carbon monoxide level is too low to have caused carbon monoxide toxicity. The burn size is too small to cause such a high lactate level. Cyanide toxicity must be considered in situations when the patient is "sicker" than the smoke inhalation and burn suggest they should be. The key is the environment (small space) and material combusted. Cyanide levels can be measured. The numerous methods of cyanide antidote are described in the chapter.

47

Nosocomial Infection in the Intensive Care Unit

CONSTANTINE TSIGRELIS, ROBERT A. WEINSTEIN, AND DENNIS G. MAKI

CHAPTER OUTLINE

Incidence and Profile
- Definitions
- Incidence
- Profile and Secular Trends

Morbidity and Economic Impact

Pathogenesis and Epidemiology
- Pathogenesis
- Reservoirs and Transmission
- Risk Factors

General Infection Control Measures
- Hospital Infection Control Programs
- Role of the Microbiology Laboratory
- Infrastructure—Architectural, Environmental, and Staffing—Issues
- Reliable Sterilization Procedures, Chemical Disinfectants, and Antiseptics
- Hand Hygiene
- Isolation Precautions for Communicable Infections
- Antibiotic Stewardship

Nosocomial Infections and Specific Infection Control Measures
- Intravascular Device–Related Bloodstream Infection
- Ventilator-Associated Pneumonia
- Catheter-Associated Urinary Tract Infection
- Control of Antibiotic Resistance

Avant Garde Infection Control Measures
- Selective Digestive Decontamination
- Preemptive Barrier Isolation

Approach to a Nosocomial Epidemic

Protection of Health Care Workers in the Intensive Care Unit
- General Precautions Against Biohazardous Exposure
- Vaccine-Preventable Diseases
- Non–Vaccine-Preventable Diseases of Major Interest

Goals for the Future

Intensive care units (ICUs) have contributed greatly to the survival of patients with trauma, shock states, and other life-threatening conditions[1–3] but are associated with a greatly increased risk of nosocomial (hospital-acquired) infection. Rates of nosocomial infection in patients requiring more than 1 week of advanced life support within an ICU are three to five times higher than in hospitalized patients who do not require ICU care.[4–8] Infection, usually nosocomial, is the most common cause of death, directly or indirectly, of patients who survive the early period after major trauma or full-thickness burns and is the most commonly identified cause of multiple-organ dysfunction syndrome.[9–11]

Although most of this book focuses on the diagnosis and management of critically ill patients in the ICU, we highlight prevention activities. Nosocomial infections are clearly one of the most common and serious complications of ICU care and are usually a consequence of invasive monitoring or life support therapies. Thus they are greatly preventable, and it is appropriate that measures to prevent nosocomial infections be addressed.

Published guidelines for prevention are now available, based increasingly on randomized trials that have established the efficacy of specific control measures. Knowledge and technology of asepsis with regard to surgery and high-risk medical devices are now sufficiently advanced that, if evidence-based preventive measures described in this chapter are applied consistently, the risk of nosocomial infection can be greatly reduced.[12–15]

Incidence and Profile

Definitions

Meaningful data on rates of nosocomial infection form the basis for tracking problems and measuring success of control measures within a hospital and, with a number of caveats, among hospitals. To monitor secular trends and to assess the efficacy of control measures, infection control programs must begin with clear, unambiguous definitions of nosocomial infections. Although there are no standardized definitions for infection at specific sites that are universally accepted by clinicians or investigators, the Centers for Disease Control and Prevention (CDC) has published definitions for the purpose of surveillance of nosocomial infection within hospitals, which most U.S. centers and an increasing number of hospitals around the world have adopted (Box 47.1).[16,17] For research purposes, more stringent definitions for specific infections will usually be necessary,[18] especially for pneumonia.[19]

• BOX 47.1 Definitions for Health Care–Associated Infections of the Centers for Disease Control and Prevention

Central Line–Associated Bloodstream Infection

1. Patient has a recognized pathogen cultured from one or more blood cultures (does not include organisms considered common commensals—see below) AND the organism cultured from blood is not related to an infection at another site
   OR
2. Patient has common commensal organisms (e.g., coagulase-negative staphylococci [including *Staphylococcus. epidermidis*], diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.) cultured from two or more blood culture samples drawn on separate occasions AND at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension AND signs and symptoms and positive laboratory results are not related to an infection at another site
   AND
3. Central line was in place for >2 days on the date of the bloodstream infection

Possible Ventilator-Associated Pneumonia

1. After a baseline period of ≥2 days of stable or decreasing daily minimum F_{IO_2} or PEEP values on the ventilator (i.e., daily minimum is defined by the lowest value of F_{IO_2} or PEEP during a day maintained for at least 1 h), patient has at least one of the following indicators of worsening oxygenation: increase in daily minimum F_{IO_2} of ≥0.20 over the baseline period for ≥2 days, or increase in daily minimum PEEP values of ≥3 cm H_2O over the baseline period for ≥2 days
   AND
2. After ≥3 days of mechanical ventilation and within 2 days before or after the onset of worsening oxygenation, the patient meets *both* of the following criteria:
   - Temperature (>38° C or < 36°C), OR white blood cell count ≥12,000 cells/mm^3 OR ≤4000 cells/mm^3.
   - New antimicrobial agent(s) is started and continued for ≥4 days
   AND
3. After ≥3 days of mechanical ventilation and within 2 days before or after the onset of worsening oxygenation, the patient meets *ONE* of the following criteria:
   - Positive quantitative culture at following threshold values (or corresponding semiquantitative result)[a] of one of the following specimens:
     Endotracheal aspirate ≥10^5 CFU/mL
     Bronchoalveolar lavage ≥10^4 CFU/mL
     Lung tissue ≥10^4 CFU/g
     Protected specimen brush ≥10^3 CFU/mL
     [a]If the laboratory does not perform quantitative cultures, use corresponding semiquantitative result that matches the quantitative thresholds (e.g., "moderate" or "heavy" growth, or 2+, 3+, or 4+ growth)
   - Purulent respiratory secretions (i.e., >25 neutrophils and <10 squamous epithelial cells per low-power field) plus organism identified from qualitative culture or quantitative/semiquantitative culture without sufficient growth to meet above threshold values from one of the following specimens: sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue, or protected specimen brush.
   - One of the following: (a) Organism identified from pleural fluid (from thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube). (b) Lung histopathology, defined as either: abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae or yeast forms); or evidence of infection with the viral pathogens listed later based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue. (c) Diagnostic test for *Legionella* species. (d) Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, or coronavirus.

Catheter-Associated Urinary Tract Infection

Must meet at least *ALL* of the following three criteria:

1. Patient had an *indwelling urinary catheter* at the time of specimen collection or onset of signs or symptoms, or had an indwelling urinary catheter *removed the day before* specimen collection or onset of signs or symptoms.
   AND
2. Patient has at least *one* of the following signs or symptoms:
   - Fever (>38°C)
   - Suprapubic tenderness or costovertebral angle pain or tenderness (with no other recognized cause)
   - Urinary urgency, urinary frequency, or dysuria (for patients without a urinary catheter)
   AND
3. Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥10^5 CFU/mL

CFU, *Colony-forming units;* F_{IO_2}, *fraction of inspired oxygen;* PEEP, *positive end-expiratory pressure.*
Data from CDC. National Healthcare Safety Network (NHSN). Patient Safety Component Manual. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf. Accessed March 21, 2017.

Incidence

The incidence of hospital-acquired infection is most commonly expressed as the number of infections per 100 patients hospitalized and is highest in burn units[7,20] and surgical ICUs,[5–7,20–23] with intermediate risk in medical ICUs,* and lowest risk in coronary care units.[4,7,8,20]

Recognizing that the risk of nosocomial infection within ICUs is heavily influenced by the length of stay and that the length of stay ranges widely among ICUs in the same hospital and among different hospitals, the CDC has advocated the use of rates expressed per 1000 patient-days to permit more meaningful intrainstitutional and, especially, interhospital comparisons.[25–27] Furthermore, recognizing the powerful influence of exposure to invasive devices on susceptibility to infection[28,29] and the great variation in use of devices among different ICUs in the same hospital and among different hospitals, the CDC has further recommended surveillance of device-associated nosocomial infections expressed as infections per 1000 device-days.[25] Representative rates of device-associated nosocomial infection in U.S. hospitals, which can be used for intrahospital and interhospital comparisons, are shown in Table 47.1.[25–27,30] In the future, device-associated infection rates will be sought in accreditation reviews by The Joint Commission[31] as this influential organization continues to move toward measurement of patient outcomes as the most effective way to improve patient care in the United States.

*References 4,5,7,20,23,24.

TABLE 47.1 Rates of Device-Related Nosocomial Infection in U.S. Hospital Intensive Care Units[a]

Type of Infection	Type of ICU	RATE (NO. OF CASES PER 1000 DEVICE-DAYS) 2002–2004[b]	2006–2008[c]	2010[d]	2013[e]
Catheter-associated urinary tract infection	Burn	6.7	7.4	4.7	4.8
	Trauma	6.0	5.4	3.2	4.3
	Surgical	4.4	4.3	2.4	2.8
	Medical	5.1	4.3	2.1	2.7
	Coronary	4.5	4.8	1.9	2.3
Ventilator-associated pneumonia	Burn	12.0	10.7	5.8	N/A
	Trauma	15.2	8.1	6.0	N/A
	Surgical	9.3	4.9	3.1	N/A
	Medical	4.9	2.3	1.2	N/A
	Coronary	4.4	2.1	1.3	N/A
Central line–associated bloodstream infection	Burn	7.0	5.5	3.5	2.9
	Trauma	7.4	3.6	1.9	1.4
	Surgical	4.6	2.3	1.2	1.0
	Medical	5.0	2.3	1.5	1.1
	Coronary	3.5	2.0	1.3	1.0

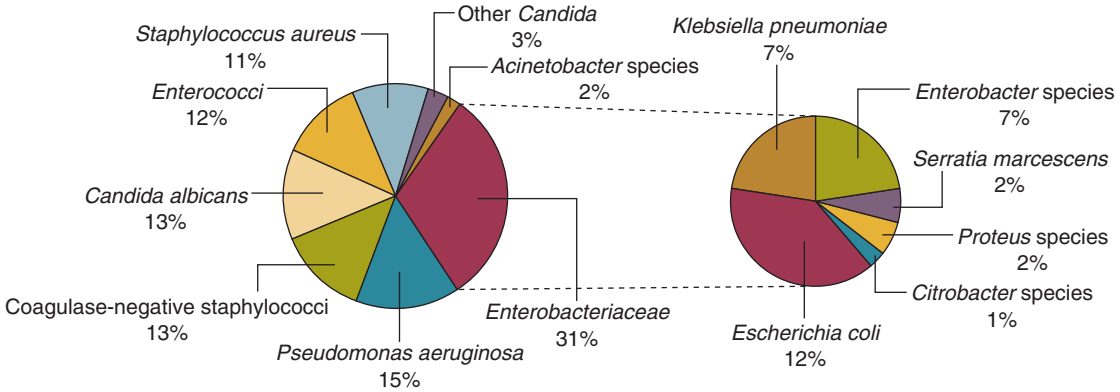
[a]Data are expressed per 1000 device days.
[b]Data from National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control.* 2004;32:470–85.
[c]Data from Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control.* 2009;37:783–805.
[d]Data from Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *Am J Infect Control.* 2011;39:798–816.
[e]Data from Dudeck MA, Edwards JR, Allen-Bridson K, et al. National Healthcare Safety Network report, data summary for 2013, Device-associated Module. *Am J Infect Control.* 2015;43:206–221.
ICU, Intensive care unit.
NOTE: Ventilator-associated pneumonia rates not included because ventilator-associated event (VAE) surveillance was introduced in 2013.

Profile and Secular Trends

Approximately 40% of endemic nosocomial infections within ICUs are catheter-related urinary tract infections, and 25% are pneumonias—most associated with endotracheal intubation and mechanical ventilatory support. Up to 10% of patients hospitalized in a medical-surgical ICU for more than 72 hours acquire a nosocomial bloodstream infection (BSI), most commonly from an intravascular device (IVD).[25,32,33] Postoperative surgical site infections, Clostridium difficile infection, nosocomial sinusitis, and nosocomial meningitis account for the remainder of ICU-related infections.[4–8,25,34–38]

Nearly 50% of nosocomial infections in the ICU are caused by aerobic gram-negative bacilli, especially Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae, and 35% are caused by gram-positive cocci, most commonly coagulase-negative staphylococci, Staphylococcus aureus, and enterococci (Fig. 47.1).39[40] Almost 15% are caused by Candida species.[39,40] Filamentous fungi such as Aspergillus and mucormycosis are being increasingly encountered in patients with hematologic malignancy or those who received solid organ transplants.[41–43] Legionella species account for up to 10% of nosocomial pneumonias in centers that make efforts to diagnose Legionella infections.[44]

The microbial profile of infections at individual sites in ICU patients is shown in Table 47.2.[40] There has been an unrelenting increase in nosocomial infections caused by intrinsically antibiotic-resistant organisms, especially P. aeruginosa, Acinetobacter species, and other resistant gram-negative bacilli; coagulase-negative staphylococci, S. aureus, enterococci; and Candida.[32,39,40,45,46] Moreover, the incidence of infection caused by organisms with acquired resistance mechanisms, especially methicillin-resistant S. aureus (MRSA); enterococci resistant to vancomycin (VRE); gram-negative bacilli resistance to extended-spectrum β-lactams and fluoroquinolones has increased even more sharply over the past several decades.[40,47] The emergence of carbapenem-resistant Enterobacteriaceae has become a significant problem as there are limited therapeutic options to treat these pathogens.[40,48] Finally, Candida auris is an emerging Candida species that has often been found to be multidrug-resistant, including in some cases to all three major antifungal classes, and has caused health care–associated outbreaks with high mortality.[49,50] There is evidence that C. auris may spread within health care settings and the CDC recommends certain preventive measures for patients colonized or infected with



• **Fig. 47.1** Microbiology of nosocomial infection in the intensive care unit (ICU). Based on 13,317 infections occurring in ICU patients in 97 participating U.S. hospitals in the Centers for Disease Control's National Nosocomial Infections Surveillance System, January 1992 through July 1997. (Data from Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med.* 1999;27:887–892.)

TABLE 47.2 Profile of Nosocomial Infections in the Intensive Care Unit

Infection	Major Pathogen(s)	Risk Factors
Urinary tract infection	*Escherichia coli*	Urinary catheter
	Pseudomonas aeruginosa	Monitoring of urine output
	Klebsiella pneumoniae Other gram-negative bacilli	Other urologic manipulation or bladder irrigations
	Enterococcus spp.	Renal transplantation
		Diabetes
		Female > male
Pneumonia	*Staphylococcus aureus*	Tracheostomy
	P. aeruginosa	Endotracheal tube, reintubation
	Acinetobacter spp.	Nasogastric tube
	Enterobacter spp.	Intracranial pressure monitoring
	K. pneumoniae Other gram-negative bacilli	Stress ulcer prophylaxis with histamine H_2-blocker or antacids Immunosuppression Granulocytopenia
Surgical site infection	*S. aureus* Coagulase-negative staphylococci Enterococci	Trauma, especially penetrating abdominal injury Gastrointestinal or radical gynecologic surgery
	E. coli and other gram-negative bacilli	Prolonged operation Immunosuppressive therapy
	Bacteroides fragilis and other bowel anaerobes	Granulocytopenia Hepatic transplantation
	Candida spp.	Central venous catheter in place >5 days
Intravascular device–related bacteremia	Coagulase-negative staphylococci *S. aureus*	Heavy colonization of insertion site skin Femoral vein insertions
	Enterococcus spp.	Catheter guidewire exchanges
	Gram-negative bacilli	
Contaminated infusate	*Enterobacter* spp. *Serratia marcescens* *Citrobacter* spp. *Pseudomonas cepacia* or *Xanthomonas maltophilia*	
Antibiotic-associated diarrhea or colitis	*Clostridium difficile*	Prolonged antibiotic therapy, especially with clindamycin or broad-spectrum β-lactams Enteral tube feeding
Candidemia	*Candida* spp.	Broad-spectrum, prolonged antimicrobial therapy Mucosal or urinary colonization Central venous catheter Hyperalimentation Renal failure

Modified from Maki DG. Nosocomial infection. In: Parrillo JE, ed. *Current Therapy in Critical Care Medicine.* 2nd ed. Philadelphia: BC Decker; 1991.

C. auris in acute-care hospitals, including Standard and Contact Precautions and thorough daily cleaning and disinfection of patient rooms.[49,50] Chlorhexidine has been shown to be active against antifungal-resistant biofilms formed by C. auris and may be an option for cutaneous disinfection.[51]

Nosocomial infections acquired in the ICU clearly differ from infections acquired in non-ICU patient care units within the same institutions. Overall rates are two to three times higher, and rates of ventilator-associated pneumonia (VAP) and primary bacteremia—most of which originate from IVDs—are 10 times higher. A far greater proportion of ICU-acquired infections are caused by antibiotic-resistant bacteria because the intensive antimicrobial therapy characteristic of modern-day ICUs grossly distorts patients' microbiomes. Moreover, more than half of all nosocomial epidemics

now occur among the 10% of hospitalized patients confined to an ICU.[20,32] Finally, the risk of occupationally acquired infection among health care workers (HCWs), particularly by bloodborne viruses and herpes simplex virus (HSV), is highest among ICU personnel, as contrasted with those who work in non-ICU patient care units (see "Protection of Health Care Workers in the Intensive Care Unit" later).

Morbidity and Economic Impact

Nosocomial infections have a considerable impact on morbidity and mortality rates and are estimated to affect more than 2 million patients in U.S. hospitals annually.[52] Table 47.3 summarizes major studies that have examined mortality, length of stay, and costs associated with the major nosocomial infections in U.S. hospitals.[2–19] Nosocomial infections have been ascribed by the National Academy of Medicine to be responsible for more than 80,000 hospital deaths each year and in 1995 resulted in more than $5 billion in excess health care costs.[52] Considering that nosocomial infections acquired by ICU patients account for nearly half of all infections in most hospitals, progress in reducing the incidence of infection acquired within ICUs could produce substantial economic benefits.

Pathogenesis and Epidemiology

Pathogenesis and Epidemiology are presented in the online supplement.

General Infection Control Measures

Hospital Infection Control Programs

Beginning in the late 1960s, scattered U.S. hospitals began to establish infection control programs to conduct surveillance, to develop infection control policies, and especially to attempt to implement control measures more consistently.[120] In 1976, The Joint Commission added to its requirements for hospital accreditation the establishment of a formal infection control program.

TABLE 47.3 Estimated Extra Days, Extra Charges, and Deaths Associated With Nosocomial Infections in U.S. Hospitals as Reported in Major Studies

Infection	Description	Average Extra Days in Hospital or ICU per Infection	Average Extra Charges or Costs per Infection ($)	EXCESS MORTALITY (%)	
				Unadjusted	Attributable
Surgical Site Infection					
Kirkland et al.[634] (1999)	CABG, vascular surgery, abdominal surgery, orthopedic surgery	6.5	3,089	NR	4.3
Whitehouse et al.[635] (2002)	Orthopedic surgery	14	17,708	NR	0.0
Hollenbeak et al.[636] (2000)	Deep chest infection after CABG	20	20,012	NR	19.4
McGarry et al.[637] (2004)	All major surgical procedures; only *Staphylococcus aureus* infections included	13	53,625	NR	16.8
Herwaldt et al.[638] (2006)	All major surgical procedures	NR	3,021	1.2	0
Ventilator-Associated Pneumonia					
Fagon et al.[639] (1993)	Medical and surgical patients	13	NR	NR	27.1
Heyland et al.[640] (1999)	Medical and surgical patients	4.3	NR	NR	5.8
Bercault et al.[641] (2001)	Medical and surgical patients	5	NR	NR	27.4
Rello et al.[642] (2002)	Medical and surgical patients	11	40,000	NR	0
Warren et al.[643] (2003)	Medical and surgical patients	25	11,897	16	NR
Cocanour et al.[644] (2005)	Trauma patients	15	57,158	NR	0
Bloodstream Infection					
Pittet et al. [287] (1994)	Surgical patients	24	40,000	NR	35%
Digiovine et al 288 (1999)	Medical patients	10	34,508	NR	4
Warren et al.[645] (2006)	Medical and surgical patients	7.5	11,971	23	NR
Catheter-Associated Urinary Tract Infection					
Bryan et al.[497] (1984)	Medical and surgical patients	NR	NR	NR	12
Tambyah et al.[500] (2002)	Medical and surgical patients	NR	589	NR	NR

CABG, Coronary artery bypass grafting; *NR*, not reported.
Studies cited in column 1 may be found in the complete list of references for this chapter provided online.

Pathogenesis and Epidemiology

Pathogenesis

The occurrence of nosocomial infection reflects the conjunction in space and time of a pathogenic microbe and a vulnerable patient, catalyzed by events associated with hospitalization and the patient's care. Many patients admitted to an ICU are intrinsically more susceptible to infection because of underlying diseases or conditions associated with impaired immunity, such as cancer, trauma,[53] or advanced age,[54] or because of immunosuppression associated with malnutrition,[55] therapy with corticosteroids,[56] cancer chemotherapeutic agents,[57] or other immunosuppressive drugs.[58] Moreover, many drugs, such as narcotics or sedatives, have indirect effects that increase susceptibility to infection that impair the capacity to protect the airway, or antacids or H_2-histamine receptor antagonists that neutralize gastric acidity, producing gastric overgrowth by gram-negative bacilli,[59] thereby increasing the risk of nosocomial pneumonia.[60] Even transfusion therapy produces immunosuppression and increases the risk of nosocomial infection.[61]

Moreover, most nosocomial pathogens exhibit resistance to antibiotics (see Fig. 47.1),[45,46,48,62–65] and many are also more virulent because of (1) their capacity to subsist or even multiply in aqueous reservoirs for prolonged periods (e.g., pseudomonads[66] or Legionella pneumophila[67]); (2) the elaboration of endotoxins (e.g., all of the gram-negative bacilli) or exotoxins (P. aeruginosa,[68] C. difficile,[69] or S. aureus[70]); or (3) the production of adhesions[71] or exoglycocalyx[72] (e.g., coagulase-negative staphylococci), conferring the capacity to adhere avidly and form biofilms on biologic and prosthetic surfaces resistant to host defenses[73] and even antibiotics.[74] Because most patients in ICUs receive broad-spectrum antibiotics, resistant nosocomial organisms have an enormous ecologic advantage and, in Darwinian fashion, predictably supplant the normal cutaneous, respiratory, and gastrointestinal microbiomes.

In most cases, colonization is the first step in the progression to nosocomial infection caused by bacteria and Candida spp,[75] especially if the patient is already vulnerable because of underlying disease, if the organism is more virulent or resistant to antibiotics, or if the patient has invasive medical devices that assist invasion by colonizing organisms, bypassing or further impairing host defenses.

Reservoirs and Transmission

The epidemiology of an infection consists of the reservoirs and mode or modes of transmission of the pathogen or pathogens and those factors associated with an increased (or decreased) risk of infection. Understanding the epidemiology of an infection is essential to developing effective strategies for its prevention.

In the ICU the major reservoir of nosocomial organisms is the infected or colonized patient (Fig. 47.e1).[28] Most aerobic bacteria—particularly S. aureus,[76] enterococci,[29] and the enteric gram-negative bacilli[77]; many viruses such as hepatitis A, respiratory syncytial virus,[78] and rotaviruses[79]; C. difficile[80]; and even Candida[81]—are spread in the ICU on the inadequately cleaned hands of medical personnel, who themselves are not infected or even permanently colonized. Most respiratory viruses, rubella,[82] influenza,[83] and some bacterial respiratory infections (e.g., Streptococcus pneumoniae)[84] are spread by large droplet nuclei that travel 3 to 6 feet from the source. True airborne spread of pathogens from infected individuals occurs for Mycobacterium tuberculosis,[85–87] measles,[88] and varicella; "opportunistic airborne transmission" (when humidity and other conditions are favorable) may occur for severe acute respiratory syndrome (SARS), pandemic influenza, and some agents of bioterrorism.[89] Airborne transmission from contaminated environments can result in infections with Legionella,[44] Aspergillus, or mucormycosis.[41–43] Surgery and exposure to invasive devices of all types greatly amplify transmission, colonization, and susceptibility to infection.[28,90]

Outbreaks of group A streptococcal infection[91] usually indicate a health care provider who is a carrier of the epidemic strain. Airborne spread of gram-negative bacilli is probably rare unless unusual environmental circumstances generate massively contaminated aerosols.[92]

Increasing evidence suggests that many nosocomial infections that develop in the ICU derive from the altered microbiome that sick patients bring into the ICU, including resistant organisms of enteric origin[93–96] or that are present on skin[93,94] or in the lower respiratory tract[95] on admission to the ICU. This explains the failure of conventional infection control practices, based on the use of barriers, to control such endogenous resistant bacteria.[97] Whereas food[98] and even enteral feeding preparations[99] and water may be heavily contaminated by microorganisms, studies have not conclusively linked such contamination to disease.

Nosocomial organisms originating from colonized or infected patients are readily perpetuated and may be spread via contaminated medical apparatus or devices[28] such as urine-collection receptacles,[100] respiratory therapy equipment,[101,102] transducers used for hemodynamic monitoring,[103] dialysis machines,[104,105] and fiberoptic bronchoscopes and endoscopes.[102,106–108] Given the implicit close proximity of vulnerable ICU patients and the HCWs who have repeated contact with them each day, it is almost predictable that the ICU is a milieu within the hospital uniquely conducive to the epidemic infection, especially infections caused by antibiotic-resistant pathogens.

Although successful immune enhancement could in theory create a protective final barrier against infection by nosocomial organisms, the unique features of nosocomial infection—enormous microbial heterogeneity, pervasive effects of invasive devices and procedures, and often large infecting inocula—can overwhelm the healthiest patient's immune defenses. Measures to eradicate reservoirs of nosocomial pathogens and to block transmission, based on a thorough understanding of epidemiology, seem much more likely to be protective at present.

Risk Factors

Risk factor analysis using statistical techniques such as multivariate analysis can identify variables that put a patient at increased risk for nosocomial infection and further guide the development of preventive strategies. Risk factors based on prospectively collected data and, in most cases, the use of multivariate analysis, are listed in Table 47.2 for urinary tract infection,[109,110] pneumonia,[111,112] surgical site infection,[113] IVD-related BSI,[114] ventriculostomy-associated meningitis,[115] C. difficile infection,[34,116] and candidemia.[117–119]

Critical care medicine is synonymous with cutting-edge, high-tech medicine; mechanical ventilatory support; hemodynamic monitoring; total parenteral nutrition; hemodialysis; intracranial pressure monitoring; innovative forms of surgery; and a huge arsenal of drugs, especially anti-infectives of every genre. This technology, more than anything else, has forced critical care medicine to embrace the necessity for nosocomial infection control. In general,

invasive devices of all types are far more important in determining susceptibility to nosocomial infection than are underlying diseases (see Tables 47.2 and 47.e1). However, this should be viewed as welcome news: There is far more hope for reducing nosocomial infections in the coming years by innovative improvements in aseptic technique and advances in the technology of invasive devices than by breakthroughs that will reverse the ravages of chronic organ failure or degenerative diseases such as type 1 diabetes mellitus.

TABLE 47.E1 Significant Risk Factors for Nosocomial Infection in Medical and Surgical Intensive Care Units as Determined by Multivariate Analysis of Prospectively Collected Databases

Risk Factor	Approximate Magnitude of Increased Risk[a]
Urinary catheter >10 days	3.2
ICU confinement >3 days	2.5
Intracranial pressure monitor	2.5
Arterial line	1.5
Shock	2.5

[a]Relative risk or odds ratio: values >1 denote significantly increased risk of infection, and ratios less than 1 denote decreased risk, vis-à-vis a protective effect.
ICU, Intensive care unit.
From Craven DE, Kunches LM, Lichtenberg DA, et al. Nosocomial infection and fatality in medical and surgical intensive care unit patients. *Arch Intern Med.* 1988;148:1161–1168.

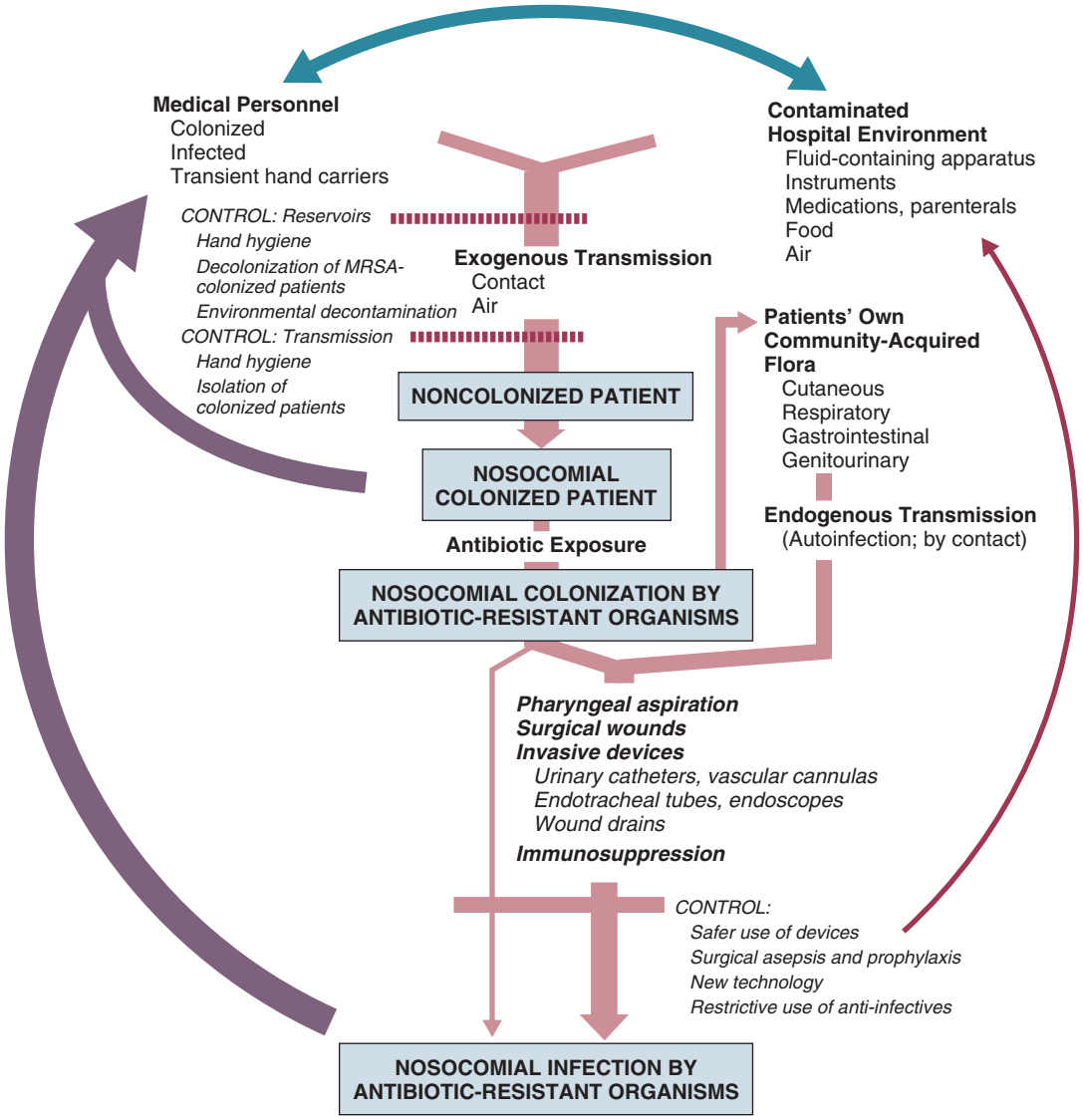


Fig. 47.e1 The epidemiology of nosocomial infection. Transmission occurs mainly by contact spread and, to a much lesser extent, the airborne route. Aspiration, surgical wounds, and exposure to invasive medical devices enormously amplify transmission, colonization, and susceptibility to infection. (From Maki DG. Control of colonization and transmission of pathogenic bacteria in the hospital. *Ann Intern Med.* 1978;89[5 Pt 2 suppl]:777–780.)

In the early 1970s the CDC studied the effectiveness of nosocomial infection surveillance and control programs in the United States through the Study on the Efficacy of Nosocomial Infection Control (SENIC). The goals of SENIC were to determine the extent to which infection control programs had been adopted by U.S. hospitals and to ascertain via a before-after comparison how much these programs had reduced rates of nosocomial infection. SENIC was launched by a survey of all U.S. hospitals to determine the characteristics of infection control programs and was completed in 1975–1976 by a review of more than 339,000 patient medical records in 338 randomly selected hospitals.[121]

The SENIC found that hospitals reduced their nosocomial infection rates by approximately 32% if their surveillance and infection control program included four components: (1) emphasis on both surveillance and an infection control program, (2) at least one full-time infection control practitioner for every 250 beds, (3) a trained hospital epidemiologist, and (4) surveillance of surgical wound infections with feedback of wound infection rates to practicing surgeons.[122] However, the relative importance of each component varied for the four major types of nosocomial infections (surgical wound infections, urinary tract infections, BSIs, and pneumonia).[122,123] SENIC suggested that nearly one-third of all nosocomial infections were in theory preventable, whereas a 1983 survey of surveillance and control programs in a random sample of U.S. hospitals found that failure to implement all essentials of the program, particularly to have an adequate number of infection control practitioners or a trained hospital epidemiologist or to disseminate wound infection rates to surgeons, greatly limited the potential for prevention: U.S. hospitals were estimated to be preventing only 9% of all infections.[124]

It is hoped that surveillance and control programs will continue to evolve. Prevention of nosocomial infections is a major priority of the U.S. Public Health Service,[125] The Joint Commission,[31] and the National Academy of Medicine.[126] With the shift to prospective-payment reimbursement and public reporting of infection rates, hospitals now have a powerful financial and public relations incentive to reduce their rates of nosocomial infection,[127] and it can be anticipated that efforts to prevent hospital-acquired infections will assume ever greater importance.

The Joint Commission mandates that all hospitals have an active program for the surveillance, prevention, and control of hospital-acquired infections, which begins in most hospitals with an institutional infection control committee with representation from the major clinical services and hospital departments, including the institution's ICUs. The most essential members of the infection control program are the infection control practitioner(s) and the hospital epidemiologist, usually a physician with training in infectious diseases or microbiology, who implement the policies developed by the committee, educate hospital personnel about nosocomial infection control, and investigate suspected outbreaks (Box 47.2).

Surveillance of nosocomial infections is the cornerstone of an effective infection control program and offers numerous potential benefits.[123,128] (1) It permits determination of baseline (expected) infection rates, assisting recognition of outbreaks and evaluation of new policies and control measures. (2) It identifies institutional problems that require attention, permitting focused infection control efforts and education. (3) It provides reliable data that can be disseminated to individual departments, increasing awareness and involvement of individual staff members. (4) It increases the visibility of the infection control staff on patient care units, providing an opportunity for consultation and ad hoc education. (5) It facilitates the earliest discovery of patients with communicable infections, permitting timely institution of isolation precautions to limit spread. Because total manual surveillance (of all infections) is labor intensive, many hospitals have focused their surveillance efforts on infections that are associated with high morbidity (e.g., nosocomial pneumonia), that greatly increase health care costs (e.g., post–cardiac surgery sternotomy infections), that are caused by antibiotic-resistant organisms with potential for spread (e.g., MRSA, C. difficile), or that are highly preventable (e.g., IVD-related BSIs).[123,129] However, electronic medical record systems and commercial computerized surveillance programs may allow for broader surveillance of nosocomial infections.[130]

The 1990s were characterized by major efforts by hospitals to apply the numerous facets of health care principles of quality improvement developed by industry. Hospital infection control programs had been working on quality improvement[131] but, influenced by The Joint Commission, were probably too heavily focused on process—namely, policies and procedures—rather than documenting outcome vis-à-vis reduced infection rates. Infection control programs in most U.S. hospitals are now closely allied with their institutional quality improvement departments.[131,132]

• BOX 47.2 Facets of a Hospital Infection Control Program

- Active infection control committee, with representation from major departments and services including the intensive care units (ICUs)
- Surveillance of nosocomial infections, especially in each intensive care unit
- Comprehensive and regularly updated institutional policies and procedures for prevention of nosocomial infection:
  - Surveillance of nosocomial infections
  - Isolation and universal precautions
  - Sterilization and disinfection
  - Indications for and management of invasive procedures and devices:
    All types of intravascular catheters
    Hemodynamic monitoring
    Tracheostomy and endotracheal intubation
    Mechanical ventilation and other respiratory therapy
    Bronchoscopy and gastrointestinal endoscopy
    Anesthesia and the operating room
    Hemodialysis
    Intra-aortic balloon pumps
    Cardiopulmonary bypass
    Intracranial pressure monitoring
- Antimicrobial stewardship program
- Guideline for investigation of an epidemic
- Strong liaison with clinical microbiology laboratory
  - Representation on the infection control committee
  - Laboratory-based surveillance
  - Monitoring and reporting of trends in antimicrobial susceptibility
  - Retaining important isolates
  - Microbiologic support of all infection control activities
  - Subtyping of isolates for investigations or studies
- Educational programs for new employees, periodic updates dealing with nosocomial infection control
- Active employee health department:
  - Free immunizations (hepatitis B, measles, mumps, rubella, varicella, pertussis, influenza A)
  - Tuberculin screening
  - Postexposure protocols
- Quality assurance review of implementation of infection control policies and practices

Modified from Maki DG. Nosocomial infection. In: Parrillo JE, ed. Current Therapy in Critical Care Medicine. *2nd ed. Philadelphia: BC Decker; 1991.*

Hospital infection control programs also must abide by the regulations of the Occupational Safety and Health Administration in terms of institutional standards and programs to protect HCWs from bloodborne pathogens[133] and tuberculosis.[134] The Environmental Protection Agency[135] has also published regulations in terms of disposal and tracking of medical waste—only a small fraction of which is truly biohazardous.[136]

Finally, it is essential that all health care personnel working in an ICU receive training in the epidemiology and control of nosocomial infections. This may be most important for house officers in teaching hospitals, who rotate through the ICU often with only the most rudimentary knowledge of asepsis but have hands-on contact with numerous patients and devices each day. ICU physicians and nurses must be especially familiar with their hospitals' guidelines for the management of invasive devices, particularly intravascular catheters of all types,[137] urinary catheters,[138,139] endotracheal tubes,[140] and tracheostomies.[140] Moreover, all physicians need to be made aware that broad-spectrum antimicrobial therapy greatly increases the risk of superinfection by antibiotic-resistant bacteria and Candida, as well as C. difficile.

Role of the Microbiology Laboratory

Accurate and timely diagnostic microbiology is as essential for nosocomial infection control as it is for the clinical management of patients' infections. Although many infections can be diagnosed on the basis of clinical criteria alone, cultures and other laboratory tests allow infections to be diagnosed with much greater certainty, and certain infections such as bacteriuria, bacteremia, and fungal and viral infections cannot be diagnosed without cultures or other laboratory tests (see Box 47.1).[16,17] Moreover, accurate antimicrobial susceptibility testing of clinical isolates is the only means of monitoring trends in antibiotic resistance of hospital organisms.[141] Most importantly, identifying the microbial cause of nosocomial infections allows epidemiologic tracking of individual pathogens within the hospital, especially those that are commonly spread from patient to patient such as S. aureus, enterococci, and the numerous gram-negative bacilli.

From an organizational standpoint, the institutional infection control program and clinical microbiology laboratory must have a close working relationship (see Box 47.2) to assist surveillance, which must be strongly laboratory based,[123,142] and to permit the detection and resolution of potential problems. The laboratory director or a senior member of the laboratory staff should be a permanent member of the infection control committee.

The primary role of the clinical microbiology laboratory in any infection control program is to provide up-to-date clinical microbiologic data for use in the surveillance of nosocomial infections and identification of potential outbreaks.[142] Protocols should be developed to ensure that laboratory staff immediately contact infection control personnel after the isolation of certain important pathogens such as MRSA or VRE or the appearance of new resistance patterns in endemic organisms, such as resistance of Klebsiella species to third-generation cephalosporins and carbapenems, or P. aeruginosa to aminoglycosides, fluoroquinolones, and carbapenems. Sifting through these data can be time-consuming, and developing electronic information systems that streamline this process is essential to improving the efficiency of the infection control program. Commercial software programs that can automate this process are now available. Many of these programs automatically collate microbiologic data, provide rudimentary geographic information, and perform basic statistical analyses that can assist in the surveillance of nosocomial infections and identification of potential outbreaks.[143,144]

Reporting cumulative summaries of antimicrobial susceptibility data (antibiograms) is another essential responsibility of the clinical microbiology laboratory.[145,146] When implemented appropriately, the timely dissemination of antibiograms helps guide the choice of empiric antimicrobials, pending the results of clinical cultures, and provides valuable data to help the infection control department monitor institutional antimicrobial resistance trends and identify potential outbreaks.[147] The Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) recommends that institutional antibiograms be updated at least annually and has recently published standards for their content and format.[148] Automated electronic systems for collating and disseminating nearly real-time antibiograms with antibiotic-use decision support exist and, when implemented properly and aggressively, have been effective in improving antimicrobial utilization within the hospital setting.[149,150]

Monitoring of sterilizers with spore tests, environmental sampling, and advanced microbiologic support for epidemiologic investigations are additional responsibilities expected of most clinical microbiology laboratories, although some university hospital programs have dedicated personnel within their infection control programs who perform these activities.[142]

The clinical microbiology laboratory is a key resource in the investigation of a suspected outbreak. One of the first and foremost actions when a nosocomial outbreak is suspected is to immediately retrieve all available isolates of the putative epidemic pathogen for possible subtyping.[151] The need to move rapidly becomes apparent when it is realized that most hospital laboratories discard cultures as soon as the isolates have been fully characterized. All blood isolates should be routinely saved for at least 1 year.[151] Laboratory personnel must be requested to save clinical isolates of any unusual organisms that are encountered for the first time or clusters of any organism and to inform infection control personnel of the findings and availability of the isolates.

The rapid evolution of molecular microbiology has revolutionized epidemiologic investigation of nosocomial outbreaks. Molecular-based tests for the rapid diagnosis of bacterial,[152] viral,[83,153] and fungal[154] infections are now routinely available in most hospital-based and reference laboratories. Modern molecular tests can reliably detect minute numbers of organisms, allowing direct testing of clinical samples without the need for culture. In modern-day clinical virology, molecular tests based on polymerase chain reaction (PCR) for amplification of the pathogen's DNA or ribonucleic acid (RNA) have supplanted tissue cultures and now allow rapid diagnosis of infections that would otherwise often not be identifiable by classic methods.

The availability of molecular subtyping systems has greatly strengthened investigations of outbreaks, as well as research on the epidemiology of nosocomial infections.[155,156] The antimicrobial susceptibility pattern (antibiogram) or the detailed biochemical profile (biotype) is often useful for the initial epidemiologic subtyping of many bacteria and may be adequate for identifying an epidemic caused by an unusual pathogen. However, if an epidemic organism is a common species such as S. aureus, it can be difficult or even impossible to know with certainty that an outbreak derives from a common source using these techniques because they lack sufficient discriminatory power.[155]

The new molecular techniques of subtyping such as plasmid profile typing by agarose gel electrophoresis or the use of restriction endonuclease digests with pulsed-field electrophoresis (DNA

fingerprinting)[155] are now available in most infection control research laboratories but should be adaptable by many hospital laboratories. Genetic probes and whole genome sequencing promise even more powerful tools for investigating outbreaks, particularly those caused by antibiotic-resistant organisms.[152]

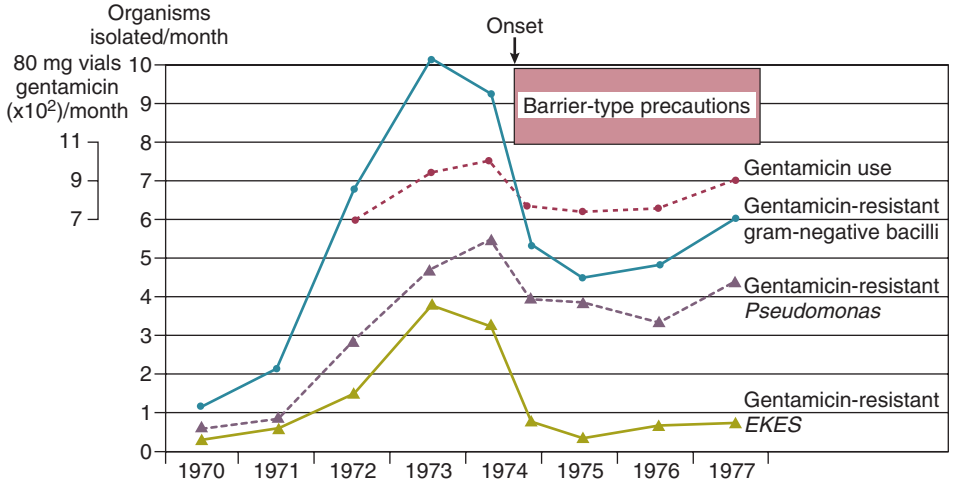
Additionally, technologies that offer rapid identification of organisms in blood cultures are available, including PCR-based detection systems, multiplex detection of pathogens, matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectroscopy, among others.[157] In one clinical trial evaluating a multiplex PCR that tested for 24 gram-positive, gram-negative and yeast pathogens and 3 antibiotic-resistance genes, directly from positive blood culture bottles, the time from blood culture bottle Gram stain to microorganism identification was significantly shorter in the multiplex PCR group (1.3 hours) compared with conventional blood culture technique (22.3 hours).[158] Also, time to escalation of antimicrobial therapy was significantly shorter in the multiplex PCR group (4 hours) compared with conventional blood culture technique (18 hours). And time to de-escalation of antimicrobial therapy was significantly shorter in the multiplex PCR group but only with involvement of the antimicrobial stewardship team (20 hours), compared with conventional blood culture technique (39 hours) or the multiplex PCR group without involvement of the antimicrobial stewardship team (36 hours).

Although molecular-based tests offer several advantages over traditional microbiologic techniques, they are not a panacea. For example, non-culture technologies may limit access to isolates for epidemiologic typing. And a number of molecular diagnostic assays (e.g., analyte-specific reagents) marketed for clinical practice do not require approval by the U.S. Food and Drug Administration.[152] In the absence of published data on their accuracy and precision, the results of these tests must be interpreted with caution and should always undergo extensive in-house validation before adoption. Moreover, the exquisite sensitivity of many of these tests renders them more susceptible to false-positive results as a consequence of environmental contamination[159,160] and mandates stringent quality control practices and procedures.

Infrastructure—Architectural, Environmental, and Staffing—Issues

The role of the inanimate environment on the transmission of nosocomial infections has been a subject of intense debate for decades. It has been shown that hospital surfaces are almost universally contaminated by potentially pathogenic bacteria such as S. aureus,[161] Enterococcus,[162] spores of C. difficile, and gram-negative bacilli such as Acinetobacter baumannii.[163] Before the 1970s, infection control personnel routinely sampled hospital surfaces. Despite this level of surface colonization, early studies found that the inanimate environment—surfaces, walls, and even air—does not contribute materially to the occurrence of most nosocomial infections,[164] other than invasive infections caused by airborne Aspergillus and other filamentous fungi in seriously immunocompromised patients.[41,42]

Although inanimate surfaces may rarely be involved in the direct transmission of infection to patients, more recent evidence suggests that surfaces may well play an important role in the nosocomial acquisition of pathogenic bacteria, indirectly, through contact with HCWs' hands and equipment (Fig. 47.2). This indirect route of infection is of particular importance in the ICU, where all patients are heavily exposed to invasive devices and have a high risk of infection. In the ICU the inanimate environment may become a reservoir for the transmission of resistant nosocomial organisms such as MRSA,[165,166] C. difficile,[80,167] VRE,[162,168] and gram-negative bacilli, particularly Pseudomonas spp. in wet environments and Acinetobacter spp.[169,170] Studies have shown that enhanced surface decontamination with hypochlorite-containing cleaning solutions has been necessary to terminate outbreaks caused by C. difficile[171] and Acinetobacter baumannii.[163]



• **Fig. 47.2** Impact of implementing barrier-type precautions (gown and gloves) with patients known to be colonized or infected by gram-negative bacilli resistant to gentamicin. Frequency of infections by gentamicin-resistant gram-negative bacilli and gentamicin use at Michael Reese Medical Center, 1970–1977. Data are plotted as the monthly average, and the averages for the first 7 and last 5 months of 1974 are plotted separately to demonstrate the effect of barrier-type precautions implemented in August 1974. *EKES, Escherichia coli, Klebsiella pneumoniae, Enterobacter* species, and *Serratia* species. (From Weinstein RA, Nathan C, Gruensfelder R, et al. Endemic aminoglycoside resistance in gram-negative bacilli: epidemiology and mechanisms. *J Infect Dis.* 1980;141:338–345.)

It has been shown that patients admitted to a room previously occupied by a patient colonized or infected with a pathogen have a higher chance of developing colonization or infection with that pathogen.[172,173] Improved terminal cleaning of rooms (i.e., disinfection of a room between occupying patients) has been demonstrated to decrease the rate of individual patient colonization and infection and also facility-wide patient colonization and infection.[172,173] However, some studies have shown that surfaces in hospital rooms are poorly cleaned and remain contaminated.[172] Therefore "no-touch" methods of terminal room cleaning such as ultraviolet (UV) light devices or hydrogen peroxide systems have been explored.[172] A multicenter cluster-randomized crossover trial involving more than 21,000 patients tested the effect of disinfecting ultraviolet (UV-C) light for terminal room disinfection on the acquisition and infection due to MRSA, VRE, C. difficile, and multidrug-resistant Acinetobacter.[173] The addition of UV-C light to quaternary ammonium disinfectant (or to bleach for C. difficile) decreased the incidence of MRSA, VRE, and multidrug-resistant Acinetobacter by 30% among exposed patients admitted to the targeted room, but it did not decrease the risk of C. difficile compared with bleach alone.[173]

Although the ICU environment cannot be made microbe free, certain organizational, architectural, and environmental issues may be addressed with the design or remodeling of an ICU. The capacity to systematically improve the care of critically ill patients and prevent nosocomial infection requires a structural foundation on which the processes of care can be optimized (i.e., make it easy for HCWs to do it right and difficult to do it wrong). Accountability for compliance with critical policies and procedures and ongoing assessment of outcomes needs to be built into the administrative structure of the ICU.

An ICU must be adequately staffed to allow the processes of care to be carried out but also ensure a high level of compliance with essential infection control measures such as hand hygiene and barrier isolation. Adequate staffing cannot be overemphasized; numerous studies have found greatly increased rates of nosocomial infection when ICUs are staffed suboptimally or when staffing requirements are met with temporary personnel who are unfamiliar with ICU infection control policies and procedures.[174,175] In a large nosocomial outbreak of Enterobacter cloacae infection in a neonatal ICU, Harbarth and colleagues[176] found that infection rates during periods of understaffing were strikingly higher than during periods with adequate levels of staffing (relative risk [RR] 6, 95% confidence interval [CI] 2.2–16.4). The effects of understaffing are likely multiple; however, erosion of basic hygienic practices with excessive patient-to-staff ratios likely explains much of this phenomenon.[177]

Many of the published recommendations for ICU architectural design[178] are empiric, and evidence that they reduce rates of nosocomial infection is, by and large, lacking. Although more research is necessary before specific features of ICU design achieve a level of evidence sufficient for an evidence-based guideline, certain facets of the ICU layout deserve attention:

- ICUs should be located in areas that limit traffic flow to essential ICU personnel.
- ICU facilities should be designed with ICU professionals in mind, ensuring appropriate space, resources, and environment for day-to-day operations.[178] Recognizing the growing variety and complexity of life support equipment required for the care of many patients, each cubicle or room should provide a minimum of 11 m^2 per bed.[179] The area should be large enough to accommodate the bed and all equipment yet allow immediate access to the patient at all times from both sides of the bed. Adequate space must also be provided for storage of nursing supplies. Facilities for disposal of biohazardous waste (e.g., bedpan flushers); for cleaning, reprocessing, and storage of ICU equipment; and for storage of housekeeping supplies should be separate from patient care areas. Single-patient rooms may increase the likelihood of attention to handwashing and improve adherence with isolation practices, reducing the risk of cross-infection. For example, Mulin and colleagues[180] found that converting from an open unit to single rooms in their ICU greatly reduced rates of patient colonization with A. baumannii, and Shirani and colleagues[181] found that renovation of their burn unit to include separate bed enclosures reduced rates of nosocomial infection by 48%.[181]
- Materials used for fixtures, furniture, and other surfaces should be smooth and easy to clean; surfaces made of porous materials foster bacterial colonization.[182]
- An adequate number of sinks must be available for convenient handwashing by ICU personnel. Ideally, a sink should be located at the entrance of each cubicle or patient room to encourage handwashing by all entering personnel who will have contact with the patient or the immediate environment.[183,184] Separate sinks should be used for cleaning and reprocessing contaminated equipment. Sinks and sink drains are normally contaminated by pseudomonads,[185] and there have been outbreaks of infections with contaminated handwashing sinks as a potential source, including from extended-spectrum β-lactamase (ESBL)-producing Klebsiella oxytoca and carbapenemase-producing Enterobacteriaceae.[186,187] Sinks should be designed to minimize aerosol formation and splash back.
- All ICUs should be equipped with one or more negative-pressure isolation rooms, which include an anteroom for gowning and handwashing and the necessary modifications (negative pressure, roofline exhaust) to permit it to be used for patients with tuberculosis or other airborne infections, such as chickenpox, measles, disseminated HSV infection, or a highly contagious emerging pathogen such as the SARS human coronavirus. If an ICU treats bone marrow transplant patients or other patients with prolonged severe granulocytopenia, positive-pressure isolation rooms using high-efficiency particulate air (HEPA) filters should be available to lessen risk of infection by airborne fungal spores such as those of Aspergillus. Doors of isolation rooms for patients with infections transmitted by the respiratory route or to protect profoundly granulocytopenic patients must be kept closed to ensure that the direction of airflow is maintained as designed.
- A centralized, filtered air-handling system that provides at least six room exchanges per hour is essential.[179,188]

A variety of microorganisms, including bacteria, mycobacteria, fungi, and parasites, can be isolated from hospital water and have been implicated in endemic and epidemic nosocomial infections.[189] Many of these outbreaks were caused by bacteria typically thought of as "water" organisms such as P. aeruginosa,[185] Stenotrophomonas maltophilia,[190] and A. baumannii[16,191,192]; however, the most important and epidemiologically linked hospital water pathogen is the Legionella group.[193]

Nosocomial legionellosis was first described in 1979,[194] and it is estimated that up to 50% of cases of legionellosis are acquired in the health care setting,[195] with a mortality rate that approaches 30%.[196] Contamination of hospital potable water remains underappreciated despite studies showing that Legionella species can be recovered from 12% to 70% of hospital water systems,[197] and a number of studies in which nosocomial cases were identified only

when specific diagnostic and surveillance methods were used.[198,199] Characteristics of hospital water systems that are associated with Legionella contamination include piping systems with dead ends that facilitate stagnation, large-volume water heaters that result in inefficient heating of hospital water, sediment buildup, water heater temperatures less than 60°C, and tap water temperatures less than 50°C, maintaining water pH greater than 8, and receiving municipal water untreated with monochloramine.[200–202]

Despite the ubiquity of water systems colonized with Legionella species and studies demonstrating a correlation between the level of colonization and risk of infection, the CDC does not recommend routine surveillance of hospital water systems,[195] although this stance is controversial.[197] Researchers from Pittsburgh, Pennsylvania, and the Allegheny County Health Department have recommended a more proactive stepwise approach that involves initial surveillance of hospital water for Legionella contamination, regardless of the presence or absence of institutional nosocomial legionellosis, followed by continued surveillance based on the level of water contamination found or the presence of institutional legionellosis.[197]

Legionella species are resistant to chlorine and heat, making it challenging to eradicate them from contaminated hospital water systems.[202] Attempts to hyperchlorinate hospital water have been partially successful if chlorine levels are continuously maintained between 2 and 6 parts per million at all times but produce rapidly accelerated corrosion of water pipes and are expensive.[203] Thermal eradication is feasible, using a "heat-and-flush" method to raise water tank temperatures to greater than 70°C and distal water sites to greater than 60°C for short periods of time.[204] Although effective, superheating is labor intensive and there is the constant fear that patients or health care personnel may sustain scald injuries if they wash or shower with tap water during a flushing period. The use of technologies such as instantaneous steam heat for incoming water[204] and UV light[205] are technically feasible with newer hospital water systems but may be incompatible with older hospital water systems.

Perhaps the most attractive, effective, safe, and cost-efficient method for Legionella eradication may be the use of continuous copper-silver ionization systems to sterilize hospital water systems. These systems have been well studied over the past decade and have proved to be highly effective for reliably eradicating Legionella contamination of hospital water and, most importantly, for eliminating nosocomial legionellosis in institutions when other interventions have failed.[206] In an institution of one of the authors (D.G.M.), two clusters of nosocomial legionellosis prompted a retrospective review that identified 10 cases over an 11-year period. Surveillance of the hospital water system found that 75% of all samples contained low levels of L. pneumophila, which were shown to be clonally related to the 10 cases of nosocomial legionellosis. Installation of a continuous copper-silver ionization system led to complete eradication of Legionella from water samples.

Reliable Sterilization Procedures, Chemical Disinfectants, and Antiseptics

Reliable sterilization, disinfection, and antisepsis are essential for prevention of nosocomial infection.[207,208] In the 1960s, Spaulding described an approach to sterilization and disinfection based on intended use of the medical device or surgical instrument.[207] Critical items, which are introduced directly into the bloodstream or into other normally sterile areas of the body, such as surgical instruments, cardiac and urinary catheters, implanted devices, and ultrasound probes used in sterile body cavities, must be reliably sterile and should be either purchased as sterile or sterilized by steam sterilization if possible.[207] Heat-sensitive objects may be sterilized with ethylene oxide, hydrogen peroxide gas plasma, vaporized hydrogen peroxide, or hydrogen peroxide vapor and ozone.[207] Liquid chemical sterilization is only recommended to be used for critical items that are heat-sensitive and not compatible with other sterilization methods.[207] Semicritical items, which come into contact with mucous membranes or nonintact skin, such as fiberoptic endoscopes, endotracheal tubes, or ventilator circuit tubing, can be decontaminated between patients by pasteurization (i.e., 65°C–77°C for 30 minutes) or the use of high-level chemical disinfection (e.g., glutaraldehyde, hydrogen peroxide, ortho-phthalaldehyde, peracetic acid, peracetic acid–hydrogen peroxide, or hypochlorite), which kill all microorganisms except high numbers of bacterial spores.[207] Noncritical items, which normally come into contact only with intact skin, such as blood pressure cuffs or electrocardiograph electrodes, require low-level disinfection (e.g., alcohol, hypochlorite, improved hydrogen peroxide, quaternary ammonium compounds, phenolics, or peracetic acid–hydrogen peroxide), which kills bacteria, some fungi and viruses, but not mycobacteria or spores.[207]

An important exception to the Spaulding classification scheme is devices that pose a risk of transmitting prion-related diseases, including Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD).[207,209,210] Prions are not readily inactivated by conventional sterilization procedures.[207,210] As a result, devices that pose a risk for transmission of prion-related diseases should undergo special sterilization procedures after cleaning that involve sodium hydroxide followed by low-temperature autoclaving (121°C) or high-temperature autoclaving (132°C for 1 hour or 134°C for ≥18 minutes).[210] Despite concerns that procedures involving semicritical items such as endoscopes and bronchoscopes may pose a risk for transmission of prion-related infections, there has not been a single report of CJD or vCJD associated with these devices. As a result, current guidelines recommend that only critical items and semicritical items that have come in contact with neurologic tissue (e.g., brain [including dura mater], spinal cord, eye, and pituitary tissue) should undergo special prion inactivation sterilization procedures.[208,210,211]

Numerous epidemics of gram-negative infection have been described in association with respiratory therapy equipment,[101,102] diagnostic equipment such as bronchoscopes and endoscopes,[102,106–108] and solutions used for cutaneous antisepsis.[212,213] Most of these outbreaks were traced to improper procedures or malfunction of automated systems used for the disinfection and sterilization of medical devices, although a number of epidemics in years past arose as a result of extrinsic contamination of solutions used for cutaneous antisepsis.[212,213] For these reasons, the importance of strict adherence to recommended policies and procedures for cleaning and reprocessing medical equipment used in the ICU cannot be overemphasized.

Endoscopes and bronchoscopes are essential diagnostic and therapeutic instruments in the ICU. Although most post-endoscopy nosocomial infections are caused by inoculation of components of mucosal microbiomes into normally sterile, vulnerable anatomic sites during the procedure, numerous epidemics have been traced to contaminated endoscopes.[102,106–108] After use for bronchoscopy, endoscopes are typically contaminated with 6×10^4 colony-forming units per milliliter (CFUs/mL).[214] Endoscopes are considered semicritical medical devices by the Spaulding classification and therefore require high-level disinfection after use.[207,211] To ensure their safe use, flexible endoscopes should be reprocessed with the

following procedures: (1) physical cleaning to reduce microbial bioburden and remove organic debris; (2) high-level disinfection with adequate contact time between the disinfectant and device surface; (3) after disinfection, rinsing with sterile or filtered tap water to remove disinfectant residue; (4) flushing of all channels with 70% to 90% ethyl or isopropyl alcohol; and (5) drying with forced air.[211] Devices used with endoscopes that violate mucosal barriers, such as biopsy forceps, need to be reprocessed as critical medical items with full sterilization.[211] Other devices used in the delivery of respiratory care are also considered semicritical under the Spaulding classification and therefore should be reprocessed in a manner similar to endoscopes before reuse.[140,207]

In 2013, an epidemic of 39 cases of carbapenem-resistant E. coli associated with duodenoscopes was reported.[215] However, there were no processing breaches or duodenoscope defects identified as had been reported with prior outbreaks, and it was hypothesized that the complicated design of duodenoscopes made cleaning and disinfection difficult.[215,216] After changing from high-level disinfection with ortho-phthalaldehyde to sterilization with ethylene oxide, no additional cases were identified.[215] This prompted the Food and Drug Administration to convene a panel in 2015 that recommended reclassifying duodenoscopes based on the Spaulding classification from semicritical to critical to support a shift from high-level disinfection to sterilization.[217]

In contrast to disinfectants that are applied only to inanimate objects, antiseptics are agents that kill microorganisms that are applied to living tissue and skin.[208] The most commonly used antiseptics are chlorhexidine (with or without alcohol), alcohol (with or without chlorhexidine or iodophors), and iodophors (with or without alcohol).[207] Other antiseptics include phenol derivatives, triclosan, and quaternary ammonium compounds.[207] Iodophors (e.g., 10% povidone-iodine) were previously the most common agents used for cutaneous disinfection in North America. However, a large, prospective, randomized trial of cutaneous antiseptics used for drawing blood for cultures showed that chlorhexidine was superior to 10% povidone-iodine and was associated with a more than twofold reduced rate of contaminated blood cultures (odds ratio [OR] 0.40, 95% CI 0.21–0.75, P = 0.004).[218] Moreover, a meta-analysis examining the impact of different cutaneous antiseptic agents found that chlorhexidine was superior to povidone-iodine for both the prevention of intravascular catheter colonization and catheter-related BSI.[219] On the basis of these and other studies,[220,221] chlorhexidine-containing solutions are the preferred cutaneous antiseptics for insertion of IVDs in the ICU.[137] Whatever agent is used, it is essential that it be applied with vigorous scrubbing for a minimum of 1 minute to allow adequate time for germicidal activity.

Hand Hygiene

The major reservoir of nosocomial infection in the ICU is infected or colonized patients, and the major mode of spread of most nosocomial bacterial pathogens, many viruses, and even Candida from patient to patient is by transient carriage on the hands of medical personnel (see Fig. 47.2). Studies of hand carriage of nosocomial pathogens by ICU personnel, using a simple rinse technique to quantify the transient microbiome,[222] have shown that, on average, approximately 60,000 CFUs (or 4.6 logs) are recovered from the hands of ICU personnel randomly sampled (Table 47.4). Nearly half of HCWs in whom cultures are obtained at any point in time will be found to be carrying gram-negative bacilli, and 10% will be carrying S. aureus.[223] Serial culturing has shown that all ICU personnel, at various times, carry gram-negative bacilli and that nearly two-thirds carry S. aureus. Carriage of both gram-negative bacilli and S. aureus is typically transient: sampling persons every other day over a prolonged period has shown S. aureus or the same gram-negative species in consecutive cultures only 16% of the time; prolonged carriage of a single gram-negative species seems to be rare—but has been reported.[224]

Hygienic handwashing before undertaking invasive procedures, handling open wounds, or having manual contact with high-risk patients (e.g., newborns or patients in ICUs) or after touching a source or object likely to be contaminated has been recognized since the time of Semmelweis and Lister as one of the most basic and important infection control measures. Despite universal acknowledgment of handwashing as a cornerstone of nosocomial infection control programs, compliance rates much above 50% have been difficult to achieve, and handwashing rates among HCWs have ranged from 9% to 50% in numerous observational studies.[177,225,226]

Recent investigations have undertaken to better understand the reasons for poor compliance in the face of the compelling evidence that hand hygiene is essential for prevention of nosocomial infection,[177] identifying cutaneous irritation, inconvenient sink location, time constraints, high workload, and understaffing. Of concern,

TABLE 47.4 Studies of Microorganisms Carried on the Hands of Hospital Personnel Working in a Neurosurgery Unit[a]

Study Parameter	All Microorganisms	Gram-Negative Bacilli	*Staphylococcus aureus*
Mean $\log_{10}$ CFUs ± SD, recovered from persons' hands[b]	4.59 ± 0.69	1.04 ± 0.44	0.44 ± 0.44
(Range of individuals' means)	(3.31–5.76)	(0.29–1.93)	(0–1.45)
% all cultures positive	100	44.5	11.2
% all personnel with at least one positive culture[b]	100	100	64

[a]At the University of Wisconsin Hospital.
[b]Based on 6–34 cultures obtained at random times from each of 25 employees working in the unit over a 4-month period.
CFUs, Colony-forming units; *SD*, standard deviation.
From Maki DG. Control of colonization and transmission of pathogenic bacteria in the hospital. *Ann Intern Med.* 1978;89:777–780.

risk factors for noncompliance with hand hygiene include being a physician (rather than a nurse); working in an ICU; and paradoxically, engaging in patient care activities with a high risk of cross-transmission.[177] Interventions to redress these deficiencies have included the current emphasis on waterless alcohol-based hand rubs; targeted education; feedback; convenient location of sinks and hand hygiene agents; use of alternative, less irritating hand hygiene agents; hand care lotions or creams[227]; and patient education.[228] Additionally, although direct observation by trained auditors is considered the gold standard for measuring hand hygiene compliance, addition of electronic hand hygiene monitoring technologies as part of a multimodal strategy deserves further investigation.[229,230] Electronic compliance monitoring (ECM) systems estimate hand hygiene compliance by monitoring both HCW entry and exit into patient rooms and the number of times alcohol-based handrub or soap dispensers are used, by using either sensors, a specialized badge, or a camera system.[229] The advantages of ECM systems include fewer personnel resources, no observer bias, and some systems can provide feedback to HCWs regarding their hand hygiene performance.[229] Disadvantages include cost, potential issues with accuracy, inability to monitor hand hygiene before clean/aseptic procedures or after body fluid exposures, inability to monitor hand hygiene technique and glove use, and privacy concerns with respect to compliance data.[229,230]

Studies done with working hospital staff have shown that hygienic handwashing with an antiseptic-containing agent reduces the count of microorganisms on the hands of the user far more effectively than handwashing with a nonmedicated soap.[222] Repeated use of some antiseptics such as chlorhexidine has a cumulative suppressive effect on the transient hand microbiome. Routine use of an antiseptic-containing handwashing agent could, in theory, enhance the effectiveness of the handwashing that is done. Moreover, if an agent that exhibits prolonged antimicrobial activity, such as chlorhexidine, is used, it might also confer protection against contaminants acquired between handwashings.[222] However, antiseptic-containing handwashing agents are more expensive and often more irritating to the skin. Irritation can result in dermatitis and, paradoxically, increased colonization by gram-negative bacilli.[231]

Clearly, antiseptic-containing soaps are more effective in removing microorganisms from the hands of users, but will routine use of these agents for hygienic handwashing reduce the incidence of nosocomial infection in patients? Discontinuation of hexachlorophene for handwashing by personnel and bathing of infants in the United States in 1973 was followed by a marked upsurge in S. aureus infections in nurseries,[232] and use of chlorhexidine-containing handwashing agents was considered an essential measure for control of hospital outbreaks caused by multiply resistant Klebsiella[233] and MRSA.[234,235] However, since Semmelweis's study, few studies have prospectively evaluated the efficacy of antiseptic-containing handwashing agents for reducing endemic nosocomial infections, particularly infections caused by gram-negative bacilli.[231,236]

In 1982 a comparative sequential trial of three handwashing agents—a nonmedicated tissue soap, 10% povidone-iodine (Betadine Surgical Scrub), and 4% chlorhexidine (Hibiclens)—was undertaken in the trauma-surgical ICU of the University of Wisconsin Hospital.[231] Each agent was used exclusively for approximately 6 weeks, during which time hand cultures of ICU personnel were done at random and surveillance of infection in patients was carried out. Risk factors for infection in patients hospitalized during the use of each agent were comparable; nearly two-thirds of the patients in each period required ventilatory support and hemodynamic monitoring, and almost all had urinary catheters. The incidence of nosocomial infection in all groups was expectedly high, but it was 30% lower during the use of the two antiseptic-containing handwashing agents than during the use of the nonmedicated soap ($P < 0.001$). Povidone-iodine was irritating to the hands of most staff, and chlorhexidine had a slightly drying effect but was well tolerated, comparable with the nonmedicated soap.

In a similar study at the University of Iowa Hospital, Massanari[236] did not find significant differences in the rates of nosocomial infection when nonmedicated soap was used exclusively compared with alternating cycles during which 4% chlorhexidine (Hibiclens) was used in surgical ICUs; however, the incidence of infection in the medical ICU was 50% lower during use of chlorhexidine ($P < 0.05$).

In the largest multiple-crossover prospective study—1894 adult patients in three ICUs—of the relative efficacy of antiseptic-containing handwashing agents used by personnel in ICUs, Doebbeling and colleagues[237] found that the use of 4% chlorhexidine (Hibiclens) was associated with a 30% reduction in nosocomial infections (OR = 0.73), as contrasted with rates when a 60% alcohol hand-rinsing agent (Cal Stat) was used. Both regimens were well tolerated.

Recently alcohol-based waterless hand rubs have become the agents of choice for hand hygiene and are now universally used in U.S. hospitals because of their convenience and broad-spectrum activity.[228] Alcohols have the most rapid and pronounced bactericidal action and greatly reduce the time needed for hand disinfection. A vigorous 1-minute rubbing with a sufficient volume of alcohol to wet the hands completely has been shown to be highly effective at reducing the density of skin bacteria.[238] Ethanol and iso- and n-propanol are the constituents of most commercially available alcohol-based hand rubs; at equal concentrations, n-propanol is most effective and ethanol the least. However, all have limited efficacy with gross soilage so that visibly soiled hands should always be washed with antiseptic soap and water.[183] Moreover, at least 3 mL of an alcohol-based rub is necessary to completely coat the hands and achieve optimal degerming. Additionally, C. difficile spores are highly resistant to killing by alcohol, and hand washing with soap and running water is recommended to physically remove C. difficile spores.[239] The use of alcohol hand rubs or gels will be augmented by making conveniently located calibrated dispensers widely available. However, many HCWs prefer individual containers that can be carried in a pocket, which makes it difficult to ensure that an adequate volume is used with each application.

Few trials have been conducted to evaluate the efficacy of alcohol-containing hand rubs for reducing nosocomial infection. Most are quasi-experimental before-after studies, and most have shown a short-term reduction in nosocomial infection rates with use of alcohol-containing hand rubs.[184,240,241]

The major factor limiting acceptance of alcohol products for hand antisepsis in the past was desiccation and irritation of skin. This is now obviated by incorporating emollients into alcohol-based hand rubs, which has enhanced acceptance by HCWs and may augment antibacterial activity by slowing the evaporation of alcohol.[242] A recent randomized clinical trial in 50 ICU HCWs compared a conventional 2% chlorhexidine gluconate wash with water to a waterless alcohol-based hand rub (61% ethanol with emollients) and showed that use of the waterless alcohol-based product produced significantly less skin scaling and irritation[243]; unfortunately, degerming was not assessed.

A recent review describes in detail the various hand hygiene agents available and their spectrum of activity.[228] Recommendations for hand hygiene by the CDC have been published (Table 47.5),183 emphasizing hand antisepsis with an antiseptic-containing soap

TABLE 47.5 Recommendations for Routine Hand Hygiene From the Centers for Disease Control and Prevention Guideline

Recommendation	Level of Evidence[a]
• When hands are visibly dirty or contaminated with proteinaceous material or are visibly soiled with blood or other body fluids, wash hands with either a nonantimicrobial soap and water or an antimicrobial soap and water.	IA
If hands are not visibly soiled, use an alcohol-based hand rub or, alternatively, wash hands with an antimicrobial soap and water, for the following situations: Before direct contact with patients Before putting on sterile gloves when inserting a central vascular catheter Before inserting a urinary catheter, peripheral vascular catheter, or other invasive procedure not requiring surgery After contact with patient's intact skin (e.g., while taking a pulse or blood pressure or lifting the patient) After contact with body fluids, mucous membranes, nonintact skin, and wound dressings if hands are not visibly soiled Moving from a contaminated body site to a clean body site during patient care After contact with inanimate objects (e.g., medical equipment) in the immediate vicinity of the patient After removing gloves	IB
Before eating and after using a restroom, wash hands with a nonantimicrobial soap and water or with an antimicrobial soap and water.	IB
Antimicrobial-impregnated wipes are not a substitute for using an alcohol-based hand rub or antimicrobial soap.	IB
If exposure to *Bacillus anthracis* is suspected or proved, wash hands with nonantimicrobial soap and water or antimicrobial soap and water.	II

[a]Categorization of recommendations: *IA*, strongly supported for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies. *IB*, Strongly recommended for implementation and supported by certain clinical or epidemiologic studies and by strong theoretical rationale. *IC*, Required for implementation, as mandated by federal or state regulation or standard. *II*, Suggested for implementation and supported by suggestive clinical or epidemiologic studies or by strong theoretical rationale. *NR* (no recommendation/unresolved issue): practices for which insufficient evidence or no consensus exists about efficacy.

Data from Boyce JM et al. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Health Care Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. *MMWR Recomm Rep.* 2002;51:1–45.

or detergent or an alcohol-based hand rub (1) before and after direct contact with patients or the environment and equipment in the immediate vicinity of the patient; and (2) before performing invasive procedures such as insertion of an IVD or urinary catheter. Use of skin care products—lotions or creams—to minimize irritant contact dermatitis associated with frequent handwashing and improve compliance with hand hygiene practices is highly recommended.

Institutional commitment is essential to improve compliance with recommended hand hygiene practices. The CDC guideline recommends that institutions (1) monitor and record adherence to hand hygiene by ward or service; (2) provide feedback to HCWs about their performance; and (3) monitor the volume of alcohol hand rubs used per 1000 patient-days.[183]

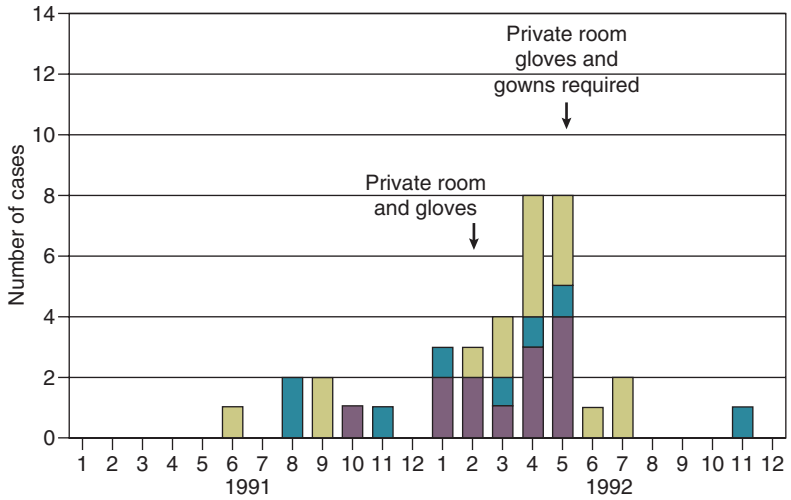
Clearly, further studies are necessary, particularly large comparative trials in which rates of nosocomial infection, rather than levels of cutaneous colonization, are used as the index of comparison. In the meantime the available data indicate that routine use of a chlorhexidine-containing product or alcohol-containing product, with the exception for C. difficile–infected patients, will be more effective than use of a nonmedicated soap for hand hygiene in the high-risk areas of the hospital, such as ICUs, where cross-infection is most likely to occur.

Isolation Precautions for Communicable Infections

Isolation, the use of special precautions in the care of infected patients, is the one means of curtailing the spread of contagious microorganisms and preventing epidemics, especially in ICUs, where the risk of cross-infection is highest. Although requiring all persons entering an infected patient's room to wear gloves and a gown, possibly even a mask, may seem ritualistic and almost archaic, each aspect of the isolation procedure is directed at interrupting a potential mode of spread and is based on the known epidemiology of the infecting organism.[244] To be maximally effective, however, isolation procedures require compliance by each person coming into contact with the patient, including physicians. Isolation is also indicated, usually for the entirety of hospitalization, for all patients infected or known to be colonized by antibiotic-resistant nosocomial pathogens such as MRSA, multidrug-resistant gram-negative bacilli, or VRE; in such cases, isolation has been shown to be effective in reducing endemic infections[245,246] (Figs. 47.2 and 47.3) and in controlling outbreaks.[246] Nevertheless, increasingly for some pathogens, particularly MRSA and VRE,[247–249] contact precautions have been viewed by many hospitals as unnecessary in the absence of an epidemic. One institution did not see an increase in MRSA or VRE isolates 1 year after elimination of routine contact precautions for MRSA and VRE, and demonstrated cost savings from decreased gown use and estimated HCW time.[249] There is less evidence, however, to support eliminating contact precautions for multidrug-resistant gram-negative bacilli and C. difficile.[245,250,251]

Isolation Systems

CDC guidelines separate basic precautions into (1) standard precautions designed for the care of all patients in hospitals, regardless of their diagnosis or presumed infection status, and (2) additional



• **Fig. 47.3** Impact of specific control measures on an institutional outbreak of vancomycin-resistant *Escherichia faecium.* Cases, by date of first positive culture for the epidemic strains (from January 1991 to December 1992). Number of cases = case patients in the intensive care unit (ICU) at time of first positive culture for the epidemic strain × other patients with previous exposure to the ICU × case patients never in the ICU. (From Boyce JM, Opal SM, Chow JW, et al. Outbreak of multidrug-resistant *Enterococcus faecium* with transferable vanB class vancomycin resistance. *J Clin Microbiol*. 1994;32:1148–1153.)

transmission-based precautions designed for the care of specified patients who are known or suspected to be infected with highly transmissible or epidemiologically important pathogens.[188] Standard precautions synthesize the major features of universal blood and body fluid precautions and are designed to reduce the risk of transmission of microorganisms from patient to patient and from patient to HCW, from both recognized and unrecognized sources of infection in the hospital. Transmission-based precautions are divided into three subgroups on the basis of the mode of transmission: contact precautions, droplet precautions, and airborne precautions. Contact precautions are recommended with multidrug-resistant bacteria that can be acquired by contact with the colonized patient or environmental surfaces or objects. Droplet precautions provide additional measures for transmission by large-particle droplets, such as during suctioning or bronchoscopy. Airborne precautions are added to standard precautions for the care of patients with tuberculosis and other microorganisms transmitted by the airborne route. In general, transmission-based precautions usually specify a private room—always for airborne precautions.

Special Issues in the ICU

An environmental issue pertaining to isolation may be most relevant in the ICU— namely, the greater potential for fomites or environmental surfaces to contribute to the spread of nosocomial infection, especially with antibiotic-resistant microorganisms. Although previous studies have not been able to demonstrate that the inanimate hospital environment, particularly surfaces, walls, or floors, contribute materially to the occurrence of nosocomial infection,[164,165] accumulating evidence suggests that this may not necessarily be true for ICUs, where uniform exposure to invasive devices makes patients unduly susceptible. A number of careful studies of the epidemiology of ICU-acquired infection with resistant organisms such as MRSA,[165,166] C. difficile,[80,167] and VRE[162,168,252] have shown heavy contamination of the inanimate environment immediately contiguous to the patient by strains implicated in nosocomial infections occurring in patients. Even if gloves are being worn as part of protective isolation or universal precautions, the possibility of transmission of microorganisms from the environment to patients on the gloved hands of HCWs is real. Prolonged wearing of gloves in the ICU, which is common, may increase the risk of nosocomial cross-infection, expanding the epidemiologic role of the inanimate environment with certain pathogens such as MRSA or VRE.[252]

Similarly, the use of common stethoscopes, sphygmomanometers, or electronic thermometers with multiple patients provides further opportunity for organisms to spread. Although stethoscopes are commonly contaminated by nosocomial organisms,[253] their role in cross-infection is less clear.[253] On the other hand, spread of VRE[254] and C. difficile[255] has been traced to contamination of electronic thermometers. All surfaces contiguous to the ICU patient should be wiped down with the general hospital disinfectant at least daily, and each ICU patient should have a dedicated stethoscope and sphygmomanometer. The use of electronic temperature measuring devices on multiple patients within an ICU bears reevaluation, unless stringent efforts are made to assure reliable decontamination of the device after each use.

As discussed, many nosocomial infections appear to derive from organisms carried on the hands of ICU personnel, who during the working day have contact with multiple patients. To improve nursing care and reduce the risk of cross-infection, ICUs must have an adequate number of staff. Although the optimal nurse-patient ratio for patients in an ICU is not known, increased rates of infection and outbreaks have occurred when nurses have been assigned to multiple critically ill patients who require complicated nursing care.[175] One-to-one nurse-patient ratios may significantly reduce the risk of cross-infection.

To contain the spread of certain resistant organisms in the ICU (e.g., MRSA, VRE), cohort nursing is strongly recommended. In cohort nursing, the care of patients known to be infected (or colonized) by the organism is provided by nurses (and respiratory therapists) who will not provide care during that shift for noninfected patients, and the nursing care of noninfected patients is restricted

to personnel who will not have contact with infected patients, except in an emergency. Cohorting of patients known to be colonized or infected with MRSA is widely practiced but has not been adequately studied. In one recent prospective study, the authors found that there was no evidence of increased transmission of MRSA when patients were not cohorted.[256]

Tuberculosis

The upsurge in tuberculosis since 1985, particularly the numerous nosocomial outbreaks caused by multidrug-resistant strains,[85–87,257,258] demonstrates the importance of isolation precautions to prevent the spread of tuberculosis within hospitals, especially within ICUs.[134] Guidelines[134] reemphasize the importance of air control by mandating the use of private negative-pressure rooms, combined with the use of UV lights or ventilatory modifications in which all air exiting the room is either filtered or exhausted directly to the roofline, away from hospital intake vents. Isolation room doors must be kept closed to maintain control over the direction of airflow, and all persons who enter a room in which tuberculosis isolation precautions are in effect must wear a disposable particulate respirator such as an N95 respirator or a powered air-purifying air respirator in which a battery-powered blower provides positive airflow through a filter, cartridge, or canister to a hood or face piece.[259] Gowns usually are not indicated. All ICUs should have one or more negative-pressure isolation rooms for the care of patients requiring respiratory isolation for tuberculosis and other airborne infections, such as chickenpox or disseminated herpes zoster, disseminated HSV infection, or emerging, highly contagious airborne infections such as SARS. To reduce the risk of contaminating a ventilator or discharging M. tuberculosis into the environment, when mechanically ventilating a patient with suspected or confirmed pulmonary tuberculosis, a bacterial filter capable of filtering particles as small as 0.3 μm, with a filter efficacy of greater than 95%, should be placed on the patient's endotracheal tube or at the expiratory side of the breathing circuit of a ventilator.[134] ICU patients with tuberculosis not requiring mechanical ventilation should wear a surgical mask if leaving the negative-pressure isolation rooms for radiographic or other procedures.[134]

Standard Precautions

In 1987 the CDC and the U.S. Department of Labor issued detailed guidelines for Universal Blood and Body Fluid Precautions[260,261] to prevent exposure of HCW workers and patients to potentially hazardous blood or body fluids. Universal precautions were based on the concept that all blood and body fluids that might be contaminated with blood should be treated as infectious because patients with bloodborne infections, such as human immunodeficiency virus (HIV), can be asymptomatic or unaware they are infected. The relevance of universal precautions to other aspects of disease transmission was recognized, and in 1996 the CDC expanded the concept and changed the term to standard precautions.[262] Standard precautions integrate and expand the elements of universal precautions into a standard of care designed to protect health care personnel and patients from pathogens that can be spread by blood or any other body fluid, excretion, or secretion. Standard precautions apply to contact with (1) blood; (2) all body fluids, secretions, and excretions (except sweat), regardless of whether they contain blood; (3) nonintact skin; and (4) mucous membranes.

Gloves are recommended for venipunctures, insertion of IVDs, and whenever it can be anticipated that the hands could become contaminated by blood or another high-risk body fluid. If there is potential for splatter or contamination of clothing, a gown is added. When there is potential for aerosolization of body fluids, such as during surgery, intubation, endoscopy, or insertion of an arterial catheter, a mask and eye shielding are included. Because the vast majority of occupationally related HIV infections have involved needle sticks or other sharps injuries, every effort must be made to avert such injuries that could result in percutaneous inoculation of HIV or other bloodborne viruses.[260,263]

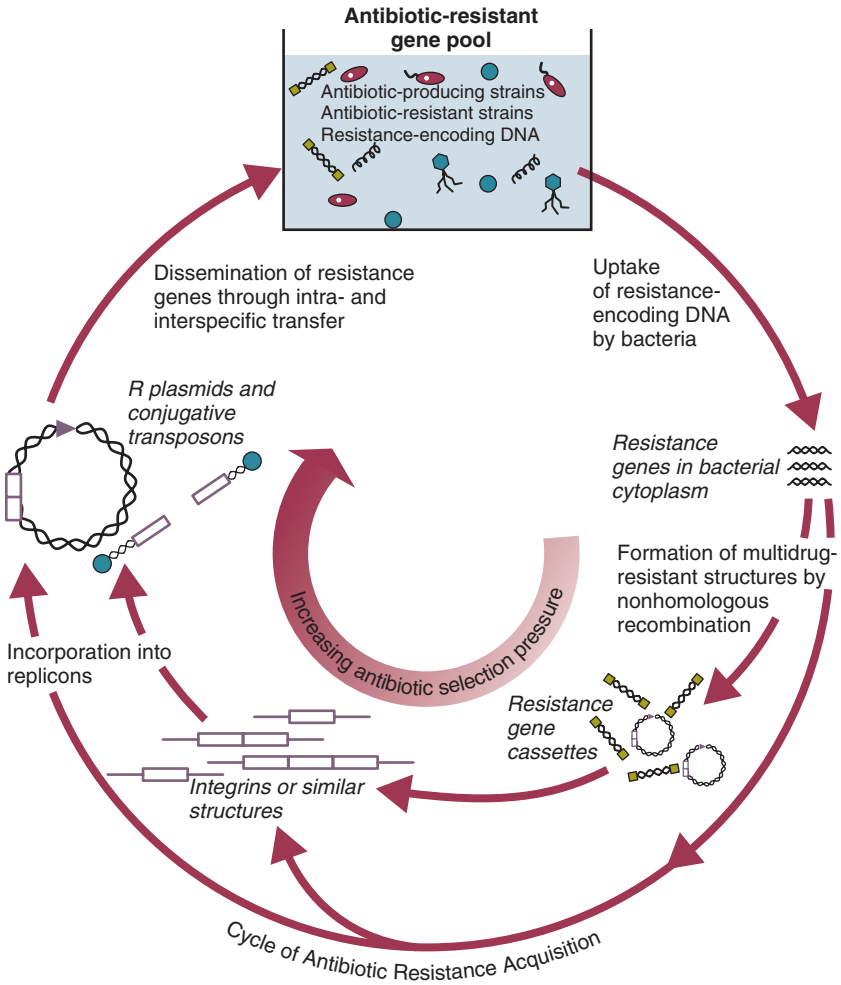
Because prophylactic use of barrier precautions appears to be of some benefit for the prevention of nosocomial infection[181,250,264] and all U.S. hospitals are currently mandated to follow standard precautions, it has been suggested that the use of gloves for all patient contacts, so-called universal gloving, as is now common in many U.S. hospitals, should implicitly reduce the risk of nosocomial infection. Several studies have demonstrated decrease infection rates with universal gloving, including in ICUs.[265–267] The greatly expanded use of gloves as part of standard precautions in hospitals must now be accompanied by educational programs on how to use gloves effectively and in a manner that will not jeopardize patients. Staff must be strongly encouraged to wash their hands after removing gloves. Moreover, if the gloved HCW has had hands-on contact with a patient colonized by MRSA or VRE, the process of removing the gloves will result in contamination of the hands of the HCW by these organisms up to one-third of the time.[266]

Antibiotic Stewardship

Antimicrobials have had a tremendous impact on the practice of critical care medicine, allowing for the treatment of once unmanageable life-threatening infections. However, it is estimated that up to 50% of antimicrobial use in U.S. acute care hospitals is either inappropriate or unnecessary, which is associated with a number of adverse outcomes, including antimicrobial resistance, C. difficile infection, treatment failures, and adverse drug reactions.[268] Antimicrobials are unique as compared with other medications in that misuse is associated with antimicrobial resistance and C. difficile, which may spread to other patients (even to the next patients to occupy that bed[172,173]), causing harm to patients not exposed to antimicrobials.[268]

There is a world crisis in antibiotic resistance, which reflects profligate antibiotic use in health care and in animal husbandry; environmental contamination with resistant bacteria, particularly in low-income countries; and intrinsic resistance elements, present long before the antimicrobial era. Antimicrobial resistance has been labeled by the World Health Organization as one of the three greatest threats to human health.[269] In the United States, it is estimated by the CDC that at least 2 million people are infected with antimicrobial-resistant microorganisms each year, resulting in at least 23,000 deaths annually.[270] Additionally, an estimated 250,000 patients are infected with C. difficile each year, resulting in at least 14,000 deaths annually in the United States.[270] More alarmingly, there are few novel antimicrobials in development for the treatment of antimicrobial-resistant microorganisms, making it imperative to optimally use currently available antimicrobials.

Antimicrobial therapy has its greatest ecologic impact in the close confines of the ICU. Most nosocomial outbreaks caused by antibiotic-resistant microorganisms[271,272] have occurred in patients hospitalized in an ICU. Antibiotic pressure, which promotes the exchange of genes encoding drug resistance by a variety of transfer mechanisms (Fig. 47.4),[273] has been shown to be the single most important factor predisposing patients to nosocomial infection



• **Fig. 47.4** Schematic depicting the route by which antibiotic-resistant genes are acquired by bacteria in response to selection pressure of antibiotic use. The resistance gene pool represents all potential sources of DNA encoding antibiotic-resistant determinants in the environment; this includes hospitals, farms, or other microenvironments where antibiotics are used to control bacterial development. After uptake of single- or double-stranded DNA by the bacterial host, the incorporation of the resistance genes into stable replicons (DNA elements capable of autonomous replication) may occur by several different pathways that have not yet been identified. The involvement of integrins, as shown here, has been demonstrated for a large class of transposable elements in the *Enterobacteriaceae.* The resulting resistance plasmids could exist in linear or circular form in bacterial hosts. The final step in the cycle, dissemination, is brought about by one or more gene transfer mechanisms. (From Davies J. Inactivation of antibiotics and the dissemination of resistance genes. *Science.* 1994;264:375–382.)

with resistant organisms. Modern-day ICUs are the breeding grounds for the multiply resistant bacteria that are now being encountered in hospitals throughout the world: MRSA; VRE; extended-spectrum β-lactamase–producing and carbapenem-resistant Enterobacteriaceae, Enterobacter, Serratia, Citrobacter; P. aeruginosa resistant to fluoroquinolones, aminoglycosides, or extended-spectrum β-lactams; and multidrug-resistant Acinetobacter.[48,62–65] Broad-spectrum antimicrobial therapy is the root cause of antibiotic-associated diarrhea and colitis caused by C. difficile.[80]

Clearly, antimicrobials are widely overused and misused; more than 75% of patients in U.S. ICUs, other than coronary care units, receive antimicrobial agents, whereas studies indicate that up to half of hospitalized patients receiving antimicrobial therapy have no evidence of infection or clear justification to be receiving antibiotics.[268] Moreover, within ICUs, a high proportion of the antibiotics used are broad-spectrum/extended-spectrum penicillins, third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, or vancomycin. Greater efforts must be directed to improving the use of systemic antibiotics, especially within ICUs.

Antibiotic stewardship is defined as coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen, including dose, duration of therapy, and route of administration.[274] Antibiotic stewardship programs have been shown to improve infection cure rates, reduce treatment failures, increase frequency of correct antibiotic prescribing, and decrease antibiotic resistance and C. difficile infection.[268] The CDC recommended in 2014 that all acute care hospitals implement an antimicrobial stewardship program.[268] Subsequently, The Joint Commission

required that all hospitals have an antibiotic stewardship program as of January 1, 2017.[275] Additionally, The Centers for Medicare & Medicaid Services proposed in June 2016 to require hospitals to have policies and procedures for, and to demonstrate evidence of, an active and hospital-wide antibiotic stewardship program.[276]

There are multiple guidelines available that outline implementation of an antibiotic stewardship program.[268,274,277] The core elements of antibiotic stewardship programs are discussed in detail later under "Control of Antibiotic Resistance."

Excellent resources,[278–280] including other chapters in this book (Chapters 20, 51 and 52), are available to guide the selection and use of anti-infective drugs in critically ill patients. However, several principles can reduce unnecessary antimicrobial therapy and improve the use of the drugs that are given:

1. Fever without other indications of infection should not mandate automatically beginning antimicrobial therapy in an ICU patient.
2. Unless antimicrobial therapy is being given for surgical prophylaxis, it is most likely being given for the treatment of suspected or proved infection. Gram-stained smears, cultures (especially of blood before any antibiotic is administered), and other appropriate diagnostic tests, as indicated, should be done without fail before beginning antimicrobial therapy for treatment of presumed infection in an ICU patient.
3. Whenever antimicrobial therapy is begun, the reason should be documented in the patient's record (e.g., "for the treatment of pneumonia," "for surgical prophylaxis").
4. When possible, the most narrow-spectrum drug or drugs should be used, especially if the infecting organism or organisms are known at the outset.
5. The need for continued antimicrobial therapy should be reassessed daily. If cultures identify the infecting microorganism or microorganisms, therapy should be modified, aiming for the most narrow-spectrum drug or drugs likely to be effective. If results of diagnostic studies are negative after 48 to 72 hours and the patient is not exhibiting signs of sepsis, antibiotic therapy should be discontinued unless the patient is profoundly granulocytopenic.
6. Beyond monitoring for efficacy and adverse drug effects such as hypersensitivity or organ toxicity, it is essential that monitoring include surveillance for superinfection by resistant bacteria or Candida and for C. difficile infection.
7. Surgical antimicrobial prophylaxis should not extend beyond 24 hours postoperatively[281,282] and in most operations can be limited to doses given intraoperatively.[281]

Nosocomial Infections and Specific Infection Control Measures

As noted earlier, most nosocomial infections, especially in immunologically competent patients and in ICUs, are causally related to exposure to invasive devices of various types or to invasive procedures such as surgery (see Tables 47.1 and 47.2). Comprehensive guidelines for the prevention of infection with procedures or devices that pose the greatest risk (urinary catheters,[138,139,283] endotracheal intubation and mechanical ventilatory support,[140] intravascular catheters and infusion therapy,[137] hemodialysis,[284] and surgery[281]) have been published and can form the basis for institutional policies and procedures. Health care professionals working in ICUs are obligated to be informed about prevention of infection associated with the procedures they perform and the devices with which they work daily.

Intravascular Device–Related Bloodstream Infection

Impact

Obtaining and maintaining reliable vascular access has become one of the most essential features of modern-day intensive care. Unfortunately, vascular access is associated with substantial and generally underappreciated potential for producing iatrogenic disease, particularly BSI originating from infection of the percutaneous IVD used for vascular access (i.e., IVD-related BSI), often referred to as "line sepsis." Nearly 60% of all nosocomial bacteremias derive from vascular access in some form,[18] and it is estimated that more than 500,000 IVD-related BSIs occur in the United States each year.[285,286] Early studies found that IVD-related BSIs are associated with excess attributable mortality rate ranging up to 35%[287]; however, subsequent case-control studies have not consistently found excess mortality rates, especially of this magnitude.[288–290] This controversy aside, all studies examining the impact of IVD-related BSI on patient outcomes have found that IVD-related BSIs are associated with increased length of hospitalization and excess health care costs, averaging $30,000 per case.[287–290]

IVD-related BSIs are largely preventable and are considered to be "never events" in many hospitals. The goal must not be simply to identify and treat these infections but rather to prevent them. By drawing on existent knowledge of the pathogenesis and epidemiology of IVD-related BSI, rational and effective guidelines for prevention can be formulated.

Definitions

IVDs are associated with both local and systemic infection. The CDC has published definitions for IVD-related infection (see Box 47.1).[16,17] These definitions are useful for the purposes of surveillance but rely heavily on the construct, central line–associated bloodstream infection, which implicitly assumes that each primary BSI (i.e., a BSI without an identifiable local infection) originates from a central venous catheter (CVC). This practice results in an overestimation of the true risk of CVC-related infection because not all primary BSIs originate from a central venous device; some are secondary BSIs deriving from unrecognized postoperative surgical site, intraabdominal infections, nosocomial pneumonias, gastrointestinal source (i.e., "translocation") in patients with severe neutropenia, or originate from other vascular devices such as peripheral venous catheters or arterial catheters used for hemodynamic monitoring.

By applying molecular subtyping techniques[114,291,292] to the results of semiquantitative or quantitative cultures of the removed IVD and blood cultures or the results of cultures of blood drawn through the IVD and a separate concomitant percutaneous peripheral blood culture, it is possible to reliably determine whether an IVD was the source of a nosocomial BSI. Using these diagnostic techniques allows the formulation of simple but more rigorous definitions for IVD-related infection (Table 47.6), which we believe bear consideration as the standard for randomized trials and epidemiologic studies of IVD-related infection.[18] Published guidelines from the Infectious Diseases Society of America have outlined clinical definitions of IVD-related BSI similar to those listed in Table 47.6, although molecular subtyping methods are not recommended for routine clinical diagnosis of IVD-related BSI.[293]

Recognition and Diagnosis

Clinical Features

Evidence-based guidelines from the American College of Critical Care Medicine and the Infectious Diseases Society of America

TABLE 47.6 Proposed Definitions for Intravascular Device–Related Colonization, Local Infection, and Bloodstream Infection Based on Microbiologic Confirmation of the Device as Source

IVD colonization	(i) A positive semiquantitative[a] (or quantitative[b]) culture of the implanted portion or portions of the IVD; (ii) absence of signs of local or systemic infection.
Local IVD infection	(i) A positive semiquantitative[a] (or quantitative[b]) culture of the removed IVD or a positive microscopic examination or culture of pus or thrombus from the cannulated vessel; (ii) clinical evidence of infection of the insertion site (i.e., erythema, induration, or purulence); but (iii) absence of systemic signs of infection and negative blood cultures, if done.
IVD-related BSI	*If the IVD is removed:* (i) A positive semiquantitative[a] (or quantitative[b]) culture of the IVD or a positive culture of the catheter hub or infusate (or positive microscopic examination or culture of pus or thrombus from the cannulated vessel) AND one or more positive blood cultures, ideally percutaneously drawn, concordant for the same species, ideally by molecular subtyping methods; (ii) clinical and microbiologic data disclose no other clear-cut source for the BSI. *If the IVD is retained:* (i) If quantitative blood cultures are available, cultures drawn both from the suspect IVD and a peripheral vein (or another IVD) are both positive and show a marked step-up in quantitative positivity (fivefold or greater) in the IVD-drawn culture; (ii) clinical and microbiologic data disclose no other clear-cut source for the BSI. OR (i) If automated monitoring of incubating blood cultures is available, blood cultures drawn concomitantly from the suspect IVD and a peripheral vein (or another IVD) show both are positive, but the IVD-drawn blood culture turns positive more than 2 hours before the peripherally drawn culture; (ii) clinical and microbiologic data disclose no other clear-cut source for the BSI.

[a]Roll plate of cannula segment(s) >15 colony-forming units (CFUs).
[b]Sonication culture of cannula segment(s) $\geq 10^3$ CFUs/mL.
BSI, Bloodstream infection; *IVD*, intravascular device.
Modified from Crnich CJ, Maki DG. The role of intravascular devices in sepsis. *Curr Infect Dis Rep.* 2001;3:497–506.

TABLE 47.7 Clinical, Epidemiologic, and Microbiologic Features of Intravascular Device–Related Bloodstream Infection

Nonspecific	Suggestive of Device-Related Etiology
Fever	Patient unlikely candidate for sepsis (e.g., young, no underlying diseases)
Chills, shaking rigors[a]	Source of sepsis inapparent, no identifiable local infection
Hypotension, shock[a]	Intravascular device in place, especially central venous catheter
Hyperventilation, respiratory failure	Inflammation or purulence at insertion site
Gastrointestinal[a]	Abrupt onset, associated with shock
Abdominal pain Vomiting Diarrhea	Bloodstream infection caused by staphylococci (especially coagulase-negative staphylococci), *Corynebacterium, Candida, Trichophyton, Fusarium,* or *Malassezia* species[b]
Neurologic[a]	Very high-grade (>25 CFUs/mL) candidemia
Confusion Seizures	Cluster of cryptogenic infusion-associated bloodstream infections caused by *Enterobacter cloacae, Pantoea agglomerans,* or *Serratia marcescens*[a,b] Sepsis refractory to antimicrobial therapy or dramatic improvement with removal of cannula and infusion[a]

[a]Commonly seen in overwhelming gram-negative sepsis originating from contaminated infusate, peripheral suppurative phlebitis, or septic thrombosis of a central vein.
[b]Conversely, bacteremia caused by streptococci, aerobic gram-negative bacilli, or anaerobes is unlikely to derive from an intravascular device.
CFUs, Colony-forming units.
Modified from Maki DG, Mermel LA, Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. *Hospital Infections.* 4th ed. Boston: Lippincott-Raven; 1998:689–724.

provide information on the evaluation of the ICU patient with fever or other signs of sepsis.[35] Before any decision regarding initiation of antimicrobial therapy or removal of an IVD, the patient must be thoroughly examined to identify all plausible sites of infection, including VAP, catheter-associated urinary tract infection, surgical site infection, IVD-related BSI, C. difficile infection, and other infections.[35]

Despite the challenge of identifying the source of a patient's signs of sepsis,[35] several clinical, epidemiologic, and microbiologic findings point strongly toward an IVD as the source of a septic episode (Table 47.7).[285] Patients with an abrupt onset of signs and symptoms of sepsis without any identifiable local infection such as pneumonia or surgical site infection should prompt suspicion of infection of an IVD. The presence of inflammation or purulence at the catheter insertion site is now uncommon in patients with IVD-related BSI.[294] However, if inflammation, especially any purulence, is seen in combination with signs and symptoms of sepsis, it is highly likely the patient has IVD-related BSI and should prompt removal of the device. Finally, recovery of certain microorganisms in multiple blood cultures, such as staphylococci, Corynebacterium or Bacillus species, or Candida or Malassezia, strongly suggests infection of an IVD.

Blood Cultures

Initiating the use of anti-infective drugs for suspected or presumed infection in the critically ill patient without first obtaining blood cultures from two separate sites, at least one of which is drawn from a peripheral vein by percutaneous venipuncture, is indefensible. The volume of blood cultured is essential to maximize the sensitivity of blood cultures for diagnosis of bacteremia or candidemia: in

adults, obtaining at least 20 mL, ideally 30 mL, per drawing (each specimen, containing 10 or 15 mL, inoculated into aerobic and anaerobic media) significantly improves the yield compared with obtaining only 5 mL at each drawing and culturing a smaller total volume.[295,296] In adults, if at least 30 mL of blood is cultured, 99% of detectable bacteremias should be identified.[295,297] Similar operating characteristics are achieved in the pediatric population using a weight-based graduated volume approach to blood cultures.[298] Standard blood samples for cultures drawn through CVCs provide excellent sensitivity for diagnosis of BSI but are less specific than cultures obtained from a peripheral vein.[299,300] If the patient has a long-term multilumen catheter, it may be reasonable to obtain a specimen from each lumen of the catheter because studies have found discordance (≈30%) among cultures obtained from different lumens of the same catheter.[301] Nevertheless, some hospitals have prohibited routinely drawing of blood for cultures from vascular access devices because of increased blood culture contamination rates and resultant overuse of vancomycin.

Every effort must be made to prevent introduced contamination when drawing samples for blood cultures because a single contaminated blood culture has been shown to prolong hospitalization by 4 days and increase the costs of hospitalization by $4100 to $4400.[302,303] Tincture of iodine, isopropyl alcohol, chlorhexidine, or povidone-iodine combined with alcohol rather than povidone-iodine alone should be used for skin antisepsis before venipuncture for blood cultures, recognizing that studies have shown significantly reduced rates of contamination with use of these agents.[218,303,304] Up to 30% of blood cultures positive for coagulase-negative Staphylococcus represent true infection[305,306]; however, the majority of single positive cultures represent contamination,[306] a finding that should reemphasize the need to obtain cultures from two separate sites whenever BSI is suspected.

Cultures of Removed Intravascular Devices

Removal and direct culture of the IVD has historically been the gold standard for confirming the presence of IVD-related BSI, particularly with short-term IVDs. Studies have shown that culturing catheter segments semiquantitatively on solid media[307] or quantitatively in liquid media (e.g., removing the adherent organisms by sonication[308]) provides superior sensitivity and specificity for diagnosis of IVD-related BSI, with a strong correlation between high colony counts and line sepsis. Growth of greater than or equal to 15 CFUs from a catheter segment by semiquantitative culture or growth of greater than or equal to 10^3 CFUs from a catheter cultured after sonication with accompanying local inflammation or signs of sepsis indicates local catheter infection. Significant growth in the absence of local or systemic inflammation suggests colonization of the device, which reinforces the recommendation that catheter tips should be cultured only for clinical indications and not routinely. If continued vascular access is necessary, a new device should be placed in a new location rather than replacing it with a new one in the same location by guidewire exchange because of greater risk of subsequent infection when the old site is used.

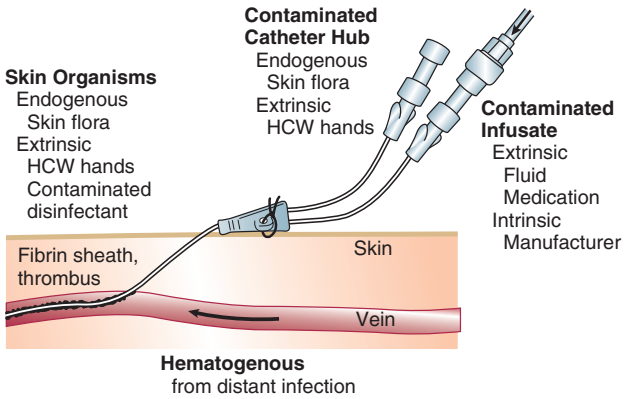
Although studies[309] have suggested that quantitative methods (e.g., sonication) are superior to the semiquantitative methods (e.g., roll plate), other studies have shown them to be equivalent.[310,311] Because hub contamination progressing to intraluminal colonization is the primary route of infection for long-term devices (e.g., devices in place >10 days), quantitative techniques may be superior to semiquantitative techniques in detecting infections from devices in place over the long term, because quantitative techniques remove organisms from both the internal and external surface of catheters.[311] In contrast, semiquantitative methods may be preferred over quantitative methods in cases of suspected infection related to a short-term device (e.g., devices in place <10 days) because the primary route of infection in this setting is caused by extraluminal ingress of skin organisms at the catheter insertion site and the semiquantitative method is simple, is the only method available in most non-research labs, is less expensive, and allows identification of the infecting organisms a day earlier.

Direct and impression Gram stains[312] or acridine orange stains[311] of intravascular segments of removed catheters have shown excellent correlation with quantitative techniques for culturing catheters and can permit rapid diagnosis of catheter-related infection.

To rigorously identify the mechanism of IVD-related BSI in prospective research studies, it is necessary to culture all potential sources of microorganisms at the time of catheter removal for cause (Fig. 47.5): skin of the insertion site, each catheter hub, infusate from each lumen, as well as implanted catheter segments. If the results of these cultures appear to link a BSI with microorganisms isolated from one or more portions of the device by phenotypic criteria, efforts then need to be made to conclusively establish concordance, beyond speciation and antimicrobial susceptibility pattern, using one or more molecular subtyping systems.[291,292,296,313]

Diagnosis of Infection With Implanted Long-Term Intravascular Devices

The methods described earlier require removal of the device for confirmation of IVD-related BSI. This can pose formidable challenges to management with long-term, surgically implanted IVDs such as Hickman and Broviac catheters, cuffed and tunneled hemodialysis catheters, and subcutaneous central venous ports. Only 15% to 45% of long-term IVDs that are removed for suspected infection are truly colonized or infected at the time of removal.[314–317] To avoid unnecessary removal of IVDs, methods have been developed to diagnose IVD-related BSI while allowing the device to remain in place: (1) paired quantitative blood culture samples drawn from the IVD and percutaneously from a peripheral vein[311] and (2) differential time to positivity (DTP) of paired standard blood cultures, one drawn from the IVD and the other from a peripheral vein.[318]



• **Fig. 47.5** Potential sources of infection of a percutaneous intravascular device (IVD): the contiguous skin flora, contamination of the catheter hub and lumen, contamination of infusate, and hematogenous colonization of the IVD from distant, unrelated sites of infection. *HCW,* Health care worker. (From Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device-related bloodstream infection. I. Pathogenesis and short-term devices. *Clin Infect Dis.* 2002;34:1232–1242.)

Although seldom available outside the research setting, automated quantitative systems for culturing blood (e.g., Isolator lysis centrifugation system, Wampole Laboratories, Cranbury, NJ), allow for samples for quantitative blood cultures to be drawn through the IVD and concomitantly by venipuncture from a peripheral vein (or another IVD), which can permit the diagnosis of IVD-related bacteremia or fungemia to be made with sensitivity and specificity in the range of 80% to 95%,[311] without removal of the catheter, if empiric antimicrobial therapy has not yet been initiated. IVD-drawn cultures demonstrating 5- to 10-fold higher concentrations of microorganisms per milliliter, as compared with counts of the same microorganism obtained in a culture drawn from a peripheral vein, confirm the presence of IVD-related BSI.

A more readily available method is the DTP of paired blood cultures, where one sample for blood culture is drawn through the IVD and the second, concomitantly from a peripheral vein. The time required for blood cultures to turn positive is accessible from the automated blood culture system, available from the microbiology department. DTP has also been shown to reliably identify IVD-related BSI of long-term IVDs if the blood for culture drawn from the IVD turns positive 2 or more hours before the culture drawn peripherally. In studies of patients with long-term IVDs, the sensitivity and specificity of DTP ranged from 82% to 94% and 88% to 91%, respectively.[311,318] The performance of DTP in short-term IVDs has been examined, with disappointing results,[319] a finding that is not entirely unexpected given the predominant extraluminal route of infection with these devices.

Detection of Contaminated Infusate

When a patient becomes acutely septic temporally related to an infusion of intravenous (IV) fluid or medication, the infusate should be considered as a source of infection. To diagnose infection caused by contaminated infusate, a sample of IV fluid, aspirated from the line, should be cultured quantitatively and qualitatively[307] and information about the infused material (manufacturer, lot number) and the infusate container should be retained; concordance with positive peripheral blood cultures, without another identifiable source for the patient's BSI, definitively implicates infected infusate as the cause of the BSI. Anaerobic culture techniques are not necessary unless blood or another biologic product is involved.

Incidence

Prospective studies, in which every attempt was made to conclusively identify the presence of an IVD-related BSI, show that every type of IVD carries some risk of causing BSI; however, the magnitude of risk varies greatly, depending on the type of device (Table 47.8).[320]

TABLE 47.8 Rates of Intravascular Device–Related Bloodstream Infection Caused by Various Types of Devices Used for Vascular Access in Adults

					RATES OF IVD-RELATED BSIS			
					Per 100 Devices		Per 1000 IVD Days	
Device	Studies *(n)*	Catheters *(n)*	IVD days *(n)*	BSIs *(n)*	Pooled Mean	95% CI	Pooled Mean	95% CI
Peripheral intravenous catheters	11	10,910	28,720	13	0.1	0.1-0.2	0.5	0.2-0.7
Arterial catheters	14	4,366	21,397	37	0.8	0.6–1.1	1.7	1.2–2.3
Short-term, nonmedicated central venous catheters	79	20,226	322,283	883	4.4	4.1–4.6	2.7	2.6–2.9
Pulmonary artery catheters	13	2,057	8143	30	1.5	0.9–2.0	3.7	2.4–5.0
Hemodialysis catheters:								
Temporary, noncuffed	16	3,066	51,840	246	8.0	7–9	4.8	4.2–5.3
Long-term, cuffed, and tunneled	16	2,806	373,563	596	21.2	19.7–22.8	1.6	1.5–1.7
Peripherally inserted central catheters (PICCs):	15	3,566	105,839	112	3.1	2.6–3.7	1.1	0.9–1.3
Long-term, tunneled, and cuffed central venous catheters	29	4,512	622,535	1013	22.5	21.2–23.7	1.6	1.5–1.7
Subcutaneous venous ports	14	3,007	983,480	81	3.6	2.9–4.3	0.1	0-0.1

BSIs, Bloodstream infections; *CI,* confidence interval; *IVD,* intravascular device.

Modified from Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81:1159–1171.

The device that poses the greatest risk of IVD-related BSI today is the CVC in its many forms (see Table 47.8). Short-term, noncuffed, single-lumen, or multilumen catheters inserted percutaneously into the subclavian or internal jugular vein have shown rates of catheter-related BSI in the range of 3% to 5% (2 to 3 per 1000 IVD days).[320] Far lower rates of infection have been encountered with surgically implanted cuffed Hickman or Broviac catheters and subcutaneous central venous ports (1 and 0.2 per 1000 IVD days, respectively).[320] Contrary to popular belief, peripherally inserted central catheters (PICCs) used in inpatients and arterial catheters are associated with rates of catheter-related BSI approaching those seen with short-term, noncuffed, and nontunneled, multilumen CVCs—up to 2.1[321] and 3.4[322] BSIs per 1000 IVD-days, respectively.

Pathogenesis and Risk Factors

Two major sources of IVD-related BSI exist: (1) colonization of the IVD, catheter-related infection, and (2) contamination of the fluid administered through the device, infusate-related infection.[285] Contaminated infusate is the cause of most epidemic IVD-related BSIs; in contrast, catheter-related infections are responsible for most endemic IVD-related BSIs.[18]

For microorganisms to cause catheter-related infection, they must first gain access to the extraluminal or intraluminal surface of the device, where they can adhere and become incorporated into a biofilm that allows sustained infection and hematogenous dissemination.[323] Microorganisms gain access to the bloodstream by one of three mechanisms (see Fig. 47.5): (1) skin organisms invade the percutaneous tract, probably assisted by capillary action, at the time of insertion or in the days following; (2) microorganisms contaminate the catheter hub (and lumen) when the catheter is inserted over a percutaneous guidewire or later manipulated; or (3) organisms are carried hematogenously to the implanted IVD from remote sources of local infection such as pneumonia.

With short-term IVDs (e.g., in place <10 days) such as peripheral IV catheters; arterial catheters; and noncuffed, nontunneled CVCs, most device-related BSIs are of cutaneous origin, from the insertion site, and gain access extraluminally, occasionally intraluminally at insertion with the guidewire.[324,325] In contrast, contamination of the catheter hub and luminal fluid is the predominant mode of invasive infection with long-term IVDs (e.g., in place >10 days) such as cuffed Hickman- and Broviac-type catheters, subcutaneous central ports, and PICCs.[326,327]

Also important is recognizing that infusate (parenteral fluid, blood products, or IV medications) administered through an IVD can also occasionally become contaminated and produce device-related BSI. Contaminated fluid is fortunately an infrequent cause of endemic infusion-related infection with most short-term IVDs; it is, however, an important cause of BSIs with arterial catheters used for hemodynamic monitoring and long-term IVDs such as Hickman or Broviac catheters, cuffed hemodialysis CVCs, and subcutaneous central venous ports.[325,328,329]

Most nosocomial epidemics of infusion-related BSI have been traced to contamination of infusate by gram-negative bacilli, introduced during its manufacture (intrinsic contamination) or during its preparation and administration in the hospital (extrinsic contamination).[151,330] If an epidemic is suspected, the epidemiologic approach must be methodical and thorough yet expeditious, directed toward establishing the bona fide nature of the putative epidemic infections (i.e., ruling out "pseudoinfections")[331] and confirming the existence of an epidemic; defining the reservoirs and modes of transmission of the epidemic pathogens; and most importantly, controlling the epidemic quickly and completely. Control measures are predicated on accurate delineation of the epidemiology of the epidemic pathogen. The essential steps in dealing with a suspected nosocomial outbreak have recently been reviewed (and are discussed later).[285]

Risk factors associated with an increased risk of IVD-related BSI are outlined in Table 47.9. Prolonged hospitalization and severity of illness clearly influence the risk, and clinical states such as granulocytopenia, AIDS, and bone marrow transplantation have been associated with fourfold to sixfold increased rates of IVD-related BSI.[332,333] However, the features of the IVD, its insertion, and its maintenance appear to have far greater impact on the overall risk of infection. In 289 patients, Merrer and colleagues[334] found that insertion of an IVD in the femoral versus the subclavian vein was associated with a greatly increased risk of infection (20 vs. 3.7 BSIs per 1000 IVD days, $P < 0.001$) and thrombotic complications (21.5% vs. 1.9%, $P < 0.001$).[334] Moreover, Robert and colleagues[335] found that patients with primary BSI were more likely to have received care during times when there was a lower nurse-to-patient ratio and a higher proportion of temporary ("float") nurses rather than the full-time nursing staff.[335]

Microbiology

Fig. 47.6 summarizes the microbial profile of IVD-related BSI from 159 published prospective studies.[336] As might be expected from knowledge of the pathogenesis of these infections, skin microorganisms account for the largest proportion of these infections.

Treatment

Treatment of IVD-related BSI is discussed in Chapter 51 (see "Device-Related Endovascular Infections").

Strategies for Prevention

Recommendations for the prevention of IVD-related BSIs were published by the Healthcare Infection Control Practices Advisory Committee (HICPAC).[137] Table 47.10 summarizes the recommendations of the 2011 HICPAC guideline for the prevention of IVD-related BSI and scores each recommendation on the basis of the quality of the available scientific evidence. It must be reaffirmed that measures for prevention of any nosocomial infection must, wherever possible, be based on the best understanding of pathophysiology and epidemiology and, whenever possible, controlled clinical trials.

At-Device Insertion

1. Choice of catheter and site of device insertion. Obviously, the choice of IVD inserted into a patient will be guided primarily by that patient's particular needs (e.g., hemodialysis vs. fluid administration). However, the astute clinician can mitigate much of the risk associated with vascular access by choosing the best device for the task at hand and inserting the IVD in a location associated with the least risk of infection. Studies suggest that multilumen IVDs are associated with a higher risk of infection than single-lumen catheters.[337] That said, if a patient has need for multiple infusions, inserting several single-lumen catheters will pose greater risks than a single multilumen catheter.

   To date, there have been no randomized studies designed to evaluate the optimal location for placement of short-term CVCs. However, the data accumulated from numerous observational studies suggest that the lowest risk of IVD-related BSI is seen with subclavian vein insertion and the highest risk with

TABLE 47.9 Risk Factors for Intravascular Device–Related Bloodstream Infection With Short-Term Use

Risk Factor (No. of Studies)	Relative Risk or Odds Ratio
Underlying Disease	
AIDS (2)	4.8
Neutropenia (2)	1–15.1
Gastrointestinal disease (1)	2.4
Surgical service (1)	4.4
ICU/CCU placement (3)	0.4–6.7
Extended hospitalization (3)	1–6.7
Other intravascular devices (2)	1–3.8
Systemic antibiotics (3)	0.1-0.5
Active infection at another site (2)	8.7–9.2
High APACHE III score (1)	4.2
Mechanical ventilation (1)	2–2.5
Transplant recipient (1)	2.6
Features of Insertion	
Difficult insertion (1)	5.4
Maximal sterile barriers (1)	0.2
Tunneling (2)	0.3–1
Insertion over a guidewire (8)	1–3.3
Insertion Site	
Internal jugular vein (6)	1–3.3
Subclavian vein (5)	0.4–1
Femoral vein (2)	3.3–4.8
Defatting insertion site (1)	1.0
Use of a multilumen catheter (8)	6.5
Catheter Management	
Routine change of IV set (2)	1.0
Staffing in SICU (nurse-to-patient ratio) (1)	
1:2	61.5
1:1.5	15.6
1:1.28	4.0
1:1	1.0
Inappropriate catheter usage (1)	5.3
Duration of catheterization >7 days (5)	1–8.7
Colonization of catheter hub (3)	17.9–44.1
Parenteral nutrition (2)	–4.8

APACHE III, Acute Physiology and Chronic Health Evaluation III; *CCU*, critical care unit; *ICU*, intensive care unit; *IV*, intravenous; *SICU*, surgical intensive care unit.
Modified from Safdar NS, Kluger DM, Maki DG. A review of risk factors for catheter-related infection caused by percutaneously inserted, noncuffed central venous catheters: implications for preventive strategies. *Medicine.* 2002;81:466–479.

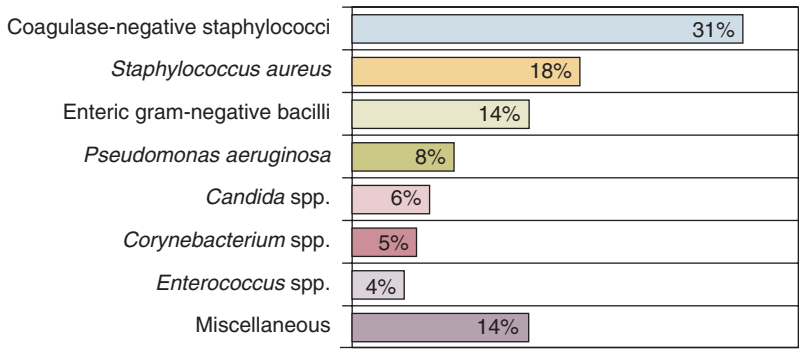
femoral vein insertion, with an intermediate level of risk associated with jugular vein insertions.[325,334]

The femoral vein is often used for central venous access, especially on nonsurgical services, because of the ease of cannulation and the lower risk of mechanical complications from insertion (i.e., bleeding or pneumothorax). Unfortunately, prospective studies evaluating the risk of femoral vein device placement have shown that CVCs placed in the femoral vein are more likely to be colonized at the time of removal than catheters placed in the internal jugular vein (RR 4.7, CI 2–8.8, P = 0.0001)[338] and are associated with an increased risk of IVD-related BSI when compared with CVCs placed in the subclavian vein (4.4% vs. 1.5%, P = 0.07).[334] Furthermore, prospective studies have found higher rates of catheter-related deep vein thrombosis with femoral catheters, in the range of 7% to 25%.[333,334] In general, we believe femoral access should be used only if emergent access is required, the inexperience of the operator limits placement in the upper body, or there is a contraindication to placement in the upper body (no available sites, an extensive burn, or severe coagulopathy). If a short-term CVC must be placed in the femoral vein or artery, we believe it is important that the catheter insertion site be located at least 2 inches (5 cm) below the inguinal crease or an intertriginous area, which is heavily colonized with bowel organisms and yeasts; this also allows a more secure protective dressing to be affixed.

In contrast to short-term CVCs, observational studies of hemodialysis catheters have not been able to confirm a lower rate of infection with catheters inserted in the subclavian vein compared with those inserted in the internal jugular vein,[339] although there is still excess risk associated with femoral vein placement.[340] More importantly, prospective studies of catheters used for hemodialysis have demonstrated a significant risk of great vein thrombosis and stenosis in catheters inserted into the subclavian vein that approaches 40% to 50% compared with rates of 0% to 10% with catheters inserted into the internal jugular vein.[341,342] On the basis of these data, internal jugular vein insertion is preferable to subclavian vein insertion for central access for hemodialysis.

2. Barrier precautions. Hand hygiene with an antiseptic-containing preparation, either conventional handwashing with chlorhexidine (2%–4%) or with a waterless alcohol rub or gel,[183] must always precede the insertion of an IVD and should also precede subsequent handling of the device or its administration set.[137] A new pair of disposable, nonsterile gloves, using a "no-touch" technique, is adequate for the placement of peripheral IV catheters in most patients; however, sterile gloves should be used during insertion in high-risk patients such as those with granulocytopenia. Sterile gloves are strongly recommended for placement of all other types of IVDs that are associated with a 1% or higher risk of associated bacteremia, specifically arterial catheters and all types of centrally placed devices including PICCs.[137]

Studies have shown that the use of maximal barriers, including a long-sleeved, sterile surgical gown, mask, cap and large sterile drape, and sterile gloves, significantly reduces the risk of CVC-related BSI (0.08 BSIs with maximal barriers vs. 0.5 BSIs per 1000 IVD days without maximal barriers, P = 0.02).[343] The use of maximal barriers has further been shown to be highly cost-effective.[343] Considering that of all IVDs, CVCs are most likely to produce nosocomial BSI, a strong case can be made for mandating maximal barrier precautions during the insertion



• **Fig. 47.6** Microbial profile of intravascular device–related bloodstream infection based on an analysis of 159 published prospective studies. (Modified from Maki DG, Kluger DM, Crnich CJ. The microbiology of intravascular device-related (IVDR) infection in adults: an analysis of 159 prospective studies and implications for prevention and treatment. In: *Abstracts and Proceedings from the 40th Annual Meeting of the Infectious Disease Society of America*. Chicago: Infectious Disease Society of America; 2002.)

TABLE 47.10 Summary of CDC/HICPAC Guideline Recommendations for Prevention of Intravascular Device–Related Bloodstream Infection in Adults

Recommendation	Strength[a]
General Measures	
• Educate health care personnel regarding indications for IVD use, proper procedures for IVD insertion/maintenance, and infection control measures. Periodically assess knowledge of and adherence to guidelines. Designate only trained personnel who demonstrate competence in IVD insertion/maintenance.	IA
• Ensure adequate nursing staffing levels in ICUs.	IB
• Use "bundles," whereby multifaceted strategies are bundled together to improve compliance with evidence-based recommended practices.	IB
Hand Hygiene, Aseptic Technique, and Maximal Sterile Barrier Precautions	
• Perform hand hygiene and maintain aseptic technique, before and after inserting, replacing, accessing, repairing, or dressing an IVD.	IB
• Use maximal sterile barrier precautions during insertion of CVCs, PICCs, or guidewire exchange: mask, cap, sterile gown, sterile gloves, sterile full-body drape.	IB
• Use minimum of cap, mask, sterile gloves, and small sterile fenestrated drape during insertion of peripheral arterial catheters.	IB
• Use maximal sterile barrier precautions during insertion of axillary or femoral artery catheters.	II
• Don new sterile gloves before handling new catheter during guidewire exchange.	II
• Use either clean or sterile gloves when changing the dressing on IVDs.	IC
IVD Insertion	
• Use subclavian site for nontunneled CVC placement, rather than jugular or femoral (IB) (except avoid subclavian site for patients undergoing dialysis or with advanced kidney disease—IA).	See text
• Avoid femoral vein for central venous access.	IA
• Weigh risks against benefits of placing CVC at recommended site to reduce infectious complications versus risk for mechanical complications (e.g., pneumothorax).	IA
• Use radial, brachial, or dorsalis pedis sites for peripheral arterial catheters, rather than femoral or axillary.	IB
• Prepare clean skin with >0.5% chlorhexidine preparation with alcohol before insertion of CVCs and peripheral arterial catheters and during dressing changes; can use tincture of iodine, an iodophor, or 70% alcohol in patients with a contraindication to use of chlorhexidine.	IA
• Use sutureless securement device to reduce risk of infection.	II
• Use sterile sleeve to protect pulmonary artery catheters during insertion.	IB
• Use either sterile gauze or sterile, transparent, semipermeable dressing to cover catheter site.	IA
IVD Maintenance	
• Promptly remove any IVD that is no longer essential.	IA
• Replace gauze dressings on short-term CVC sites every 2 days.	II
• Replace transparent dressings on short-term CVC sites at least every 7 days.	IB
• Replace dressing if it becomes damp, loosened, or visibly soiled.	IB
• Monitor IVD insertion site when changing dressing or by palpation through intact dressing on regular basis; dressing should be removed to examine site if local or systemic signs of infection are present.	IB
• Do not use systemic antibiotic prophylaxis; and do not use topical antibiotic ointments on IVD exit sites, except for dialysis catheters.	IB

Continued

TABLE 47.10 Summary of CDC/HICPAC Guideline Recommendations for Prevention of Intravascular Device–Related Bloodstream Infection in Adults—cont'd

Recommendation	Strength[a]
• Use a 2% chlorhexidine wash for daily skin cleansing.	II
• Replace administration sets in continuous use no more frequently than at 96-h intervals but at least every 7 days (IA). When blood, blood products, or fat emulsions are given, replace tubing within 24 h of initiating the infusion (IB). With propofol infusions, replace tubing every 6 or 12 h, when the vial is changed (IA).	See text
• Change needleless IV catheter system components at least as frequently as the administration set, but no more frequently than every 72 h (for needleless connectors, do not change more frequently than every 72 h or according to manufacturers' recommendations).	II
• Minimize contamination of needleless IV catheter systems by scrubbing the access port with an appropriate antiseptic (chlorhexidine, povidone-iodine, an iodophor, or 70% alcohol) and accessing the port only with sterile devices.	IA
• Replace peripheral IV lines every 72–96 h.	IB
• Do not routinely replace CVCs, PICCs, hemodialysis catheters, pulmonary artery catheters (IB), or arterial catheters (II) solely for prevention of infection.	See text
• Do not remove CVCs or PICCs solely because of fever unless IVD infection is suspected, but replace catheter if purulence is seen at the exit site, especially if the patient is hemodynamically unstable and IVD-related BSI is suspected.	II
• Do not use guidewire exchanges to replace a non-tunneled catheter suspected of infection; a new device should be placed in a new location.	IB
• When adherence to aseptic technique cannot be ensured (e.g., with insertion of catheter during a medical emergency), replace the catheter as soon as possible (i.e., within 48 h).	IB
Technology	
• Use chlorhexidine–silver sulfadiazine or minocycline-rifampin–impregnated CVC in patients whose catheter is expected to remain in place >5 days, if the rate of IVD-related BSI is not decreasing after successful implementation of a comprehensive strategy to reduce rates of such infections.	IA
• Use chlorhexidine-impregnated sponge dressing for temporary short-term catheters if the IVD-related BSI rate is not decreasing despite adherence to basic prevention measures.	IB
• Use prophylactic antibiotic lock solution *only* in patients with long-term IVDs who have continued to experience IVD-related BSIs despite consistent application of infection control practices.	II

[a]From the CDC/HICPAC system of weighting recommendations based on scientific evidence: *IA,* strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies. *IB,* Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale; or an accepted practice (e.g., aseptic technique) supported by limited evidence. *IC,* Required by state or federal regulations, rules, or standards. *II,* Suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale.

CDC, Centers for Disease Control and Prevention; *CVC,* central venous catheter; *HICPAC,* HICPAC, Healthcare Infection Control Practices Advisory Committee; *ICU,* intensive care unit; IV, intravenous; *IVD,* intravascular device; *PICC,* peripherally inserted central venous catheter.

Data from O'Grady NP, Alexander M, Burns LA, et al, Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis.* 2011;52:e162–e193.

of all central IVDs.[137] They are not necessary, however, for arterial catheters used for hemodynamic monitoring, during which sterile gloves and a sterile fenestrated drape will suffice, because using maximal sterile barrier precautions does not appear to reduce the risk of arterial catheter-related BSI.[344] However, guidelines for the prevention of IVD-related BSI[137] recommend that in addition to a using a minimum of a cap, mask, sterile gloves, and a small sterile fenestrated drape during the insertion of all peripheral arterial catheters, maximal sterile barrier precautions should be used for axillary and femoral artery catheter insertion (see Table 47.10), although the evidence to support this recommendation is not strong.[345]

3. IV teams. Good technique is also essential. Studies have shown that the use of special IV therapy teams, consisting of trained nurses or technicians who can ensure a consistent and high level of aseptic technique during catheter insertion and in follow-up care of the catheter, has been associated with substantially lower rates of catheter-related BSI and is cost-effective.[346,347] But even if an institution does not have an IV team, it can greatly reduce its rate of IVD-related BSI by formal education of nurses and physicians and stringent adherence to IVD care protocols.[348,349]
4. Cutaneous antisepsis. Given the evidence for the importance of cutaneous microorganisms in the pathogenesis of short-term IVD-related infections, measures to reduce colonization of the insertion site would seem of the highest priority, particularly the choice of chemical antiseptics for disinfection of the site. Nine randomized, prospective trials comparing a chlorhexidine-containing antiseptic to either povidone-iodine or alcohol for preparation of the skin before insertion of a short-term IVD have been reported.[219–221,350] In the largest study to date, a randomized trial in 1050 CVCs and arterial catheters placed in a university hospital ICU, cutaneous antisepsis with 1% tincture of chlorhexidine showed a highly significant reduction in IVD-related BSIs compared with an iodophor (RR 0.35, $P < 0.01$).[350] A meta-analysis that examined results from eight of the nine aforementioned studies found that use of chlorhexidine was associated with a nearly 50% reduction in the risk of

IVD-related infections compared with povidone-iodine (RR 0.49, 95% CI 0.28–0.88).[219]

Insertion Site Care and IVD Maintenance

1. IVD dressings. IVDs can be dressed with sterile gauze and tape or with a sterile transparent, semipermeable, polyurethane film dressing. The available data suggest that the two types of dressings are equivalent in terms of their impact on IVD-related BSI with peripheral IVs and short-term CVCs.[351–353] In contrast, results from studies of arterial catheters have found that polyurethane dressings greatly increase the risk of IVD-related BSI.[351,354] As a result, polyurethane dressings should probably not be used on arterial catheters until future studies confirm their safety.
2. Topical antimicrobial ointments. In theory, application of a topical antimicrobial agent to the catheter insertion site should confer some protection against microbial invasion. Clinical trials of a topical combination antibacterial ointment containing polymyxin, neomycin, and bacitracin with peripheral IVs have shown marginal benefit,[355] but the use of polyantibiotic ointments has been associated with a fivefold increased frequency of Candida infection, limiting their utility.[355,356] One double-blind, placebo-controlled, randomized clinical trial in hemodialysis patients with permanent tunneled cuffed dialysis catheters showed that the use of topical bacitracin, gramicidin, and polymyxin B at the catheter exit site, compared with topical placebo, was associated with a reduction in catheter-related bacteremia (0.63 vs. 2.48 per 1000 IVD days, $P = 0.0004$) and mortality rate (3 vs. 13 deaths, $P = 0.004$), without an increase in Candida infection.[357]

   The topical antibacterial mupirocin, which is active primarily against gram-positive organisms, was shown in one study to significantly reduce colonization of internal jugular catheters without increasing colonization by Candida spp.,[358] and a study by Sesso and colleagues[359] showed significant reductions in hemodialysis catheter colonization (3.17 vs. 14.27 per 1000 IVD days, $P \leq 0.001$) and S. aureus IVD-related BSIs (0.71 vs. 8.92 BSIs per 1000 IVD days, $P \leq 0.001$).[359] Unfortunately, resistance of S. aureus[360] and coagulase-negative staphylococci[361] rapidly emerges during wide-scale mupirocin use,[362] which contravenes its use as a topical agent for the prevention of IVD-related BSI at this time.[137]

   Three prospective studies of topical povidone-iodine ointment applied to CVC sites have failed to show a statistical benefit to its use,[355,363,364] but a single comparative trial in subclavian hemodialysis catheters showed that the use of topical povidone-iodine ointment was associated with a fourfold reduction in the incidence of IVD-related S. aureus BSI.[365]

   Based on these data, if a topical agent is to be used with hemodialysis catheters, either an iodophor or topical bacitracin, gramicidin, and polymyxin B (not currently available in the United States) may be most desirable.[137]
3. Replacement of the device. Studies have shown that peripheral IVs may be safely left in place for up to 96 hours if the patient and the insertion site are monitored closely.[366] Studies have suggested that the duration of peripheral catheterization may be prolonged even further,[367] but viewing reports of nosocomial S. aureus bacteremias linked to prolonged peripheral venous catheterization,[368] more studies are required before this can become considered acceptable routinely.

   Scheduled replacement of short-term, noncuffed, nontunneled CVCs has long been practiced in many centers; however, some studies have called this practice into question.[369] Moreover, a meta-analysis found no benefit to routine replacement of short-term CVCs.[370] On the basis of these data, there appears to be no indication for scheduled replacement of short-term CVCs that are functioning well and show no clinical signs of infection.
4. Guidewire exchanges of CVCs. The management of CVCs that must be replaced, either because of mechanical malfunction or suspected infection, deserves special attention. Replacement of CVCs by guidewire exchange is associated with a reduced risk of mechanical complications[369,370]; however, it is also associated with an increased risk of the newly placed CVC becoming infected and causing CVC-related BSI.[369] As a result, if circumstances necessitate guidewire exchange for placement of a new catheter (e.g., the patient has limited sites for access, is morbidly obese, or is at high risk of mechanical complications because of underlying coagulopathy), the same strict aseptic technique, which includes full barrier precautions, must be used. However, the tip or intracutaneous segment(s) of the removed CVC should routinely be sent for culture to determine whether the insertion tract is colonized. If it is, the newly inserted CVC should be promptly removed and a new CVC placed percutaneously in a new site. If the tract is not colonized, the newly exchanged CVC can remain in the old insertion site.

   Although small studies have found some utility of guidewire exchange in the management of CVCs suspected of being infected,[371,372] we believe that, in the absence of randomized studies demonstrating its safety, guidewire exchange generally should not be performed if there is suspicion of IVD-related BSI, especially if there are signs of local infection such as purulence or erythema at the insertion site or signs of systemic sepsis without a source. In these cases the old catheter should be removed and cultured, and a new catheter should be inserted in a new site.
5. Replacing the delivery system. Whereas most infusion-related BSIs are caused by infection of the device used for vascular access, infusate can occasionally become contaminated and cause endemic BSIs.[325,373] If an infusion runs continuously for an extended period, the cumulative risk of contamination increases, and there is further risk that contaminants can grow to concentrations that could produce BSI in the recipient of the fluid. For more than 25 years, most U.S. hospitals have routinely replaced the entire delivery system of patients' IV infusions at 24- or 48-hour intervals[374] to reduce the risk of BSI from extrinsically contaminated fluid. Prospective studies indicate that IV delivery systems need not be replaced more frequently than every 72 to 96 hours, including infusions used for total parenteral nutrition or any infusions in ICU patients[366,375]; extending the duration of use can permit cost savings to hospitals.[375]

   Four clinical settings might be regarded as exceptions to using 72 hours as an interval for routine set change[375]: (1) administration of blood products, (2) administration of lipid emulsion, (3) arterial pressure monitoring, and (4) suspicion of an epidemic of infusion-related BSI. In these circumstances, it may be most prudent for administration sets to be changed routinely at 24- or 48-hour intervals or in the case of suspected infusion-related BSI, immediately.

   Arterial infusions used for hemodynamic monitoring appear to be more vulnerable to becoming contaminated during use and producing endemic[373] or epidemic septicemia,[103] caused by gram-negative bacilli. If the infusion for hemodynamic monitoring is set up so that the fluid flows continuously through

the system, thus eliminating a blind stagnant column of fluid, extrinsic contamination appears to be greatly reduced and may even eliminate the need to replace the administration set, transducer assembly, and other components of the system at frequent intervals.[376,377] If disposable transducers are used, there appears to be no need to replace the transducer assembly and other components of the delivery system more frequently than every 4 days,[376] and it may be safe to replace them even less frequently.[377]

6. Anticoagulation. Thrombus formation on an IVD is associated with an increased risk of infection.[378,379] Two prospective studies have been performed to examine the efficacy of warfarin anticoagulation for reducing rates of IVD-associated thrombosis with long-term IVDs.[380,381] Both studies found that use of warfarin in a dose of 1 mg/day was associated with significantly reduced rates of thrombosis with long-term IVDs, although no data were provided on rates of IVD-related BSI.

   The use of prophylactic heparin for reducing rates of IVD-related thrombosis and infection has been evaluated in a meta-analysis.[382] Examining a variety of different administration techniques in 14 randomized controlled studies, Randolph and colleagues[382] concluded that systemic heparinization significantly reduced the risk of IVD-associated thrombosis (RR 0.43, CI 0.23–0.78) and device colonization (RR 0.18, CI 0.06–0.6) but failed to show a reduction in IVD-related BSIs. Heparin-bonded pulmonary artery catheters may be less prone to IVD-related BSI than nonheparinized catheters.[325,383,384]

   On the basis of these studies, low-level anticoagulation with warfarin is warranted for long-term IVDs as long as there is no contraindication (bleeding diathesis, brain tumor, or predilection to falls) and the international normalized ratio is maintained below 1.6.[380] For short-term IVDs, the use of low-dose subcutaneous heparin is more appropriate; it is commonly given to patients with CVCs or arterial lines as part of ICU thromboembolism prophylaxis.

Novel Technology

Despite compliance with recommended guidelines, many centers continue to have high rates of IVD-related BSI. Novel technology holds much promise (Box 47.3). Innovative technologies designed to reduce the risk of IVD-related BSI have proved not only to be effective but also to reduce health care costs, both with short-term and long-term IVDs.[323,385]

1. Novel securement devices. In a randomized trial of a novel sutureless device for securing noncuffed vascular catheters (StatLock, Venetec International, San Diego, CA), premature loss of pediatric PICCs caused by accidental extrusion and PICC-associated thrombosis were significantly reduced,[386] and in two additional trials the incidence of catheter-related BSI was significantly reduced with the use of the novel securement device, both in adults and children with PICCs.[386,387]

   The promise of this device for reducing infection may derive from elimination of a festering skin suture wound contiguous to the newly inserted catheter and minimizing to-and-fro movement of the catheter, which may promote invasion of the tract by cutaneous microorganisms through capillary action.[388]

2. Novel dressings. Studies of polyurethane dressings, which contain antiseptics such as povidone-iodine or ionized silver, have been disappointing. However, on the basis of demonstrated superiority of chlorhexidine for cutaneous disinfection of access sites, a novel chlorhexidine-impregnated sponge dressing has been developed (BioPatch, Johnson and Johnson Medical, Inc., Brunswick, NJ). It maintains a high concentration of the antiseptic on the insertion site under the dressing. The largest study to date found that use of the chlorhexidine-impregnated sponge dressing was associated with a 60% reduction in catheter-related BSI (RR 0.37, P = 0.01).[389] Although there were no adverse side effects associated with the use of this dressing in this trial in adults, a pediatric trial found that 15% of low-birth-weight neonates developed local dermatotoxicity.[390]

3. Anti-infective impregnated catheters. IVDs directly coated or impregnated with antimicrobials or antiseptics have been intensively studied over the past several decades. Eighteen randomized trials evaluating the efficacy of chlorhexidine-silver-sulfadiazine–impregnated or minocycline-rifampin–impregnated CVCs have been published in full article or abstract form since 1994.[291,292,313,391,392]

   Of the 16 published studies that examined the effect of antimicrobial-impregnated CVCs on rates of CVC-related BSI, 12 found either a statistically significant reduction or a strong trend toward a reduction in rates of CVC-related BSI.[391,392]

• BOX 47.3 Novel Technology for Prevention of Intravascular Device–Related Bloodstream Infection That Has Been Examined in Randomized Clinical Trials

- Sutureless securement devices
  - Topical antimicrobials/antiseptics
  - Topical anti-infective creams or ointments
  - Polymyxin-neomycin-bacitracin polyantibiotic ointment
  - Bacitracin, gramicidin, and polymyxin B ointment
  - Povidone-iodine ointment
  - Mupirocin ointment
- Dressings
  - Transparent, polyurethane film dressings
  - Hyperpermeable polyurethane dressings
  - Hydrocolloid dressings
  - Chlorhexidine-impregnated sponge dressings
- Innovative IVD design
  - Cuffed and tunneled central venous catheters
  - Subcutaneous central venous ports
  - Attachable silver-impregnated cuffs
- Anti-infective-coated catheters
  - Benzalkonium chloride–impregnated catheters
  - Chlorhexidine–silver sulfadiazine–coated catheters
  - Cefazolin-coated catheters
  - Minocycline-rifampin–coated catheters
  - Silver-impregnated catheters
- Anti-infective catheter hubs
  - Iodinated chamber
  - External povidone-iodine–saturated sponge cap
- Anti-infective lock solutions for long-term intravascular devices
  - Gentamicin
  - Vancomycin
  - Vancomycin-ciprofloxacin
  - Trisodium citrate–gentamicin
  - Minocycline–ethylenediaminetetraacetic acid
  - Ethanol
  - Taurolidine
  - Scheduled (prophylactic) thrombolysis with urokinase

Modified from Crnich CJ, Maki DG: The promise of novel technology for the prevention of intravascular device-related bloodstream infection. I. Pathogenesis and short-term devices. Clin Infect Dis. *2002;34:1232–1242.*

Aggregate analysis of the 15 studies that compared antimicrobial-impregnated CVCs with nonimpregnated CVCs,[391,392] encompassing a total of 4250 CVCs, shows that antimicrobial-impregnated CVCs are associated with a 40% reduction in CVC-related BSI (61 BSIs/2129 devices vs. 101 BSIs/2118 devices, OR 0.60, 95% CI 0.44–0.82, P = 0.001), a result remarkably similar to the findings of three published meta-analyses.[323,393,394]

Finally, two rigorous and sophisticated economic analyses have found that antimicrobial-impregnated CVCs are cost-effective.[395,396] Veenstra and colleagues showed that antimicrobial-impregnated CVCs remained cost-effective even if the cost of a CVC-related BSI was as low as $687 per case; cost savings were $196 per antimicrobial-impregnated CVC when a more realistic cost of a CVC-related BSI of $9738 was used in the analysis.[395] Shorr and colleagues[396] showed that use of antimicrobial-impregnated CVCs was associated with a cost savings of $9600 per CVC-related BSI prevented and that $165 to $280 would be saved for every patient who received an antimicrobial-impregnated CVC.

On the basis of this large body of data, two national advisory panels have recommended the use of antimicrobial-impregnated CVCs in clinical settings where, despite rigorous application of other preventive interventions, rates of IVD-related BSI remain unacceptably high (i.e., ≥3.3 BSIs per 1000 IVD days).[137,397]

4. Antimicrobial lock solutions. Given the importance of hub contamination and intraluminal colonization in the genesis of IVD-related BSI with long-term IVDs, intraluminal instillation of an antibiotic or antiseptic solution has the potential to reduce the risk of BSI associated with these devices. Six randomized, prospective trials have examined a vancomycin-containing antibiotic lock solution for the prevention of IVD-related BSI, the largest of which found that use of a vancomycin or vancomycin/ciprofloxacin lock solution reduced the risk of IVD-related BSI nearly 80% (P = 0.005), with no evidence that the use of the lock solution promoted colonization or infection by vancomycin-resistant bacteria or fungi.[398,399] Yet concern about the emergence of resistance with prophylactic antibiotic-containing lock solutions has limited their wider acceptance to date. However, the use of prophylactic antibiotic lock solution is considered acceptable in the 2011 HICPAC Guideline if a patient with an essential long-term IVD has continued to experience recurrent IVD-related BSIs despite consistent application of infection control practices.[137]

   Various other prophylactic lock solutions have been studied as a means of preventing IVD-related BSI including trisodium citrate/gentamicin,[400] minocycline/ethylenediaminetetraacetic acid,[401] ethanol,[402] and taurolidine-containing solutions.[403] Concerns about increased IVD complication rates[403] and drug-related toxicity[400] associated with the use of certain types of lock solutions, combined with the limited number of patients who have been studied while receiving these agents, preclude their routine use at this time.
5. Catheter hubs. A novel catheter hub that contains a chamber filled with iodinated alcohol has been shown to be effective in preventing colonization of IVDs in an animal model.[404] Use of this same hub model in some clinical studies has demonstrated significantly lower rates of IVD colonization compared with IVDs with control hubs.[405,406] One clinical trial has also demonstrated reduced rates of IVD-related BSIs with use of this hub (4% vs. 16%, P < 0.01). A subsequent study also showed a reduction in hub-related IVD-related BSIs (1.7% vs. 7%, P < 0.049), but overall rates of IVD-related BSIs in both groups were similar.[406] Another study was unable to find any benefit with regard to IVD colonization or IVD-related BSI with use of the novel hub.[407] This device is not yet available in the United States and until further studies more conclusively demonstrate its benefit, its use cannot be recommended at this time.

Ventilator-Associated Pneumonia

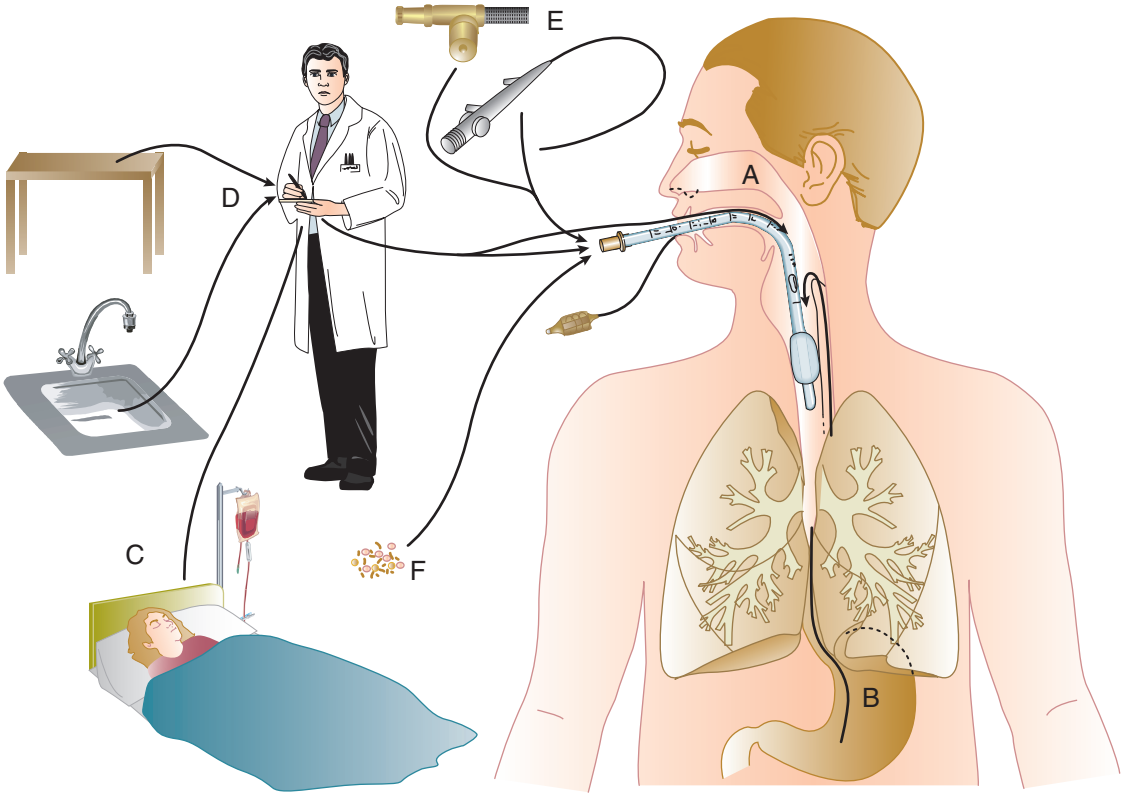
Incidence and Impact

Hospital-acquired pneumonia (HAP) is defined as pneumonia that develops more than 48 hours after hospitalization.[408,409] VAP is a subset of HAP and is defined as pneumonia that occurs more than 48 to 72 hours after initiating mechanical ventilation.[408,409] Nearly 300,000 episodes of HAP occur in U.S. hospitals each year.[410] More than 90% of HAPs occur in patients undergoing mechanical ventilation, and VAP develops in 10% to 20% of mechanically ventilated patients.[411] Incidence rates of VAP are highest in trauma, burn, neurosurgical, neurologic, and surgical ICUs (see Table 47.1).[25] VAP increases length of hospitalization by 6.1 days and health care costs by $10,019 when compared with matched control subjects in whom VAP did not develop.[411] More importantly, VAP is associated with more nosocomial deaths than is infection at any other site[412]—at least 50,000 deaths in U.S. centers annually—and increases hospital mortality rate at least twofold in affected individuals.[411]

Pathogenesis

In the normal nonsmoking host, multiple host defense mechanisms contribute to protection against pneumonia.[413] The respiratory tract above the vocal cords is normally heavily colonized by bacteria, but unless the person has chronic bronchitis or has had respiratory tract instrumentation, the lower respiratory tract is normally sterile; although healthy adults aspirate frequently during sleep, the lower airways and pulmonary parenchyma of healthy, nonsmoking persons without lung disease are remarkably free of microbial colonization.[414] The major defense mechanisms include anatomic airway barriers, the cough reflex, mucus,[415] and mucociliary clearance.[416] Below the terminal bronchioles, the cellular and humoral immune systems are essential components of host defense.[417] Alveolar macrophages and leukocytes remove particulate matter and potential pathogens, produce cytokines that activate the systemic cellular immune response, and act as antigen-presenting cells to the humoral arm of immunity.[418] Immunoglobulins and complement opsonize bacteria and bacterial products within the respiratory tract, assisting phagocytosis.

In the mechanically ventilated patient, numerous factors conspire to compromise host defenses; critical illness, comorbid conditions, and malnutrition impair the immune system.[419,420] Endotracheal intubation thwarts the cough reflex; compromises mucociliary clearance; injures the tracheal epithelial surface; and provides a direct conduit for bacteria from the mouth, hypopharynx, and stomach to gain direct access to the lower respiratory tract.[421] Moreover, the cuff of the endotracheal tube allows pooling of oropharyngeal secretions in the subglottic region, forming an ideal medium for microbial growth, which periodically leaks around the cuff into the trachea. It would probably be more accurate pathogenically to rename VAP as "endotracheal intubation–related pneumonia." This combination of impaired host defenses and continuous exposure of the lower respiratory tract to large numbers of potential pathogens through the endotracheal tube



• **Fig, 47.7** Routes of colonization/infection in mechanically ventilated patients. Colonization of the aerodigestive tract may occur endogenously (A and B) or exogenously (C through F). Exogenous colonization may result in primary colonization of the oropharynx or may be the result of direct inoculation into the lower respiratory tract during manipulations of respiratory equipment (D), during use of respiratory devices (E), or from contaminated aerosols (F). (From Crnich CJ, Safdar NS, Maki DG. The role of the intensive care environment in the pathogenesis and prevention of ventilator-associated pneumonia. *Respir Care.* 2005;50:813–836.)

puts the mechanically ventilated patient at great jeopardy of developing VAP.

For microorganisms to cause VAP, they must first gain access to the normally sterile lower respiratory tract, where they can adhere to the mucosa and produce sustained infection. Microorganisms gain access by one of four mechanisms (Fig. 47.7): (1) aspiration of microbe-laden secretions, either from the oropharynx directly or, secondarily, by reflux from the stomach into the oropharynx, then into the lower respiratory tract[422–424]; (2) inhalation of contaminated air or medical aerosols[425]; (3) direct extension of a contiguous infection such as a pleural space infection[426]; or (4) hematogenous carriage of microorganisms to the lung from remote sites of local infection such as an IVD-related BSI.[427]

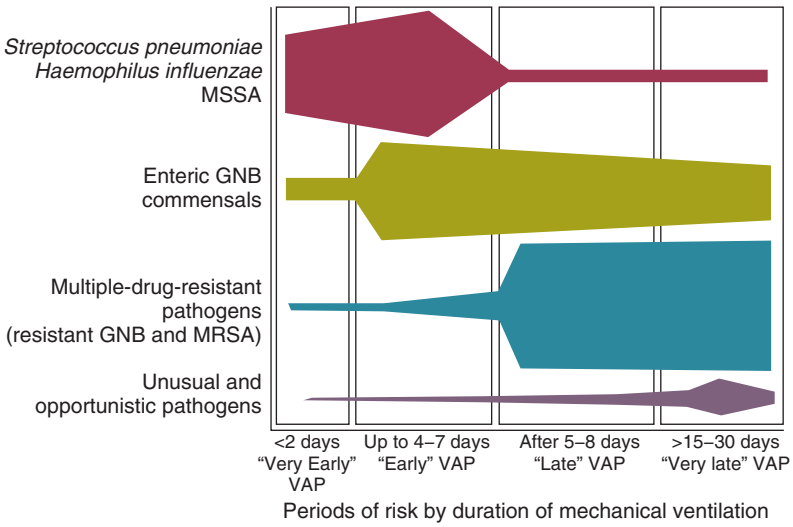
Although numerous epidemics of VAP have been caused by contaminated aerosols or medical respiratory devices,[101,102,107] the preponderance of evidence suggests that most endemic VAPs derive from aspiration of endogenous or hospital-acquired oropharyngeal organisms[42,428]:

- The oropharynx of critically ill patients is rapidly colonized with the pathogens that cause VAP, especially aerobic gram-negative organisms and S. aureus.[419]
- Studies in which multiple anatomic sites are cultured simultaneously over time have shown that the pathogenic microorganisms implicated in VAP are usually first recovered from the oropharynx and later from the tracheobronchial tree and stomach.[422–424,429] Moreover, heavy oropharyngeal colonization is a powerful independent predictor of subsequent tracheobronchial colonization and VAP.[424]
- Reducing oropharyngeal colonization with topical antimicrobials and antiseptics has been shown to significantly reduce the risk of VAP.[430–433]

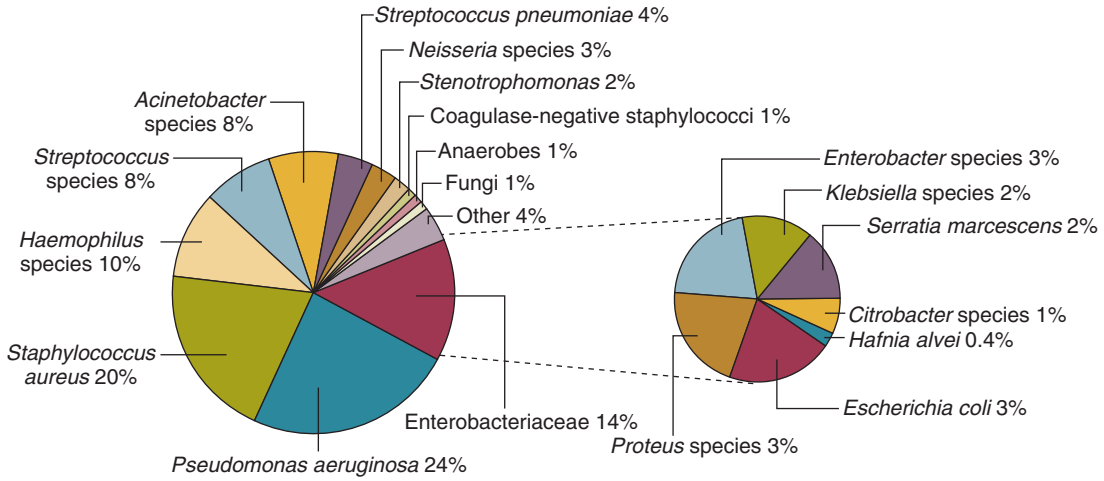
By this route, aspiration of oropharyngeal contents containing a large microbial inoculum overwhelms host defenses already compromised by critical illness and the presence of an endotracheal tube, readily leading to the development of VAP.

Microbiology

Pathogens causing VAP may be part of the host's endogenous microbiome at the time of hospitalization or may be acquired exogenously after admission to the health care institution from the hands, apparel, or equipment of HCWs; hospital environment; and use of invasive devices (Fig. 47.8). The normal flora of the oropharynx in the nonintubated patient without critical illness is composed predominantly of viridans streptococci, Haemophilus species, and anaerobes. Salivary flow and proteins (immunoglobulin, fibronectin) are the major host factors maintaining the normal microbiome of the mouth (and dental plaque). Aerobic gram-negative bacilli are rarely recovered from the oral secretions of healthy patients.[434] During critical illness, especially in ICU patients, the oral microbiome shifts dramatically to a predominance of aerobic gram-negative bacilli and S. aureus.[419] Bacterial adherence to the orotracheal mucosa of the mechanically ventilated patient



• **Fig. 47.8** Microbial causes of ventilator-associated pneumonia based on increasing length of mechanical ventilation. The relative importance of each microbial category is indicated by the thickness of the bars as they progress through each stage from left to right. *GNB,* Gram-negative bacilli; *MRSA,* methicillin-resistant *S. aureus*; *MSSA,* methicillin-susceptible *S. aureus*; *VAP,* ventilator-associated pneumonia. (Data from Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165(7):867–903.)



• **Fig. 47.9** Microbial causes of ventilator-associated pneumonia. The relative proportions of microbial causes of ventilator-associated pneumonia from 1689 bronchoscopically confirmed cases involving 2490 individual isolates reported in 24 published studies. (From Park DR. The microbiology of ventilator-assisted pneumonia. *Respir Care.* 2005;50:742–765.)

is assisted by reduced mucosal IgA and increased protease production, exposed and denuded mucous membranes, elevated airway pH, increased numbers of airway receptors for bacteria because of acute illness, and antimicrobial use.

Early-onset VAP, which manifests within the first 4 days of hospitalization, is most often caused by community-acquired pathogens, such as S. pneumoniae and Haemophilus species (Fig. 47.8).[435] However, the microbial spectrum of VAP shifts to typical nosocomial pathogens with increasing lengths of mechanical ventilation and exposure to broad-spectrum antimicrobials (Fig. 47.9).[435] That the preponderance of episodes of VAP have a late onset is supported by the fact that the most common pathogens recovered from mechanically ventilated patients with pneumonia are P. aeruginosa, S. aureus, and the Enterobacteriaceae (see Fig. 47.9).[435,436] VAP is polymicrobial in up to 20% to 40% of cases. The role of anaerobic bacteria in VAP is not well defined.

Diagnosis

The CDC's National Healthcare Safety Network definition for VAP was revised in 2013 owing to the lack of objective and reliable criteria, and was replaced with the term ventilator-associated events,[17] which was intended to be used for surveillance purposes and not for the diagnosis and treatment of VAP.[409] Within ventilator associated events, a new more specific term, possible ventilator-associated pneumonia, was also introduced, based on the following criteria: increase in fraction of inspired oxygen or positive end-expiratory pressure; and fever or hypothermia or leukocytosis or leukopenia; and new antimicrobial agent started; and, positive respiratory culture or other criteria (see Box 47.1), but did not include radiographic criteria.[16,17] Clinical criteria for the diagnosis of HAP/VAP, which were initially developed empirically more than three decades ago,[437] and recommended by the 2005 and 2016 Infectious Disease Society

of America/American Thoracic Society HAP/VAP guidelines,[408,409] include (1) a new or worsening infiltrate on chest radiograph, and (2) signs of infection that suggest the infiltrate is of infectious origin—fever, leukocytosis or leukopenia, purulent sputum, and decline in oxygenation.[408,409] Positive qualitative cultures of endotracheal aspirates are used to support the clinical diagnosis of HAP/VAP. Unfortunately, even when used in combination, the specificity of clinical criteria is poor, with an overall diagnostic accuracy of approximately 60% in published studies.[438,439]

Many experts have advocated routine use of invasive procedures when VAP is suspected—bronchoalveolar lavage (BAL), cultures of protected specimen brush (PSB) samples obtained by bronchoscopy, or blind (mini)-BAL—on the grounds that these diagnostic techniques have comparable sensitivity, greater specificity, and superior accuracy compared with clinical criteria alone.[436,440–443] More rigorous clinical criteria such as the Clinical Pulmonary Infection Score have relatively poor sensitivity (65%) and specificity (64%) for the diagnosis of VAP.[409,444] Whether or not the use of quantitative cultures of endotracheal aspirates improves diagnostic accuracy without the need for invasive procedures is an unsettled issue.[445]

Although invasive procedures—BAL, PSB, and mini-BAL—are clearly more specific than clinical criteria, their impact on patient outcomes is much less clear.[409,446,447] Fagon and colleagues[446] found that patients with suspected VAP who were managed using an invasive diagnostic approach—bronchoscopic-guided PSB or BAL—had a significantly reduced 14-day mortality rate, reduced antibiotic days, and reduced 28-day mortality rate on multivariate analysis, compared with patients managed using a clinical diagnostic approach (hazard ratio [HR] 0.65, 95% CI 0.46–0.91, P = 0.01).[446] However, Heyland and colleagues[447] found in a large multicenter Canadian trial that the 28-day mortality rate and targeted antimicrobial use were identical among patients randomly assigned to an invasive versus a clinical diagnostic approach. This study has been criticized for its exclusion of subjects at high risk for infection with antimicrobial-resistant pathogens.[448] In the absence of definitive data demonstrating superior outcomes with invasively obtained specimens or quantitative cultures, the 2016 Infectious Disease Society of America/American Thoracic Society HAP/VAP guidelines recommended that noninvasive sampling with semiquantitative culture be used to diagnose HAP and VAP rather than invasive sampling with quantitative cultures or noninvasive sampling with quantitative cultures.[409] The guideline panel acknowledged that there was potential for invasive sampling with quantitative cultures to lead to less antibiotic exposure if growth below the defined thresholds was used as a trigger to discontinue antibiotics.[409]

Risk Factors

A number of independent risk factors have been shown to increase the likelihood of developing VAP (Table 47.11).[140,436] In general, these risk factors can be categorized as (1) factors that increase the likelihood or duration of mechanical ventilation, (2) factors that increase colonization of the oropharynx and gastric mucosa, (3) factors that increase the likelihood of aspiration, and (4) host factors that increase susceptibility to infection.

Prolonged mechanical ventilation, reintubation, or both are the most powerful predictors of developing VAP. Cunnion and colleagues[449] found that mechanical ventilation in excess of 24 hours was associated with a 12-fold increased risk of developing VAP, and Trouillet and associates found that ventilation longer than 7 days was associated with a sixfold increased risk.[450] Emergent reintubation also carries a high risk of aspiration and was associated with a sixfold increased risk of VAP in a retrospective study.[451]

TABLE 47.11 Independent Risk Factors for Ventilator-Associated Pneumonia in Multivariate Analysis of Data From Published Studies

Host Factors	Intervention Factors
Serum albumin, <2.2 g/dL	Histamine H_2-receptor blockers ± antacids
Age ≥60 years	Paralytic agents, continuous intravenous sedation
Acute respiratory distress syndrome	Receipt of >4 units of blood
Chronic obstructive pulmonary disease or other chronic pulmonary diseases	Intracranial pressure monitoring
Coma or impaired consciousness	Mechanical ventilation in excess of 48 hours
Burns, trauma	Positive end-expiratory pressure
Organ failure	Frequent ventilator circuit changes
Advanced severity of illness	Reintubation
Large-volume gastric aspiration	Nasogastric tube
Gastric colonization and high gastric pH	Supine head position
Upper respiratory tract colonization	Transport out of the intensive care unit
Sinusitis	Prior antibiotic therapy

Modified from Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165:867–903.

Poor dental hygiene increases the bacterial burden in the oropharynx and is an independent risk factor for nosocomial pneumonia.[452] Likewise, a high gastric pH (>5) is associated with greatly increased bacterial colonization of the gastric contents,[453] as well as an increased risk of VAP.[454] A number of studies have found that exposure to antacids or H_2-blockers is associated with an increased risk of VAP,[60] although this has not been a universal finding.[455]

Depressed levels of consciousness, nasogastric tubes, and endotracheal tubes are ubiquitous in the ICU and all increase a patient's risk of aspiration. That an altered level of cognition is associated with an increased risk of aspiration is supported by surveillance data showing increased rates of VAP in trauma and neurosurgical ICUs.[25] Joshi and colleagues[456] found that the use of a nasogastric tube was an independent predictor of VAP in a multivariate analysis (OR 6.5, 95% CI 2.1–19.8). Finally, as noted, endotracheal tubes allow pooling of hypopharyngeal secretions that can leak around the cuff directly into the trachea, and a supine position appears to increase the risk of aspiration around the cuff.[457]

Host factors also contribute to an increased risk of developing VAP (see Table 47.11). Conditions such as advanced age, increased severity of illness, and the postsurgical state are rarely modifiable. However, poor nutritional status,[423] oversedation,[458] transfusion therapy,[459] and exposure to broad-spectrum antimicrobials[450] are associated with an increased risk of VAP and are under the control of the clinician.

Treatment

Treatment of VAP is discussed in the Therapy section of Chapter 40.

Prevention

With an understanding of pathogenesis and epidemiology in hand, clinicians caring for mechanically ventilated patients can implement

preventive strategies that can materially reduce the risk of VAP (Table 47.12). Both the CDC HICPAC and Canadian Critical Care Trials Group offer evidence-based guidelines for the prevention of VAP.[140,460] Their recommendations are very similar. The Canadian guideline focuses exclusively on specific interventions for the prevention of VAP,[460] whereas the HICPAC guideline incorporates additional guidance for the prevention of nosocomial influenza, legionellosis, and invasive filamentous fungal infections in the hospital.[140] Recommendations from both guidelines can be divided into general, nonpharmacologic, and pharmacologic preventive measures (see Table 47.12).[461] The general measures used to reduce VAP, including education, infection control, hand hygiene, and reliable disinfection and sterilization of respiratory care equipment, are discussed elsewhere in this chapter.

Nonpharmacologic Preventive Measures

Avoiding prolonged intubation and reintubation—if avoiding intubation altogether is not feasible—offers the greatest promise for reducing an individual patient's risk of developing VAP.[451] The use of noninvasive ventilation to avoid endotracheal intubation has been shown to be successful in reducing rates of nosocomial pneumonia in a number of studies[462,463] and may abrogate the need for reintubation in selected patients who prematurely extubate themselves.[140] The implementation of .weaning protocols has also been shown to significantly reduce the duration of mechanical ventilation,[464,465] health care costs,[464,465] and institutional rates of VAP.[466,467] The effect of daily sedation interruption has shown conflicting results in meta-analyses.[468,469] Early tracheostomy—within 1 week of intubation—has been advocated as a method for reducing

TABLE 47.12 Recommendations for the Prevention of Ventilator-Associated Pneumonia

Preventive Measure	HICPAC Grade[a]	CCCTG Recommendation
General Measures		
• Educate all health care workers involved with the care of mechanically ventilated patients on the risks and methods of preventing ventilator-associated pneumonia.	IA	—
• Perform adequate hand hygiene between patient contacts.	IA	—
• Use gloves for handling respiratory secretions or objects contaminated with respiratory secretions.	IB	—
• Conduct surveillance for bacterial pneumonia in ICU patients using NNIS definitions. Include data on causative organisms and their antimicrobial susceptibility patterns. Express data as rates to assist intrahospital comparisons.	IB	—
• Do not routinely perform cultures of patients, equipment, or environment in the absence of an outbreak.	II	—
• Thoroughly clean all devices to be sterilized and disinfected.	IA	—
• Use steam sterilization or wet heat pasteurization for reprocessing of heat-stable semicritical devices and low-temperature sterilization for heat- or moisture-sensitive devices.	IA	—
• Use sterile water for rinsing reusable semicritical devices.	IB	—
• Change ventilator circuits only when they become soiled.	IA	Recommended
• Periodically drain and discard condensate from ventilator circuits.	IB	—
• Clean, disinfect, rinse with sterile water, and dry in-line nebulizers between treatments on the same patient.	IB	—
• When possible, use aerosolized medications in single-use vials.	IB	—
Nonpharmacologic Measures to Reduce Pneumonia		
• Oral (non-nasal) intubation	IB	Recommended
• Remove nasogastric and endotracheal tubes as soon as clinically feasible.	IB	—
• Avoid unnecessary reintubation.	II	—
• When feasible, use noninvasive ventilation to avoid the need for intubation or reintubation.	II	—
• Early tracheostomy	—	No recommendation
• Semirecumbent positioning of the patient	II	Recommended
• Implement a comprehensive oral hygiene program for mechanically ventilated patients.	II	—
• If feasible, use an endotracheal catheter that allows for continuous or frequent subglottic suctioning.	II	Consider
• Humidification with HME	NR	Recommended[b]
• Closed multiuse catheters for airway secretion suctioning	NR	Recommended
• Kinetic bed therapy	NR	Consider

TABLE 47.12 Recommendations for the Prevention of Ventilator-Associated Pneumonia—cont'd

Preventive Measure	HICPAC Grade[a]	CCCTG Recommendation
Pharmacologic Measures to Reduce Pneumonia		
• Immunize all patients at risk for pneumococcal infection.	IA	—
• Immunize all patients at risk for influenza.	IA	—
• Routine use of chlorhexidine oral rinse	NR	—
• Targeted use of chlorhexidine oral rinse in post–cardiac surgery patients	II	—
• Oral decontamination with topical antimicrobial agents	NR	—
• Preferential use of sucralfate for stress bleeding prophylaxis	NR	Not recommended
• Selective digestive decontamination	NR	Not recommended[c]
• Acidification of gastric feedings	NR	—
• Systemic antimicrobials to prevent development of pneumonia	NR	Not recommended[c]
• Cycling of antibiotic classes to reduce resistance in the ICU	NR	—

[a]From the CDC/HICPAC system of weighting recommendations based on scientific evidence: *IA,* strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiologic studies. *IB,* Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale. *IC,* required by state or federal regulations, rules, or standards. II, Suggested for implementation and supported by suggestive clinical or epidemiologic trials or a theoretic rationale. Unresolved issue, an unresolved issue for which evidence is insufficient or no consensus regarding efficacy exists. *NR,* No recommendation for or against at this time.

[b]Recommended in patients without hemoptysis or high minute ventilation. Exchanger should be replaced weekly.

[c]Topical or systemic antimicrobial agents alone are not recommended. Insufficient evidence on antibiotic resistance and cost-effectiveness exists to recommend combination topical and systemic therapy.

CCCTG, Canadian Critical Care Trials Group; *CDC,* Centers for Disease Control and Prevention; *HICPAC,* Healthcare Infection Control Practices Advisory Committee; *HME,* heat and moisture exchanger; *ICU,* intensive care unit; *NNIS,* National Nosocomial Infections Surveillance System.

Modified from Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep.* 2004;53(RR-3):1–36; and Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med.* 2004;141:305–313.

the risk of VAP in patients likely to require prolonged mechanical ventilation. However, randomized trials, admittedly of limited power, have not found significant benefit with this approach[470] and early tracheostomy is not currently recommended by most authorities.[140,460]

As noted earlier, supine positioning of the mechanically ventilated patient's head has been shown to increase the risk of gastroesophageal-pharyngeal aspiration.[457] A simple solution to this threat is to elevate the head of the patient's bed 35 to 45 degrees. Drakulovic and colleagues[471] found that patients whose torso and head were kept elevated at 45 degrees had much lower rates of microbiologically confirmed pneumonia compared with patients cared for in a 0-degree supine position (5% vs. 23%, P = 0.018).[471] In reality, maintaining elevation of the head in excess of 45 degrees on a consistent basis is actually quite difficult and uncommonly achieved in practice. A randomized study that sought to maintain head elevation above 45 degrees for 85% of the study period found that head elevation in the intervention arm averaged only 28.1 degrees.[472] Perhaps as a result of failure to successfully achieve adequate elevation, no reductions in the rate of VAP were seen.

Although data on the effect of comprehensive oral care on the risk of infection are limited,[473] maintaining adequate dental hygiene is considered an important component of VAP prevention.[140] Binkley and colleagues[474] found that although a majority of nurses caring for patients undergoing mechanical ventilation appreciated the importance of dental hygiene, the methods used to provide this varied considerably. Until more data are available on specific dental hygienic practices, it is recommended that mechanically ventilated patients have their teeth brushed daily, undergo oral cleansing every 2 to 4 hours, undergo routine suctioning to reduce accumulation of fluids in the oropharynx, and have a mouth moisturizer applied to their lips to prevent cracking.[475] The periodic instillation of a topical oral antiseptic solution is an additional promising intervention[475] and is discussed in "Pharmacologic Preventive Measures" later.

The use of a modified endotracheal tube with a separate ventral drainage tube for continuous or intermittent suctioning of subglottic secretions has been evaluated in a number of studies.[476,477] Subglottic suctioning reduced the rate of VAP significantly in all but one of these studies.[477] However, in the study by Kollef et al. the time to onset of VAP was delayed significantly (5.9 days vs. 2.9 days, P = 0.006),[477] and recent evidence-based guidelines have recommended the use of endotracheal tubes that allow for suctioning of subglottic secretions.[140,460] Nevertheless, the use of an endotracheal tube that allows for subglottic suctioning did not reduce the duration of mechanical ventilation or rate of ICU mortality in the studies done, which, coupled with the increased cost of the tube and propensity of the suction lumen to occlude, has limited wider adoption of this technology in practice.[478]

The evidence that heat and moisture exchangers (HMEs) are associated with a reduced risk of VAP is mixed. Only one of six published trials found a statistically significant reduction in VAP with use of HMEs (RR 0.41, 95% CI 0.20–0.86, P = 0.02).[479] However, pooling data from a recent systematic review[480] and a subsequently published randomized trial[481] shows that HMEs reduce the risk of VAP by 38% (RR 0.62, 95% CI 0.43–0.89, P = 0.012). The use of HMEs has been recommended by authors of a systematic review[482] and is currently recommended by the Canadian Critical

Care Trials Group.[460] However, HICPAC made no recommendation for the use of HMEs because five of six published trials failed to demonstrate a statistically significant reduction in the rate of VAP.[140] Heat exchange moisturizers become readily occluded in patients with airway hemorrhage and can increase airway resistance. As a result, they should not be used in patients with hemoptysis or those requiring high minute ventilation.[460] Finally, the membranes of HMEs can become colonized with bacteria and should be replaced weekly, according to current guidelines.[460]

The availability of in-line multiuse suction catheters abrogates the need to open and manipulate the endotracheal circuit, theoretically reducing the risk of exogenous contamination.[483] Despite their theoretical benefit, prospective studies have not consistently shown that in-line suction catheters are associated with a reduced risk of VAP.[484–486] Although in-line suction catheters do not appear to increase the risk of VAP, they are more time efficient for nursing personnel and respiratory therapists and are more cost-effective than open suction catheters.[460] Kollef and colleagues[487] found that rates of VAP were identical in patients random assigned to as-needed changes of their inline suction catheter versus those who had their catheter changed every 24 hours (14.7% vs. 14.8%). As a result, there is no compelling evidence that in-line suction catheters should be periodically changed, unless clinically indicated.

Pharmacologic Preventive Measures

Antacids and H_2-blockers have been used extensively in the ICU setting to prevent stress ulcer bleeding but have been associated with an increased risk of developing VAP because they lead to bacterial overgrowth of the gastric contents.[60] Sucralfate prevents stress ulcer bleeding without reducing gastric pH but is more difficult to administer and is less effective than acid-reducing agents.[455] The results of clinical trials examining these two competing strategies for preventing gastrointestinal hemorrhage in the ICU have been mixed, with earlier trials favoring the use of sucralfate.[60] However, additional published trials suggest only a small incremental increased risk of VAP with H_2-blockers,[455,488,489] and most experts feel that this risk is more than offset by their superior capacity to prevent stress ulcer bleeding.[140,460]

Selective digestive decontamination (SDD) is one of the most extensively studied preventive interventions in critical care medicine, yet the role for SDD continues to generate vigorous debate as to its overall benefit.[490,491] A more detailed discussion on the risks and benefits of this intervention is provided later in this chapter. Most U.S. experts believe that SDD has the potential to increase infection caused by multiresistant bacteria, particularly in settings with high rates of endemic antimicrobial resistance.[492,493] Until well-designed multicenter trials are done, proving that SDD does not adversely affect the ICU ecology in settings where multiresistant bacteria are common, it is likely that North American guidelines will continue to discourage its use.[140,460]

The use of parenteral antimicrobials as a single measure for prevention of VAP has not met with much success,[492] but selective antimicrobial decontamination of the oropharynx, without the use of enteral or systemic agents, reduced the risk of VAP nearly 70% (RR 0.33, 95% CI 0.16–0.67, P = 0.001) in one trial.[431] This study reemphasized the primary role of oropharyngeal colonization in the pathogenesis of VAP but engendered the same concerns as SDD over its potential for promoting antimicrobial resistance. However, it has facilitated the idea that topical decolonization of the oropharynx with nonantimicrobial agents might be able to materially reduce the risk of VAP without the potential for emergence of antimicrobial resistance. A meta-analysis of seven randomized trials that enrolled 914 mechanically ventilated patients found that topical chlorhexidine applied to the oropharynx reduced the risk of VAP by nearly 30% (RR 0.74, 95% CI 0.56–0.96, P = 0.02), although there was no significant impact on mortality.[433] The beneficial effects of chlorhexidine appear to be most pronounced in post––cardiac surgery patients,[494,495] prompting HICPAC to recommend its use in this subpopulation.[140]

Catheter-Associated Urinary Tract Infection

Incidence and Impact

Each year, urinary catheters are inserted in more than 5 million patients in acute-care hospitals and extended-care facilities.[496] Catheter-associated urinary tract infection (CAUTI) is one of the most common infections in ICUs, and incidence rates are highest in burn, neurologic, neurosurgical, and trauma ICUs, with intermediate risk in surgical and medical ICUs, and lowest risk in coronary care units (see Table 47.1).[25]

Nosocomial bacteriuria or candiduria develops in up to 25% of patients requiring a urinary catheter for more than 7 days, with a daily risk of 5%.[496] CAUTI is the second most common cause of nosocomial BSI[497]; some studies have also found increased mortality rates associated with CAUTI.[498] Although most CAUTIs are asymptomatic,[499] rarely extend hospitalization, and add only $500 to $1000 to the direct costs of acute-care hospitalization,[500] asymptomatic infections commonly precipitate unnecessary antimicrobial-drug therapy.[501] And CAUTIs comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens, the most important of which are multidrug-resistant Enterobacteriaceae other than E. coli such as Klebsiella, Enterobacter, Proteus, and Citrobacter; P. aeruginosa; enterococci and staphylococci; and Candida spp.[502]

Pathogenesis

Excluding rare hematogenously derived pyelonephritis, caused almost exclusively by S. aureus, most microorganisms causing endemic CAUTIs derive from the patient's own colonic and perineal microbiomes or from the hands of health care personnel and gain access to the patient's urinary tract during catheter insertion or manipulation of the collection system.[283] Organisms gain access in one of two ways. Extraluminal contamination may occur early, by direct inoculation when the catheter is inserted, or later, by organisms ascending from the perineum by capillary action in the thin mucous film between the external catheter surface and the urethral wall. Intraluminal contamination occurs by reflux of microorganisms gaining access to the catheter lumen from failure of closed drainage or contamination of urine in the collection bag. Recent studies suggest that CAUTIs most frequently stem from microorganisms gaining access to the bladder extraluminally,[503] but both routes are important.

Most infected urinary catheters are covered by a thick biofilm containing the infecting microorganisms embedded in a matrix of host proteins and microbial exoglycocalyx.[504] A biofilm forms on the intraluminal or extraluminal surface of the implanted catheter, or both, usually advancing in a retrograde fashion. The role of the biofilm in the pathogenesis of CAUTI has not been established. However, anti-infective–impregnated and silver-hydrogel catheters, which inhibit adherence of microorganisms to the catheter surface, significantly reduce the risk of CAUTI,[505] particularly infections caused by gram-positive organisms or yeasts, which are most likely to be acquired extraluminally from the periurethral flora. These data suggest that microbial adherence

to the catheter surface is important in the pathogenesis of many, but not all, CAUTIs. Infections in which the biofilm does not play a pathogenic role are probably caused by mass transport of intraluminal contaminants into the bladder by retrograde reflux of microbe-laden urine when a catheter or collection system is moved or manipulated.

Prevention

Several catheter-care practices are universally recommended to prevent or at least delay the onset of CAUTI[283]: most important are avoiding unnecessary catheterizations; considering use of a condom catheter in a male or a suprapubic catheter; having trained professionals insert catheters aseptically; removing the catheter as soon as no longer needed; maintaining uncompromising closed drainage; ensuring dependent drainage as much as possible; minimizing manipulations of the system; and separating catheterized patients geographically on the patient care unit.

As noted earlier, technologic innovations to prevent nosocomial infection are most likely to be effective if they are based on a clear understanding of the pathogenesis and epidemiology of the infection. Novel technologies must be designed to block CAUTI by either the extraluminal or intraluminal routes, or both. Medicated catheters, which reduce adherence of microorganisms to the catheter surface, may confer the greatest benefit for preventing CAUTI. Two catheters impregnated with anti-infective solutions have been studied in randomized trials, one impregnated with the urinary antiseptic nitrofurazone[506] and the other with a broad-spectrum antimicrobial drug combination, minocycline and rifampin.[507] Both catheters showed a modest reduction in bacterial CAUTIs; however, the studies were small, and the risk of selection of antimicrobial drug–resistant uropathogens was not satisfactorily resolved. Silver compounds have also been studied for coating urinary catheters. A meta-analysis of eight randomized trials comparing silver oxide or silver alloy catheters with standard nonimpregnated catheters found that silver alloy, but not silver oxide, catheters were associated with a reduced risk of CAUTI.[508] Recommendations for the prevention of CAUTI are summarized in Table 47.13.[138]

TABLE 47.13 CDC/HICPAC Guideline Recommendations for Prevention of Catheter-Associated Urinary Tract Infection

Recommendation	Strength[a]
Appropriate Urinary Catheter Use	

• Insert catheters only for appropriate indications:
  • Appropriate indications (based primarily on expert consensus) include acute urinary retention or bladder outlet obstruction; measurement of urinary output in critically ill patients; perioperative use for selected surgical procedures—remove as soon as possible; promoting healing of open sacral wounds in incontinent patients; prolonged immobilization from multiple traumatic injuries; and improved comfort for end-of-life care.
  • Inappropriate indications (based primarily on expert consensus) include substitute for nursing care of the patient with incontinence; obtaining urine for diagnostic tests when patient can void; and prolonged postoperative use without appropriate indications.
	IB

• Promptly remove catheter when no longer needed.	• IB
• Consider alternatives to use of indwelling urethral catheters in select patients (e.g., external catheters in cooperative male patients without urinary retention or bladder outlet obstruction; intermittent catheterization in spinal cord injury patients or patients with bladder emptying dysfunction).	• II
• Further research is needed regarding use of suprapubic catheters as alternative to indwelling urethral catheters.	NR
Urinary Catheter Insertion	
• Perform hand hygiene before and after insertion or manipulation of catheter.	IB
• Only properly trained personnel should insert and maintain catheters.	IB
• Insert catheter using aseptic technique and sterile equipment (sterile gloves, drape, antiseptic or sterile solution for periurethral cleaning).	IB
• Properly secure catheter to prevent movement and urethral traction.	IB
• Use smallest-bore catheter possible that allows for good drainage to minimize bladder neck and urethral trauma.	II
Urinary Catheter Maintenance	
• Maintain a closed drainage system; if break in aseptic technique, disconnection, or leakage occurs, replace catheter and collecting system.	IB
• Maintain unobstructed urine flow (e.g., keep collecting bag below level of bladder at all times; keep catheter and collecting tube free from kinking; empty collecting bag regularly).	IB
• Use standard precautions, including the use of gloves and gown as appropriate, during any manipulation of catheter or collecting system.	IB
• Do not change catheters or drainage bags at routine, fixed intervals.	II
• Do not use systemic antimicrobials to prevent CAUTI.	IB
• Do not clean periurethral area with antiseptics; routine hygiene is appropriate (e.g., cleansing meatal surface during bathing).	IB

TABLE 47.13 CDC/HICPAC Guideline Recommendations for Prevention of Catheter-Associated Urinary Tract Infection—cont'd`

Recommendation	Strength[a]
• Unless obstruction is anticipated, bladder irrigation is not recommended.	II
• If obstruction occurs, change catheter.	IB
• Irrigation of bladder with antimicrobials and instillation of antiseptic or antimicrobial solutions into drainage bags are not recommended.	II
• Obtain urine samples aseptically.	IB
• If CAUTI rate is not decreasing after implementing a comprehensive strategy to reduce CAUTI rates, consider using antimicrobial/antiseptic-impregnated catheters.	IB
• Further research is needed on use of bacterial interference (i.e., bladder inoculation with a nonpathogenic bacterial strain) to prevent CAUTI.	NR
• Further research is needed regarding spatial separation of patients with catheters to prevent transmission of pathogens colonizing urinary drainage systems.	NR
Other Measures	
• Implement quality improvement strategies to enhance appropriate use of catheters and to reduce the risk of CAUTI.	IB
• Ensure that health care personnel are given periodic training regarding catheter insertion, maintenance, and removal; CAUTI; and alternatives to indwelling catheters.	IB
• Consider surveillance for CAUTI when indicated.	II
• Do not routinely screen catheterized patients for asymptomatic bacteriuria.	II

[a]Recommendations: *IA*, strong recommendation supported by high- to moderate-quality evidence suggesting net clinical benefit or harm. *IB*, Strong recommendation supported by low-quality evidence suggesting net clinical benefit or harm or an accepted practice (e.g., aseptic technique) supported by low- to very-low-quality evidence. *IC*, Strong recommendation required by state or federal regulation. *II*, Weak recommendation supported by any-quality evidence suggesting a trade-off between clinical benefit and harm. No recommendation/unresolved issue *(NR)*, unresolved issue for which there is low- to very-low-quality evidence with uncertain tradeoffs between benefit and harm.

CAUTI, catheter-associated urinary tract infection; *CCCTG*, Canadian Critical Care Trials Group; *CDC*, Centers for Disease Control and Prevention.

Data from Gould CV, Umscheid CA, Agarwal RK, et al. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol.* 2010;31:319–326.

Control of Antibiotic Resistance

Between 1940 and 1962, more than 20 new classes of antimicrobials were marketed. Since then, only two new classes have reached the market.[508a] In the 1960s, public health officials confidently declared that the war against infectious diseases was almost over. Unfortunately, it is not clear which side will be victorious. Although the greatest strides in our struggles with infectious diseases have resulted from improvements in hygiene and social conditions, the growing losses of our antibiotic armamentarium as a result of surging bacterial resistance could ultimately be disastrous for ICU patients if the tide is not stemmed.

Evolution of Antibiotic Resistance in ICUs

Antimicrobial resistance has evolved through several phases. In the 1970s and 1980s, resistance of aerobic gram-negative bacilli was the major concern, and P. aeruginosa, with its broad range of intrinsic and acquired resistances, was the quintessential nosocomial pathogen. By the 1990s, the availability of antibiotics from a variety of distinct classes—aminoglycosides, broad-spectrum penicillins (e.g., piperacillin), monobactams (e.g., aztreonam), carbapenems (e.g., imipenem), β-lactam–β-lactamase inhibitors (e.g., piperacillin-tazobactam), trimethoprim-sulfamethoxazole, and fluoroquinolones—promised a respite from concerns about resistance in aerobic gram-negative bacilli. During this period, however, gram-positive cocci gained prominence, and MRSA, β-lactam–resistant coagulase-negative staphylococci, and VRE became the major problem nosocomial pathogens. Co-emerging as nosocomial pathogens with MRSA have been methicillin-resistant coagulase-negative staphylococci, which have become the leading cause of IVD-related BSI and prosthesis-related surgical site infections.

In the early 1990s VRE burst onto the hospital and ICU scene in the United States and within a few years became entrenched in most tertiary medical centers. Heavy use of vancomycin, often as empiric treatment in response to concerns about MRSA, has been cited as an initial factor driving the emergence of VRE. In most settings, however, exposure to cephalosporins and antimicrobials with antianaerobic activity has emerged as the greatest risk factors for nosocomial colonization or infection by VRE. The mid-1990s witnessed growing problems with resistance in fungi and shifts to non–Candida albicans species, representing the effects of heavy empirical use of azoles such as fluconazole in hospitals during this period.

Multidrug-resistant gram-negative bacilli have also emerged as a serious threat, including multidrug-resistant P. aeruginosa and Acinetobacter, ESBL-producing Enterobacteriaceae in the 1980s, carbapenemase-producing Enterobacteriaceae in the 1990s, and AmpC β-lactamase–producing bacteria, with some of these pathogens resistant to all available antibiotics.[48]

Forces Driving Resistance in ICUs

To a large extent, the emergence of antimicrobial resistance reflects the combined effects of genetic selection, antibiotic pressures, and the frequency of cross-infection in ICUs.[48] For some resistance mechanisms (e.g., ESBL that confers resistance to third-generation cephalosporins such as ceftazidime), a shift of a single amino acid

in existing resistance genes can lead to new, inactivating enzymes. For other resistant bacteria, such as penicillin-resistant pneumococci, multiple resistance genes must be cobbled together in a specific, exacting sequence, which may take years to evolve, emerge, and spread.

Antibiotic pressures provide the necessary Darwinian forces that amplify these genetic changes.[509] Usually, resistance emerges to a specific agent that is used most heavily and, hence, provides the greatest pressure. In some instances, genetic linkage of resistance mechanisms to unrelated classes of antimicrobials results in the capacity of heavy use of one drug class to select for resistance to a different class. For example, use of trimethoprim-sulfamethoxazole has been associated statistically with the emergence of ceftazidime-resistant E. coli and K. pneumoniae as a result of linkage on a single plasmid of genes that encode production of ESBL and trimethoprim-sulfamethoxazole resistance. A large proportion of extended-spectrum β-lactamase–producing gram-negative bacilli are also resistant to fluoroquinolones.[510,511]

In epidemiologic and clinical studies of antibiotic resistance, there is always a proportion of patients in whom resistance is found without exposure to the problem antibiotic. These patients usually have other important risk factors, such as increased severity of underlying disease, extremes of age, presence of invasive devices, recent surgery, or proximity to patients who are infected or colonized with antibiotic-resistant bacteria. In these cases the presence of antibiotic-resistant strains is most often the consequence of patient-to-patient spread, usually on the contaminated hands of HCWs; occasionally, spread results from a contaminated common source, such as an inadequately cleaned piece of equipment. Studies of HCW hand hygiene show that rates of handwashing between patient contacts range from 25% to 50%, at best, and are inadequate to control resistance, especially in ICUs, where the staff are extremely busy and less likely to be attentive to hand hygiene.[177]

Controlling Antimicrobial Resistance in the ICU

Stemming the tide of antimicrobial resistance requires a multifaceted approach, especially in ICUs, where antibiotic pressures and lapses in hospital hygiene are usually greatest. First, active surveillance for resistant bacteria is essential to provide an understanding of local problems and needs. To support surveillance and treatment, cultures must be obtained from suspected sites of infection before empiric antibiotic therapy is initiated. The benefit of routine surveillance cultures (e.g., periodic cultures of sputum specimens or rectal swabs) for assessing rates of colonization by resistant bacteria in ICUs will depend on how such cultures are used.

Second, when rates of resistance begin to increase, molecular typing, such as by pulsed-field gel electrophoresis or more recently by whole genome sequencing, can differentiate spread of a single strain (clonal expansion)—usually the result of indirect person-to-person spread on the inadequately cleaned hands of HCWs or common source transmission—from spread of multiple strains (polyclonal expansion), which suggests emergence of resistance in individual patients as a result of antibiotic pressures or exogenous introduction of multiple resistant strains. Often, these problems—clonal and polyclonal—coexist.

Third, the importance of hand hygiene must be stressed at all times. Aggressive hand hygiene campaigns, with adherence monitoring and feedback of ward and even individual results, may achieve compliance rates as high as 70%. For some situations (e.g., when there is extensive patient colonization by antibiotic-resistant bacteria), these levels of adherence may not be sufficient to control cross-infection. Response to this problem has been to encourage "universal gloving," in addition to wider use of alcohol-based hand rubs (a "belt-and-suspender" approach) to bridge the gap left by incomplete attention to hand hygiene even in the best of circumstances. Use of universal gloving has been successful in controlling the spread of aminoglycoside-resistant gram-negative bacilli in ICUs and C. difficile–related diarrhea.[245,250] Because patients' intact skin and the environment in patient rooms may be a source of resistant bacteria, such as VRE, we recommend that disposable examination gloves be worn for all contact with ICU patients or their environment. Because gloves are not a total barrier, they must be removed and hands disinfected by an alcohol hand rub between patient contacts.

Fourth, antimicrobial stewardship is essential (Table 47.14).[277] See "Antibiotic Stewardship" earlier for an introduction to antimicrobial stewardship. The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, such as toxicity, emergence of resistance, and C. difficile infection.[268,274,277] Because antimicrobial use drives antimicrobial resistance, the frequency of inappropriate antimicrobial use can be used as a surrogate marker for antimicrobial resistance. Both antimicrobial stewardship and a comprehensive infection control program are essential to limiting the emergence and transmission of antimicrobial-resistant pathogens. Many studies assessing the utility of antimicrobial stewardship have focused on adults in ICUs, where the burden of antimicrobial resistance is greatest.

A comprehensive evidence-based stewardship program to combat antimicrobial resistance is typically a multifaceted, multidisciplinary program; the size and complexity of the management team and the specific measures applied to optimize prescribing vary on the basis of local antimicrobial use patterns, resistance trends, and available resources. The two core strategies that provide the foundation for a successful antimicrobial stewardship program are (1) audits, with intervention and feedback, and (2) formulary restriction and preauthorization.[268,274,277]

Several studies have shown that real-time audits of antimicrobial use with intervention and feedback are an effective means of reducing inappropriate antimicrobial use.[512,513] In a randomized trial conducted at a 600-bed tertiary teaching hospital, inpatients receiving parenteral antimicrobial therapy were randomly assigned to an intervention group that received suggestions for optimal antimicrobial use from an infectious disease physician or to no interventions. Physicians in the intervention group implemented 85% of the suggestions they received, which resulted in 1.6 fewer days of parenteral therapy and $400 savings per patient. Similar results have been noted in trials undertaken in community hospitals.[512] If daily review of antimicrobial use is not feasible, review of antimicrobial usage 3 days a week may still have a significant impact. Effective auditing with intervention and feedback can be undertaken most easily with automated computer surveillance of antimicrobial use, allowing the targeting of specific units where the problems are greatest.

Formulary restriction and preauthorization requirements for specific agents are now common in most hospitals. Antimicrobial restriction is unequivocally the most effective method of controlling antimicrobial use.[514,515] However, it is unclear whether antimicrobial restriction achieves the more important outcome, reducing antimicrobial resistance. Several studies of outbreaks of C. difficile–associated diarrhea have shown abrupt cessation of the outbreak following restriction (and greatly reduced use) of one or more key antimicrobials such as clindamycin or third-generation cephalosporins.[514] However, other studies have documented

TABLE 47.14 Recommendations for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Recommendation	Level of Evidence[a]
• Create a multidisciplinary antimicrobial stewardship team, including an infectious disease physician and a clinical pharmacist with infectious disease training.	A-II
• Include, if possible, a clinical microbiologist, an information systems specialist, an infection control professional, and the hospital epidemiologist.	A-III
• Foster collaboration between the antimicrobial stewardship team and the hospital infection control committee.	A-III
• Create a climate of support and collaboration between the antimicrobial stewardship team and the hospital administration and medical staff leadership.	A-III
• Develop infrastructure to measure antimicrobial use, and track use on ongoing basis.	A-II
• Use a system of prospective audit of antimicrobial use with direct interaction and feedback to the prescriber by an infectious disease physician or a clinical pharmacist with infectious disease training.	A-I
• Use formulary restrictions and preauthorization requirement to reduce antimicrobial use and cost.	A-II
• Provide education to health care providers regarding stewardship strategies.	A-III
• Education must be combined with active interventions to improve antimicrobial prescribing practices.	B-II
• Develop evidence-based multidisciplinary guidelines incorporating local microbiology and resistance patterns to improve antimicrobial utilization.	A-I
• No recommendation can be made regarding antimicrobial cycling as a means of preventing or reducing antimicrobial resistance.	C-II
• Use antimicrobial order forms as a component of antimicrobial stewardship.	B-II
• No recommendation can be made regarding the routine use of combination therapy to prevent emergence of resistance.	C-II
• Streamline or de-escalate antimicrobial therapy on the basis of culture results.	A-II
• Optimize antimicrobial dosing on the basis of individual patient characteristics, causative organisms, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug.	A-II
• Use health care information technology. such as electronic medical records, computerized physician order entry, and clinical decision support, to improve antimicrobial prescribing.	B-II
• Use computer-based surveillance for more efficient targeting of antimicrobial interventions, tracking of resistance patterns, and identification of nosocomial infections and adverse drug reactions.	B-II
• Engage the clinical microbiology laboratory to participate in antimicrobial stewardship by providing patient-specific culture and susceptibility data and by assisting infection control efforts in the surveillance of resistant organisms and in the molecular epidemiologic investigation of outbreaks.	A-III
• Determine the impact of antimicrobial stewardship by measuring process and outcomes.	B-III

[a]Based on the Infectious Diseases Society of America grading system for ranking recommendations in clinical guidelines. *A,* Good evidence to support a recommendation for use. *B,* Moderate evidence to support a recommendation for use. *C,* Poor evidence to support a recommendation for use. *I,* Evidence from more than1 properly randomized, controlled trial. *II,* Evidence from more than 1 well-designed clinical trial, without randomization, from cohort or case-controlled analytic studies, or from multiple time-series. *III,* Evidence from expert opinion.

Modified from Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44:159–177.

inexorably rising resistance rates in nosocomial pathogens despite a rigorous program of antimicrobial restriction.[516] One explanation for this increase in resistance may be the compensatory increase in usage of broad-spectrum antimicrobials other than the restricted agent, thus counteracting any benefit of restriction. Furthermore, restricting the use of a single drug to reduce antimicrobial resistance may be ineffective because cross-resistance in bacterial species to more than one class of antimicrobials is the rule in nosocomial organisms.

One or both of the core strategies—audits with intervention and formulary restriction—should be adopted and supplemented by close collaboration of an antimicrobial stewardship team, infection control personnel, health care providers, and hospital administration.

Beyond the two core mechanisms of antimicrobial stewardship, other elements that should be incorporated into an institutional antimicrobial stewardship program include education of health care providers; however, passive educational efforts, such as conference presentations, teaching sessions, and provision of guidelines, are only marginally effective in the absence of other active interventions.[517] Clinical practice guidelines are being introduced with increasing frequency; however, the impact of these guidelines on

provider behavior and clinical outcomes has been difficult to measure. Guidelines tailored to local antimicrobial resistance patterns and antimicrobial use trends may have more impact than a generic clinical pathway. Finally, technologies that offer rapid identification of organisms in blood cultures are a promising new application that has improved time to escalation of antimicrobial therapy, and also de-escalation of antimicrobial therapy but only with involvement of the antimicrobial stewardship team (see "Role of the Microbiology Laboratory").[157,158]

Interest has been sparked in ICUs by the reborn concept of antibiotic cycling.[518,519] Switch therapy[520] has been evaluated for empiric antibiotic use, rather than actual cycling, and has shown beneficial reductions in resistance among gram-negative bacilli[521] and in the prevalence of VRE. Such approaches, as well as true cycling through different antimicrobial classes, may be effective over limited periods in closed environments such as ICUs, by transiently reducing selection pressure and thus resistance to the restricted agent. Yet studies have thus far not shown a consistent long-term benefit with cycling, and mathematical models do predict that cycling will not be an effective measure to reduce antimicrobial resistance.[522]

Antimicrobial order forms with automatic stop orders and the requirement for physician justification reduce antimicrobial usage.[523] Streamlining or de-escalation of therapy based on culture data is an essential component of appropriate antimicrobial use, with studies showing substantial reductions in days of antimicrobial use and cost savings.[524,525]

Computer order entry provides needed information at the moment in a neutral, nonjudgmental, fact-based format; this system is efficient, well accepted, and holds the promise to change prescribing behaviors materially.[526,527]

Effective antimicrobial stewardship programs can be financially self-supporting and improve patient care. Studies have shown reductions in antimicrobial usage from 22% to 36%, with annual savings of $200,000 to $900,000 in larger teaching hospitals and community hospitals. Guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America provide detailed recommendations for developing institutional programs of antimicrobial stewardship, which are summarized in Table 47.14.[277]

Avant Garde Infection Control Measures

Selective Digestive Decontamination

Intense interest has arisen in Europe and the United States[485–487] over the use of (SDD) for the prevention of bacterial pneumonia and other nosocomial infections in mechanically ventilated ICU patients. This novel therapy is based on the premise that the upper respiratory tract flora exists in a continuum with the gastrointestinal flora and that these mucosal microorganisms make up the major reservoir of pathogens causing pneumonia and many other nosocomial infections, especially in mechanically ventilated patients. Most ventilated ICU patients have a nasogastric tube that provides a direct conduit for reflux of microorganisms from the heavily colonized stomach to the oropharynx, from which organisms gain access to the lower respiratory tract.

SDD consists of four components: (1) a broad-spectrum parenteral antibiotic given for approximately 3 days to treat infections incubating at the time of admission to the ICU; (2) topical antimicrobials (usually polymyxin E, tobramycin, and amphotericin B) periodically applied to the oropharynx and instilled into the gut for a variable period, usually for the entire duration of ICU stay, to reduce the mucosal burden of gram-negative bacteria and yeasts while preserving the anaerobic flora; (3) a reemphasized adherence to hand hygiene to prevent nosocomial transmission of bacteria, and in some European centers, empiric barrier isolation; and (4) serial surveillance cultures of the oropharynx and rectum to monitor the efficacy of the treatment.[528,529]

Twelve meta-analyses assessing the efficacy of SDD for reducing infection and mortality rates have been published (Table 47.15).[530–541] All have found a reduction in pneumonia. Some, but not all, have found a reduced mortality rate. However, a review showed that the results of the meta-analyses were inversely related to study design,[542] which in the case of SDD may overestimate its efficacy. Most studies and meta-analyses of SDD did not make a distinction between parenteral and topical SDD; the few meta-analyses that undertook subgroup analyses found that topical antibiotics alone reduced infection but not the mortality rate.[535] In a large clinical trial of SDD and selective oropharyngeal decontamination in 5939 ICU patients, a large reduction in ICU-acquired bacteremia caused by gram-negative bacilli and S. aureus was seen, and an estimated reduction in the mortality rate of 3.5 percentage points with SDD and 2.9 percentage points with selective oropharyngeal decontamination was seen, providing further evidence of the efficacy of SDD.[543]

However, the greatest deterrent to widespread acceptance of SDD is the fear that it will promote the emergence and spread of antimicrobial-resistant microorganisms. Antibiotic pressure is without question the single most powerful force driving the selection of resistant microorganisms, and any strategy for prevention of infection in the ICU that has the potential to increase infections caused by multiresistant organisms must be approached very cautiously. A number of studies underlie the concern of promoting antimicrobial resistance with SDD. Numerous studies have documented major shifts in the microbial ecology of the ICU with the use of SDD.[544–547] In a study by Lingnau and colleagues,[544] 4.5 years of SDD with ciprofloxacin led to a marked increase in MRSA infection from 17% to 81% and of ciprofloxacin-resistant S. aureus from 33% to 80%. The number of infections caused by other multiresistant bacteria such as Acinetobacter was also increased by SDD.[544]

A distinction must also be made between the risk to an individual receiving SDD of infection caused by a resistant pathogen and the institutional risk of an increased prevalence of antimicrobial-resistant organisms related to the use of SDD. Although both consequences are undesirable, given the skyrocketing rates of endemic nosocomial MRSA and VRE infections worldwide, any—however small—potential for increased antimicrobial resistance must be taken seriously.[548] To better address this issue, well-designed, cluster-randomized trials that use multilevel modeling and specifically address the effects of SDD on antimicrobial resistance across the entire spectrum of microbial pathogens at the institutional level are necessary. Until such data are available, we believe that continued North American concerns about the effects of SDD on antimicrobial resistance are justified, particularly in institutions where MRSA and VRE are endemic, which encompasses virtually all larger hospitals. Given that other effective measures for the prevention of nosocomial infection exist, we believe that SDD should be restricted to select patients, such as certain trauma patients, or as a potential adjunctive control measure for a nosocomial outbreak caused by multiply resistant organisms.[549]

Randomized trials have identified several novel measures for prevention of VAP such as semirecumbent positioning[471] and subglottic suction endotracheal tubes.[550] We believe that these approaches are ecologically more attractive control measures for

TABLE 47.15 Meta-Analyses of Randomized Controlled Trials of Selective Digestive Decontamination

Study (Year)	No. of RCTs Included	Description	Pneumonia Point Estimate OR or RR (95% CI)	Mortality Point Estimate OR or RR (95% CI)
Vandenbroucke-Grauls et al.[530] (1991)	6	Medical and surgical patients	0.12 (0.08–0.19)	0.70 (0.45–1.09)
SDD Trialists Collaborative Group[531] (1993)	22	Medical and surgical patients	0.37 (0.31–0.43)	0.90 (0.79–1.04)
Kollef[532] (1994)	16	Medical and surgical patients	0.28 (0.21–0.38)	0.90 (0.74–1.1)
Heyland et al.[533] (1994)	25	Medical and surgical patients	0.46 (0.39–0.56)	0.87 (0.79–0.97)
Hurley[534] (1995)	26	Medical and surgical patients	0.35 (0.30–0.42)	0.86 (0.74–0.99)
D'Amico et al.[535] (1998)	33	Medical and surgical patients	0.35 (0.29–0.41)	0.88 (0.78–0.98)
Nathens et al.[536] (1999)	21	Medical and surgical patients	Medical: 0.45 (0.33–0.62) Surgical: 0.19 (0.15–0.26)	Medical: 0.91 (0.71–1.18) Surgical: 0.70 (0.52–0.93)
Safdar et al.[537] (2004)	4	Liver transplant patients	0.88 (0.73–1.09)[a]	0.82 (0.22–2.45)
Liberati et al.[538] (2004)	36	Medical and surgical patients	0.35 (0.29–0.41)	0.78 (0.68–0.89)
Silvestri et al.[539] (2005)	42	Medical and surgical patients	0.30 (0.17–0.53)[b]	NR
Silvestri et al.[540] (2007)	51	Medical and surgical patients	0.73 (0.59–0.90)[c]	0.80 (0.69–0.94)
Liberati et al.[541] (2009)	36	Medical and surgical patients	0.28 (0.20–0.38)	0.75 (0.65–0.87)

[a]Overall infection.
[b]Fungal infections.
[c]Bloodstream infection.
CI, Confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial; *RR*, relative risk.
Studies cited in table (column 1) may be found in the complete list of references for this chapter provided online.

ventilated ICU patients than prophylactic topical and systemic antibiotics.

Preemptive Barrier Isolation

Having fewer patients in a room, improving the facilities for handwashing, and using cohort nursing (i.e., assigning each nurse to designated patients) have reduced the incidence of endemic nosocomial infection in neonatal and pediatric ICUs.[181,551] Complicated forms of protective isolation have reduced the high rates of nosocomial infection in patients with profound granulocytopenia[552] or full-thickness burns.[181,264] Moreover, the routine use of gowns and gloves on a special pediatric unit was associated with a marked decline in the incidence of nosocomial infection with respiratory syncytial virus,[78] and the routine use of gloves for all patient contacts was shown to reduce the incidence of nosocomial C. difficile infection nearly fivefold in a large veterans hospital.[250]

Unfortunately, the few studies that have prospectively evaluated protective isolation of ICU patients have been performed in newborns and pediatric patients and have yielded conflicting and generally disappointing results[553–556]; however, most of these studies had major weaknesses in design.[557] More recently, several studies have shown that preemptive use of barrier precautions can effectively reduce the spread of multiresistant organisms such as MRSA or VRE in epidemic[558,559] and endemic settings (Table 47.16).[78,250,554,560–567] If colonization by nosocomial organisms could be prevented or at least delayed until invasive devices are removed, the incidence of infection might be significantly reduced.

One major prospective trial that assessed the efficacy of simple protective isolation—which we prefer to call preemptive barrier precautions—to reduce the incidence of nosocomial infection during pediatric intensive care studied 70 high-risk children over 30 months who were not immunosuppressed but who required prolonged mechanical ventilatory support and exposure to invasive devices in a pediatric ICU and were randomly assigned to receive standard care without any special precautions or preemptive barrier isolation, with the use of disposable nonwoven polypropylene gowns and nonsterile latex gloves for all patient contacts.[560] Risk factors predisposing patients to infection were comparable in the two groups. Nosocomial colonization occurred later among isolated patients (median 12 vs. 7 days) and was associated with subsequent infection in 2 patients, as compared with 12 patients given standard care. Among children who were isolated, the interval before the first infection was significantly longer (median, 20 vs. 8 days), the daily infection rate was twofold lower (86 vs. 44 infections per 1000 ICU days), and there were 50% fewer days with fever. The benefit of isolation was most notable after 7 days of ICU care. Isolation was well tolerated by patients and their families. Unannounced monitoring showed that children in each group were touched and handled comparably often by hospital personnel and families.

The study concluded that the use of disposable high-barrier gowns and gloves for the care of select high-risk children who require prolonged ICU care can substantially reduce the incidence of nosocomial infection, is well tolerated, and does not compromise the delivery of care. Simple forms of protective isolation as a general control measure would also seem preferable to attempts to suppress

TABLE 47.16 Studies of Preemptive Barrier Isolation to Contain Spread of Multiresistant Organisms

Organism/Infection Requiring Use of Preemptive Barrier Isolation Precautions for All High-Risk Patients	CONTROL OF EPIDEMIC SPREAD		CONTROL OF ENDEMIC INFECTIONS			
			BEFORE-AFTER AND NONRANDOMIZED TRIALS		RANDOMIZED TRIALS	
	No. of Outbreaks/Study	No. Totally Controlled	Study	RR (95% CI)	Study	RR (95% CI)
Methicillin-resistant *Staphylococcus aureus*	2 Maki et al.[558]	2 (100%) Maki et al.[558]	Safdar et al.[564]	0.36 (0.13–0.98)[a]	None	
Vancomycin-resistant enterococci	2 Maki et al.,[558] van Hoorhis et al.[559]	2 (100%) Maki et al.,[558] van Hoorhis et al.[559]	Montecalvo et al.[566]	0.22 (0.05–0.92)[a]	None	
			Slaughter et al.[265]	2.66 (1.00–6.77)[b]		
			Morriset al.[567]	1.18 (NR)[b]		
			Srinivasan et al.[565]	0.47 (NR)[a]		
			All studies	0.22–2.66		
Resistant gram-negative bacilli	None		McManus et al.[646]	0.38 (0.31–0.46)[a]	None	
Clostridium difficile	None		Johnson et al.[250]	0.19 (NR)[a]	None	
Other						
Necrotizing enterocolitis			Agbayani et al.[554]	0.13 (0.02–0.84)[a]		
Respiratory syncytial virus			Leclair et al.[78]	0.34 (0.17–0.60)[a]		
All nosocomial infections			Slaughter et al.[265]	1.51 (0.74–3.12)[b]	Slota et al.[561]	0.48 (NR)[a]
					Klein et al.[560]	0.19 (0.05–0.70)[a]
					Koss et al.[563]	1.86 (1.10–3.16)[a]

[a] $P < 0.05$.
[b] $P > 0.05$.
NR, Not reported; *RR*, relative risk.
Studies cited (by main author) in table may be found in the complete list of references for this chapter provided online.

nosocomial colonization with SDD. Further studies are necessary to determine the cost-effectiveness of prophylactic barrier precautions in the ICU and especially the efficacy of protective isolation in adult surgical ICUs, where the incidence of nosocomial infection is as high as 35%. Studies should also determine the relative importance of wearing a gown, as compared with wearing gloves alone.

Patients with prolonged severe granulocytopenia or those who are receiving high dosages of corticosteroids, usually as part of immunosuppressive regimens to prevent transplant rejection, are at risk for invasive pulmonary infection caused by Aspergillus species, mucormycosis, and other filamentous airborne fungi, which is associated with a high mortality rate.[41–43,568] The risk of invasive infection appears to be directly related to the likelihood of airborne fungi, and numerous outbreaks have been linked to building construction or failure of air-control systems. Studies have shown that the isolation of vulnerable patients in positive-pressure rooms with spore-free HEPA-filtered air greatly reduces the risk of invasive infection.[41,43] HEPA-filtered ICU rooms should be available for the care of patients who have received bone marrow or solid organ transplants and who require intensive care, especially in the early post-transplant period or during the treatment of rejection, when dosages of immunosuppressive drugs are high.

Preemptive use of barrier isolation precautions (e.g., universal gloving or gowns and gloves) and providing dedicated patient care items such as stethoscopes and sphygmomanometers in all high-risk patients from the time of admission is a simple and effective strategy to prevent HCWs from acquiring hand contamination by multiresistant organisms when having contact with patients with unrecognized colonization or infection and to block transmission to other as yet uncolonized patients.

Approach to a Nosocomial Epidemic

See the online supplement for Approach to a Nosocomial Epidemic.

Protection of Health Care Workers in the Intensive Care Unit

HCWs in general, but especially those working in ICUs who are exposed daily to critically ill patients, many of whom have contagious but undiagnosed infections, are at increased risk of acquiring occupationally related infections, including tuberculosis; herpes

Approach to a Nosocomial Epidemic

As noted earlier, most recognized nosocomial epidemics now occur in ICUs. If an epidemic is suspected, the epidemiologic approach must be methodical and thorough yet expeditious, directed toward establishing the bona fide nature of the putative epidemic infections (i.e., ruling out "pseudoinfections"[331]); confirming the existence of an epidemic (i.e., ruling out a "pseudoepidemic"[331]); defining the reservoirs and modes of transmission of the epidemic pathogens; and most importantly, controlling the epidemic quickly and completely. Control measures are predicated on accurate delineation of the epidemiology of the epidemic pathogen.

Each hospital, through its infection control committee, must be prepared administratively to conduct an investigation and implement needed control measures. The essential steps in dealing with a suspected outbreak of nosocomial BSI are summarized in Box 47.e1 [151] To illustrate the approach to a nosocomial epidemic, the epidemiologic investigation of an unusual and complicated outbreak of infusion-related bacteremia[329] is reviewed.

During a 2-week period in late March 1985, three patients in a university hospital developed primary nosocomial bacteremia with a similar nonfermentative gram-negative bacillus. All three patients had had open-heart surgery between March 11 and March 25 (Fig. 47.e2) and became bacteremic 48 to 148 hours after the operation.

The bloodstream pathogen in each case was shown to be Pseudomonas pickettii biovariant 1. The organism was also cultured from the IV fluid of two of the patients at the time because, serendipitously, during the outbreak most adult patients in the hospital receiving IV fluids were participating in a study of IV catheter dressings[569]: As part of the study protocol, specimens were routinely obtained from patients' IV fluid when the catheter was removed. Review of nearly 1000 cultures of IV fluid from the infusions of participants in the study since its outset 3 months earlier showed that three additional surgical patients operated on in March had had IV fluid cultures positive for P. pickettii biovariant 1 (see Fig. 47.e2), even though none had shown clinical signs of bacteremia. Molecular subtyping by restriction enzyme digestion and pulsed-field electrophoresis to delineate restriction polymorphism patterns showed all six isolates to be the clonal. Three more patients who had been operated on in January had had IV fluid that cultured positive for a similar nonfermentative gram-negative bacillus; although the three isolates were no longer available, the results of screening by AP-20E biochemical panel (API Analytab Products, Inc., Plainville, NY) at the time were identical to those of the six patients with P. pickettii contamination of IV, with or without associated bacteremia.

All three septic patients had had multiple positive blood cultures and were clinically in septic shock. P. pickettii had not been isolated from any local site of infection such as the urinary tract, lower respiratory tract, or surgical wound in any of the patients.

Review of nosocomial bacteremias over the past 7 years showed that P. pickettii had not previously been identified in any positive blood cultures from the institution, indicating that the cluster of three cases and six instances of contaminated infusate without bacteremia represented a true epidemic, and with the results of the subtyping, a common source epidemic.

The CDC and the manufacturer were contacted: none of more than 70 NNIS hospitals had reported P. pickettii bacteremias in the past year, and the manufacturer had never identified contamination with P. pickettii in quality-control microbiologic sampling of fentanyl before distribution, or received any complaints from users about suspected contamination of their fentanyl. Moreover, survey of surrounding [Wisconsin] hospitals that also used the manufacturer's fentanyl revealed none experiencing nosocomial [bacteremias] with P. pickettii.

A case-control study comparing the 9 cases, all of whom had had recent surgery, with 19 operated patients who had had negative IV fluid cultures in the IV dressing study (Table 47.e2), showed that all 9 cases but only 9/19 operated controls had received fentanyl intravenously in the operating room ($P = 0.05$; the mean total dose given to the 9 cases was far greater than that given to control-patients who received the drug, 3080 μg vs. 840 μg, $P < 0.001$).

In the hospital at the time, fentanyl was used [only in the operating rooms as part of balanced anesthesia]. The drug was

• BOX 47.E1 Evaluation of a Suspected Epidemic of Nosocomial Infections

Administrative Preparedness

Immediately retrieve putative epidemic isolates for confirmation of identity through species and subtyping by one or more methods:

- Biotyping
- Antimicrobial susceptibility pattern (antibiogram)
- Serotyping
- Phage typing
- Bacteriocin typing
- SDS-PAGE protein electrophoresis
- Immunoblot pattern
- Multifocus enzyme electrophoresis
- Restriction enzyme digestion and restriction fragment polymorphism patterns
- DNA probes
- Whole genome sequencing

Preliminary Evaluations and Control Measures

- Identify and characterize individual cases in time, place, risk factors.
- Strive to identify source of infections.
- Ascertain whether cases represent a true infection rather than a "pseudoinfection."
- Ascertain whether cases represent a true epidemic, rather than a "pseudoepidemic."
- Develop and implement provisional control measures.
- Intensify surveillance to detect each new case.
- Review general infection control policies and procedures.
- Determine the need for assistance, especially extramural (local, state, CDC).

Epidemiologic Investigations

- Clinicoepidemiologic studies, especially case-control studies
- Microbiologic studies

Definitive Control Measures and Follow-up

- Develop and implement definitive control measures.
- Confirm control of epidemic by intensified follow-up surveillance.

Reporting/Publishing Findings

Report the findings:

- Intramurally
- State health department, CDC

Publish the report.

CDC, *Centers for Disease Control and Prevention;* SDS-PAGE, *sodium dodecyl sulfate—polyacrylamide gel electrophoresis.*

Modified from Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. Hospital Infections. *4th ed. Boston: Lippincott-Raven; 1998.*

received in 20-mL ampules from the manufacturer and each week one of three pharmacy technicians, by rotation, pre-drew into sterile syringes all fentanyl likely to be needed the following week in the operating rooms. Each day, one of the technicians delivered enough pre-drawn syringes to the operating rooms]to meet the needs of the cases being done that day. Cultures of pre-drawn fentanyl in syringes in the central pharmacy, prompted by the findings of the case-control study, showed that 20/50 (40%) 30-mL syringes sampled were contaminated by P. pickettii in a concentration of $>10^4$ CFUs/mL; none of 35 5- or 2-mL syringes showed contamination (P = 0.001).

Extensive culturing within the central pharmacy was negative for evidence of environmental contamination by P. pickettii with one exception: P. pickettii biovariant 1, with an identical antimicrobial susceptibility pattern and restriction enzyme fragment pattern to the epidemic strain recovered from blood cultures or patients' intravenous infusions, was cultured in a concentration of 28 to 80 CFUs/mL from five specimens of distilled water drawn from a tap in the central pharmacy. The epidemic strain was shown to multiply well in the fentanyl solution, attaining concentrations exceeding 10^4 CFUs/mL within 48 hours.

A second case-control study suggested strongly that the epidemic was caused by theft of fentanyl from 30-mL syringes by one pharmacy staff member and replacement by distilled water that the individual thought was sterile but which, unfortunately, was contaminated by P. pickettii. The pharmacy member resigned early in the investigation and no longer works in the hospital. On April 29, 1985, the hospital's system for providing fentanyl and other narcotics to the operating rooms was changed; narcotics are no longer predrawn into syringes in the central pharmacy but are delivered to the operating rooms in unopened vials or ampules, and anesthesiologists' orders for narcotics are filled by a staff pharmacist assigned to the operating room. No further bacteremias with P. pickettii have occurred since March 25, 1985 (see Fig. 47.e2), and cultures of more than 6000 samples of hospitalized patients' intravenous fluid in research studies since then have shown no further contamination by P. pickettii.

This outbreak illustrates the power of genetic subtyping[155] and case-control analyses to identify the cause of an epidemic. It further illustrates the potential for contamination of parenteral drugs or admixtures and the extraordinary range of epidemiologic mechanisms of nosocomial BSI deriving from such contamination.[114]

If epidemiologic or microbiologic studies suggest or indicate intrinsic contamination of a widely distributed commercial product or device, the local and state health authorities, U.S. Food and Drug Administration, CDC, and manufacturer should be informed immediately. Remaining products should be quarantined and retained for evaluation by the public health authorities.

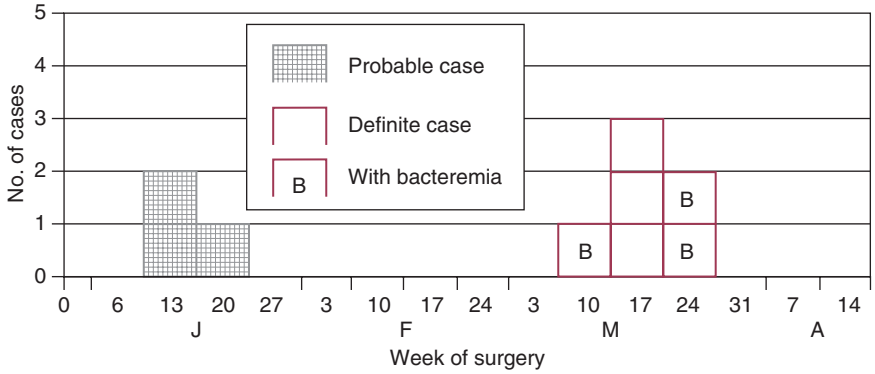


Fig. 47.e2 Epidemic curve for an outbreak of *Pseudomonas pickettii* bacteremias and contaminated intravenous infusions traced to contaminated fentanyl given intravenously. Isolates from blood or intravenous fluid of six definite cases (March 1985) were available for reconfirmation and subtyping as *P. pickettii* biovariant 1; isolates from intravenous fluid of three probable cases (January 1985) were not available for retesting but were considered likely to have also been *P. pickettii* biovariant 1 on review of the results of 20 biochemical tests common to these three and the six confirmed isolates. (From Maki DG, Klein BS, McCormick RD, et al. Nosocomial *Pseudomonas pickettii* bacteremias traced to narcotic tampering. A case for selective drug screening of health care personnel. *JAMA.* 1991;265:981–986.)

TABLE 47.E2 Case-Control Analysis of Risk Factors for Bacteremia or Contaminated Intravenous Fluid With *Pseudomonas pickettii*

Variable	Cases ($n = 9$) no. (%)[b]	Controls[a] ($n = 19$) no. (%)[b]	*P* Value
Age, mean (years)	50	46	NS[c]
Duration of surgery, mean (h)	4.0	3.7	NS
Type of Surgery			
Cardiovascular	5 (55)	3 (16)	NS
General	4 (45)	16 (84)	
Intravenous Fluids			
Lactated Ringer solution	8 (89)	11 (58)	NS
Dextrose in Ringer lactate	5 (55)	14 (74)	NS
Saline solution 0.9%	6 (67)	4 (21)	NS
Blood products	7 (78)	4 (21)	NS
Albumin, fresh frozen plasma	4 (44)	2 (10	NS
Intraoperative Intravenous Medications			
Pentothal	4 (45)	13 (68)	NS
Lidocaine	5 (55)	5 (26)	NS
Pancuronium	5 (55)	4 (21)	v
Heparin	5 (55)	0 (0)	<0.001
Cefazolin	9 (100)	10 (53)	NS
Fentanyl	9 (100)	9 (47)	0.05
Volume of intravenous fentanyl, mean	61.6 mL	16.8 mL[d]	<0.001

[a]Patients randomly selected who had had surgery on the same day as cases but who had negative cultures of intravenous fluid from their infusion begun in the operating room.
[b]Number and percent of cases or controls with each variable, unless otherwise specified.
[c]*NS,* not significant at $P < 0.05$.
[d]For the nine control patients who received fentanyl.
From Maki DG, Klein BS, McCormick RD, et al. Nosocomial *Pseudomonas pickettii* bacteremias traced to narcotic tampering. A case for selective drug screening of health care personnel. *JAMA.* 1991;265:981–986.

simplex virus infection; chickenpox; cytomegalovirus infection; hepatitis A, B, or C; HIV infection; influenza; measles; rubella; mumps; pertussis; and viral conjunctivitis.[570–572]

Fortunately, the risk posed by many of these infections can be eliminated by immunization of the HCW,[573] and recommendations from the Advisory Committee on Immunization Practices (ACIP) for the vaccination of HCWs were recently published in 2011.[574] However, a considerable number of occupational infections exist for which there are currently no vaccines. Because this is an area of active research, careful review of current guidelines is recommended, such as from the CDC.[575]

See the online supplement for additional material on Protection of Health Care Workers in the Intensive Care Unit.

Goals for the Future

Clearly, nosocomial infection is one of the most important causes of iatrogenic morbidity and death in patients who require prolonged life support care in an ICU. Much has been learned over the past three decades about the relative risks and especially the pathogenesis and epidemiology of these infections, information that has provided the scientific underpinnings for preventive strategies that have proved effective. However, there is an urgent need for better research to prevent nosocomial infection in ICU patients (Box 47.4),[627] particularly with respect to strategies to prevent colonization by multiresistant microorganisms, and to prevent infection when colonization has already occurred.[28]

Most of our understanding of the epidemiology of nosocomial infection, especially in ICUs, is based on studies of epidemics. Well-designed studies are necessary to better define the epidemiology of endemic nosocomial infections, especially those caused by resistant staphylococci, enterococci and gram-negative bacilli, and yeasts. The importance of hand carriage of pathogens by hospital personnel, the role of airborne and water-borne transmission in the ICU, and the relevance of contamination of the inanimate hospital environment by resistant pathogens all need to be better delineated, as well as the factors influencing nosocomial colonization and superinfection by resistant bacteria and yeasts.

In addition, larger and more sophisticated studies, using multivariate techniques of statistical analysis to define risk factors for the major forms of nosocomial infection in the ICU and whole genome sequencing of study pathogens to differentiate clonal from polyclonal spread, are necessary to guide allocation of infection control resources and to target future research efforts.

Considering that the period of greatly increased susceptibility to infection of ICU patients is limited—until the invasive devices have been removed—a major commitment must be made to devise and evaluate strategies for blocking transmission of organisms between patients and preventing, or at least delaying, nosocomial colonization.

One of the oldest yet most important infection control measures—hand hygiene—is still done almost indifferently by HCWs in most hospitals including within ICUs. Innovative approaches are necessary to improve the frequency and the quality of handwashing after patient contacts likely to result in acquisition of nosocomial organisms. Exactly how should hands be washed for maximal benefit and with what agents? The question can be posed: Could very frequent handwashing, which approaches 40 times per 8-hour shift in neonatal ICUs, increase the potential for transmission of microorganisms, such as methicillin-resistant coagulase-negative staphylococci? Should the frequency of handwashing, as well as the agents used, be critically reexamined? Beyond a certain frequency, more may not necessarily be better. Should handwashing machines, which substantially augment degerming,[628,629] be adopted widely? Could regular application of chlorhexidine-containing evaporative lotions, used without water, replace some of the conventional handwashing or at least compensate for the suboptimal handwashing currently practiced?[242,630,631] Large clinical trials, ideally in multiple centers, are necessary to ascertain the efficacy or lack of efficacy of innovative approaches to hand degerming in reducing infections in high-risk patients, particularly in nurseries and ICUs.

Whereas SDD with topical nonabsorbable antibiotics has shown promise for the prevention of nosocomial respiratory infection in ICU patients, as noted, the potential effect on the microbial ecology

• BOX 47.4 Directions for Future Research in Nosocomial Infection Control

Studies to Better Define the Epidemiology of Endemic Nosocomial Infections:

- Especially those caused by resistant staphylococci, gram-negative bacilli, and *Candida*
- The relevance of hand carriage of pathogens by hospital personnel
- The role of airborne transmission
- The relative importance of contamination of the inanimate hospital environment, especially with methicillin-resistant *Staphylococcus aureus, Clostridium difficile,* and other resistant organisms
- The biologic factors influencing colonization by nosocomial organisms
- The factors governing superinfection by resistant bacteria and *Candida*
- Better understanding of risk factors predisposing to infection, especially in the ICU, to guide allocation of resources in infection control and focus research efforts

Innovative Strategies to Prevent Nosocomial Colonization and Interrupt Cross-Infection, Especially in ICUs:

- New approaches to improving compliance with and improving the effectiveness of handwashing between patients
- Various types of barrier precautions (forms of protective isolation)
- The true efficacy and cost-benefit ratio of selective digestive decontamination, with careful assessment of the ecologic effects of long-term use
- Dedicated device care teams
- Large, randomized clinical trials of the various cutaneous antiseptics available, with infection, rather than colonization, as the index of comparison, for handwashing by personnel, site disinfection with invasive devices, patient bathing, and decolonization

Research on Devices:

- Innovative designs to implicitly reduce contamination
- Colonization-resistant polymers, possibly incorporating antimicrobials onto the surface or into the polymer itself
- Better techniques of use to enhance safety
- Cost-effective "needleless" systems to protect health care personnel
- Improved laboratory tests to identify infection more accurately and rapidly, especially tracheobronchitis and pneumonia, to reduce unnecessary antibiotic therapy yet permit early therapy to avert progression to life-threatening sepsis
- Measures to restrict and improve the use of antibiotics, especially in ICUs
- Expanded, more effective approaches to education in infection control for health care personnel, especially physicians, with respect to handwashing, use of isolation, invasive devices, and use of antibiotics

ICU, *Intensive care unit.*

Modified from Maki DG. Risk factors for nosocomial infection in intensive care. "Devices vs. nature" and goals for the next decade. Arch Intern Med. *1989;149:30–35.*

General Precautions Against Biohazardous Exposure

All hospitals, as mandated by The Joint Commission,[31] must have an employee health service and written protocols for the management of biohazardous exposures (Box 47.e2).[133,576] Such protocols permit expeditious and comprehensive evaluation and timely administration of postexposure prophylaxis (PEP) with antiretrovirals after HIV exposure, immune serum globulin or hepatitis B immune globulin after exposure to hepatitis A or B, or antimicrobial prophylaxis after exposure to contagious bacterial pathogens such as Neisseria meningitidis or Bordetella pertussis.

The single greatest measure a hospital can take to reduce the risk of biohazardous exposures is to implement a comprehensive program that actively monitors occupational exposures,[577] educates HCWs about the consequences and ways to prevent exposures,[578] and advocates for and rigorously evaluates new safety technologies as a means of reducing exposures further.[579]

The importance of uncompromising compliance with universal precautions to protect HCWs from unknowing exposure to HIV and other blood-borne viruses has been discussed. Importantly, the greatest emphasis in training on universal precautions should be placed on measures to prevent needle sticks and other sharps injuries,[576] prohibition of recapping used needles, and making impervious needle disposal containers[580] available at the bedside of each ICU patient.[581] The use of engineered controls such as needleless systems holds the greatest promise for effecting a material reduction in hazardous sharps injuries.[579]

• BOX 47.E2 Guidelines for Prevention and Management of Biohazardous Injuries in the Hospital[a]

1. Hospital personnel must be made more personally aware of the potential catastrophic sequelae of sharps injuries and other biohazardous exposures and of guidelines for prevention. This must be conveyed in initial orientation programs for all new personnel, including physicians, and by periodic updates on each patient care unit and presentations at staff conferences. The topic also can be periodically reviewed in the hospital's newsletter for personnel. Prominently placed posters warning of the hazards of sharps injuries and listing simple precautions to avert such injuries, especially in areas where sharps are heavily used, also may be of value.
2. Sharps disposal units should be made widely and conveniently available throughout the hospital, especially in locations that facilitate their immediate use: in individual patient rooms, nursing stations, pharmacy units, and utility rooms; in all clinical laboratories; on anesthesia carts; and in each operating room. Receptacles should be made of impervious material such as plastic or metal and should be emptied according to an established routine by personnel who have been properly instructed in the correct procedure. Disposal units should consist of impervious receptacles into which a used needle and syringe or other sharps can be immediately dropped without handling it further. If it is necessary to remove a used needle from a syringe or Vacutainer, an instrument should always be used.
3. Recapping or resheathing of used needles must be strongly discouraged except when rare circumstances do not permit immediate disposal, in which case capping must be done using a "one-handed technique" or special sheath.
4. Medical or nursing personnel must be apprised of the importance of obtaining adequate assistance when administering injections or infusion therapy to patients who may not be able to cooperate.
5. Personnel must be apprised of the need to use extreme care in cleaning up after procedures that involve needles or other sharps, such as lumbar punctures, thoracentesis, or central venous catheter placement.
6. A strong institutional commitment to the continuous evaluation and selective adoption of technology-based approaches to prevention of sharps injuries will have the greatest impact.
7. With accidental sharps injuries, unless the injury occurred with a clean sharp not used on a patient, the injury should be immediately reported to the employee health service, where work-related injuries in general can be evaluated and managed most consistently and inexpensively and surveillance of all work-related injuries can be assisted. A mechanism to ensure prompt management of biohazardous injuries 24 hours a day (including during nights and weekends by emergency department personnel who have been trained in the institutional biohazardous injury protocol) must be available.

   All hospital personnel who render care or services to patients, including all staff physicians, house officers, and health care students, should be covered by this institutional service to ensure consistent reporting and treatment of injuries.

   Employee health service personnel should meet with each employee who sustains a biohazardous injury, ascertain the exact reason for the accident, and review how to prevent a similar injury in the future. Particular attention should be given to those health care workers who have sustained repeated injuries to identify accident-prone activities or individuals or high-risk work situations that should be modified.
8. Institutions should carry out continuous surveillance and reporting of all biohazardous injuries, which can form the basis for preventive programs and determine their effectiveness. Risk management personnel should include sharps injury reduction as a major institutional priority.
9. Management of sharps injuries: A comprehensive protocol for management of sharps injuries would be beyond the scope of these guidelines; however, it is imperative that all hospitals have a protocol that provides unambiguous guidelines for management, specifically the following:
   a. Clear definitions of biohazardous injuries
   b. Procedures for immediate care of the injury at the time of occurrence (e.g., squeezing the puncture wound to induce bleeding, disinfection with a virucidal agent, such as an iodophor)
   c. Procedures to determine expeditiously the magnitude of risk (i.e., screening the source patient for evidence of active infection by hepatitis B virus; hepatitis C virus; and human immunodeficiency virus [HIV]). With regard to HIV screening, the protocol must be in compliance with state statutes governing HIV testing.
   d. The responsibilities of the injured health care worker; the worker's supervisor; the employee health service; and, after working hours, the emergency department
   e. Guidelines for postexposure immunoprophylaxis and drug therapy, especially with exposures to the following:
      Hepatitis A, B, and C
      HIV infection
      Jakob-Creutzfeldt disease
      Syphilis
      Malaria
      Bacteremia
   f. Follow-up evaluation of the exposed health care worker, especially after exposures to HIV and hepatitis B and C virus
   g. Administrative follow-up evaluation of all injuries to minimize recurrences, and institutional surveillance of biohazardous injuries
   h. Periodic review of the protocol, with revision as indicated

[a]*The Biohazardous Exposure Protocol of the University of Wisconsin Hospital and Clinics is available from the authors on request.*

Modified and updated from McCormick RD, et al. Epidemiology of hospital sharps injuries: a 14-year prospective study in the pre-AIDS and AIDS eras. Am J Med. *1991;91:301S–307S.*

Vaccine-Preventable Diseases

Hepatitis B

Percutaneous exposure of an unvaccinated HCW to blood from a patient who is positive for hepatitis B surface antigen (HBsAg) carries considerable risk of seroconversion (23%–37%) and development of clinical disease (1%–6%).[133] This risk is greatly magnified if the source patient is hepatitis B e antigen (HBeAg) positive: the risk of seroconversion is 37% to 62%, and the risk of developing clinical disease is 22% to 31%.[133] The introduction of the recombinant hepatitis B vaccine in 1986 has greatly reduced the risk of occupationally acquired disease, and it is recommended that all HCWs receive a complete three-dose hepatitis B vaccine series.[574,582] Furthermore, ACIP recommends that all HCWs have documentation of protective serum titers (hepatitis B surface antibody [HBsAb] serum titer ≥10 mIU/mL) 1 to 2 months after completion of their primary series. Those HCWs who do not mount protective titers should be revaccinated with a second complete three-dose series, followed by HBsAb testing 1 to 2 months after the third dose.[574] HCWs exposed to hepatitis B who have not developed protective titers after a primary or secondary immunization series or who have not completed a primary immunization series should be given postexposure prophylaxis (PEP) as detailed by the U.S. Public Health Service[133] or ACIP.[574] In light of universal vaccination of all newborns, at least for those raised in the United States, the proportion of HCWs already vaccinated against hepatitis B will increase over time.

Measles, Mumps, and Rubella

Reported cases of measles, mumps, and rubella (MMR) have declined steadily in the United States since the introduction of mandatory childhood immunizations.[583–585] However, epidemics of measles and, more recently, mumps continue to be a problem in many parts of the country.[586–588] Severe measles in susceptible HCWs who themselves exposed additional patients while in the incubation phase of infection have been well described in the literature.[88,589] As a result, it is recommended that all HCWs born after 1956 have evidence of immunity to measles, mumps, and rubella by any of the following: (1) laboratory evidence of a protective titer; (2) laboratory confirmation of disease; or (3) written documentation of appropriate vaccination.[574] When nonimmune HCWs are exposed to measles, PEP with MMR vaccination has been shown to reduce the likelihood of developing fulminant disease.[574,590] Measles immunoglobulin is another PEP option for nonimmune HCWs who have a contraindication to immunization—pregnancy—but it provides only temporary protection.[574,590] When nonimmune HCWs are exposed to mumps, PEP with MMR vaccine is not recommended for prophylactic purposes because antibody response is not believed to develop soon enough to provide effective prophylaxis; however, the first dose of MMR vaccine should be offered as soon as possible.[574] PEP for rubella with vaccine or immune globulin is not effective.[574]

Varicella

Occupational acquisition of varicella-zoster virus is well described, with transmission rates among susceptible HCWs ranging from 2% to 16% in published studies.[573,591] Infected HCWs pose a threat for transmission to other susceptible patients, and HCWs, when compared with persons who acquire varicella during adolescence, often experience more severe disease,[592] particularly if pregnant.[593] All HCWs should have evidence of immunity to varicella, which includes any of the following: (1) laboratory evidence of immunity or laboratory confirmation of disease; (2) written documentation of vaccination with two doses of varicella vaccine; or (3) diagnosis or verification of a history of varicella disease or herpes zoster by a health care provider.[574,582,594] HCWs without evidence of immunity to varicella should be given two doses of varicella vaccine administered 4 to 8 weeks apart.[574,594]

HCWs, particularly if they are pregnant, without evidence of immunity to varicella should not care for patients with suspected or confirmed varicella or zoster infections.[574] In the event of an accidental exposure, HCWs without evidence of immunity to varicella should be given PEP with varicella vaccine as soon as possible, and preferably within 3 to 5 days of exposure on the basis of studies demonstrating a reduced risk of developing clinical infection and attenuated clinical disease.[574,594] For HCWs without evidence of immunity to varicella, who have been exposed to varicella or herpes zoster, and who are at high risk for severe disease and complications and for whom varicella vaccine is contraindicated (e.g., pregnant women, immunocompromised patients), varicella-zoster immune globulin is recommended as soon as possible after exposure, but can be given up to 10 days after exposure.[574,594,595]

Influenza

Influenza is responsible for 226,000 hospitalizations and 36,000 deaths in the United States each year.[596] Nosocomial outbreaks of influenza are common and put HCWs at considerable risk of acquiring and transmitting influenza to others.[574,597,598] These outbreaks impose considerable economic burden on health care institutions and increase adverse events among HCWs and patients alike.[599] Influenza immunization of HCWs has significantly reduced days of febrile illness and sick leave in randomized controlled trials,[600,601] and surveys suggest that HCWs tend to view influenza immunization as a means of protecting themselves from illness.[602,603] However, accumulating evidence suggests that influenza immunization of HCWs also significantly reduces rates of influenza-related morbidity and mortality among potentially exposed patients in a variety of health care settings.[604–606] Moreover, expanding immunization rates of HCWs has been shown to be cost-saving from an institutional perspective.[607] Despite this evidence and the recommendation that all HCWs receive annual influenza vaccination,[574] voluntary immunization rates among U.S. HCWs remain disappointingly low—in the range of 40%.[608] For these reasons, some experts are beginning to call for mandatory influenza immunization of HCWs (i.e., a condition of employment) in much the same way that hepatitis B and MMR vaccinations are mandatory for HCWs in most hospitals.[609]

Pertussis

HCWs are at increased risk of developing pertussis as a result of waning immunity in adulthood,[574,610] and numerous pertussis epidemics among HCWs have been reported in recent years.[611,612] Pertussis outbreaks are associated with considerable economic consequences,[612,613] and studies have shown that routinely providing a pertussis booster to HCWs in the form of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis adsorbed vaccine (Tdap) is cost-effective.[612] The ACIP recommends that all HCWs receive a single dose of Tdap as soon as feasible if they have not previously received Tdap and regardless of the time since their most recent tetanus-diphtheria vaccination.[574] Despite this recommendation, Tdap vaccination coverage among HCWs in the United States remains low and was only 17% in 2009.[574]

Non–Vaccine-Preventable Diseases of Major Interest

Herpetic Whitlow

Primary HSV paronychia has long been an occupational hazard of being an ICU nurse or physician[614,615] and is usually associated with a great deal of pain and discomfort, fever, and lymphadenitis. Leave from work for 2 to 3 weeks is not uncommon. One of the most compelling reasons for ICU HCWs to routinely wash their hands after contact with an ICU patient and to wear gloves during any contact with a patient's airway—including gloves on both hands during tracheal suctioning—is to protect themselves from this miserable condition.

Tuberculosis

Numerous reports of tuberculosis outbreaks in hospitals and other health care settings in the early and mid-1990s reminded the health care community of the risk associated with the care of patients with active pulmonary tuberculosis.[85–87,257] The feature common to most of these outbreaks was failure to recognize patients with active pulmonary tuberculosis. The most important measure for preventing the transmission of tuberculosis is to (1) rapidly identify and isolate patients with suspected tuberculosis and (2) promptly initiate appropriate therapy when tuberculosis is confirmed to reduce the duration of infectiousness.[616] Guidelines for the prevention of nosocomial tuberculosis have been published that stress the importance of administrative, environmental, and personal respiratory protection controls.[134] Implementation of these recommendations has led to remarkable reductions in nosocomial transmission rates.[258]

Hepatitis C

Nearly 4 million persons in the United States are infected with hepatitis C virus (HCV), which is responsible for 8000 to 10,000 deaths every year.[617] Although the already high and rising prevalence of HCV infection in the population potentially exposes HCWs to occupationally acquired infection, most studies have failed to find a higher seroprevalence to HCV among HCWs than in the general population.[618] However, at least one study found that a previous history of a needle stick injury is associated with an increased risk of HCV infection,[619] and pooled analyses of published studies suggest that the seroconversion rate after a percutaneous injury involving HCV-positive persons is about 0.5%, a risk that is similar to that seen with percutaneous injuries involving needle stick exposures to HIV.[618] Guidelines from the U.S. Public Health Service for the management of HCWs exposed to HCV recommend serologic testing and measurement of serum alanine aminotransferase levels, with or without HCV PCR testing, at baseline and again 4 to 6 months later, and do not recommend PEP with human immune globulin preparations or antiviral agents.[133] More recent guidelines from the Infectious Diseases Society of America and American Association for the Study of Liver Diseases do not recommend postexposure prophylaxis with antiviral therapy.[620] Although direct-acting antiviral-based regimens have shown very high efficacy for chronic HCV infection, there are no data regarding the efficacy or cost-effectiveness of direct-acting antiviral-based regimens for postexposure prophylaxis of HCV infection.[620] Furthermore, there is a 20% to 50% chance of spontaneous resolution of acute HCV infection; therefore monitoring HCV ribonucleic acid for at least 12 to 16 weeks is recommended to allow for spontaneous clearance, before considering starting treatment.[620]

Human Immunodeficiency Virus

Although the risk of occupationally acquired HIV infection is low, it is not zero. As of 2002, there had been 57 probable and an additional 139 possible cases of occupationally acquired HIV in the United States.[621] The vast majority involved percutaneous injuries from hollow-bore needles contaminated with blood.[618] Other types of sharps injuries are less likely to transmit HIV, and only a single documented case of occupational HIV transmission caused by a body fluid exposure other than blood—bloody pleural fluid—has been reported in the literature.[622] Although no randomized trials exist, there are considerable data from animal[623] and observational studies[624] to suggest that PEP with antiretrovirals can significantly reduce the likelihood of HIV transmission after a high-risk exposure. For this reason, the U.S. Public Health Service has issued detailed recommendations on occupational HIV PEP with the choice and number of drugs driven by characteristics of the HCW, type of exposure, and characteristics of the source patient.[625] Additionally, a PEP hotline is available through the University of California, San Francisco, Clinician Consultation Center (phone: 888-448-4911).[626]

of the ICU must be viewed with caution, and the cost-benefit and long-term effects of SDD need better clarification. The uses of simple barrier precautions to prevent colonization and infection have shown promise and warrant further study, especially in ICUs.

Universal decolonization (e.g., daily bathing with chlorhexidine) may become routine for all ICU patients. In a study involving 74,256 patients among 74 ICUs, patients were randomly assigned to one of three strategies: (1) universal decolonization (i.e., daily bathing with chlorhexidine-impregnated cloths for the entire ICU stay along with twice-daily intranasal mupirocin for 5 days), (2) targeted decolonization (i.e., MRSA nares screening and if positive, contact precautions implemented along with twice-daily intranasal mupirocin for 5 days), or (3) screening and isolation (i.e., MRSA nares screening and if positive, contact precautions implemented).[632] Universal decolonization of ICU patients was the most effective strategy and reduced positive MRSA clinical cultures, but not MRSA BSI. Universal decolonization also reduced BSIs from any pathogen.

Studies have shown that the use of dedicated IV therapy teams, consisting of trained nurses or technicians to ensure a high level of aseptic technique during catheter insertion and in follow-up care of the catheter, has been associated with greatly reduced rates of catheter-related infection and appears to be cost-effective.[346,347,633] The use of teams of trained ICU personnel to insert all urethral catheters and provide follow-up care for these catheters, all IVDs, and percutaneous tubes in the ICU deserves study.

Remarkably, there have been few comparative clinical trials of the various chemical antiseptics available for disinfecting skin before inserting IVDs or assisting in surgery or studies of antiseptic handwashing agents. Large, randomized clinical trials, ideally in multiple centers, are necessary in which infection, rather than cutaneous colonization or positive cultures, is used as the index of comparison.

Considerable evidence indicates that the material used in construction of an implanted device plays an important role in the pathogenesis of device-related infection—namely, whether the material provides an attractive surface for adherence by pathogenic microorganisms such as coagulase-negative staphylococci. Studies are necessary to delineate fully the molecular mechanisms of microbial adherence to prosthetic surfaces to develop new materials intrinsically resistant to colonization for use with implantable devices and to design devices that intrinsically deny microbial access.

Increased use of diagnostic tests has greatly increased awareness of infectious diseases. Improved laboratory techniques to identify infection more accurately and rapidly, especially methods to reliably distinguish colonization of the lower respiratory tract from early infection that merits antimicrobial therapy, could greatly reduce unnecessary antimicrobial therapy yet detect infections earlier, before they progress to sepsis with multiple-organ failure.

Antimicrobials are not used optimally in most ICUs, and there is much overuse in hospitals, particularly of extended-spectrum penicillins and cephalosporins, carbapenems, vancomycin, and fluoroquinolones. Antibiotic pressure has had a powerful effect on the hospital microbial ecology and, as noted previously, on the profile of nosocomial infection, especially in ICUs. We must and can do better.

Last, but certainly not least, many physicians remain remarkably oblivious to the most basic precepts of infection control, and nurses are in general far better informed and are a more effective force for ensuring compliance with infection control practices. More effective ways to communicate essential information on nosocomial infection control to hospital personnel, especially with regard to handwashing, aseptic use of devices, and antibiotic therapy, and to apply it more consistently in all hospitals, would have vast immediate benefits.

Key Points

- Patients in modern-day ICUs experience rates of nosocomial infection three to five times higher than non-ICU hospitalized patients. Rates of primary bacteremia and nosocomial pneumonia are up to 10 times higher.
- Patients who are severely immunocompromised or who are critically ill and have high severity of illness scores have a substantially increased risk of nosocomial infection. However, most nosocomial infections in the ICU appear causally to be most directly related to lifesaving technology, particularly invasive devices such as endotracheal tubes and mechanical ventilatory support, urethral and intravascular catheters, and intraventricular catheters, which facilitate colonization by nosocomial organisms and greatly increase vulnerability to infection.
- The major reservoir of bacterial nosocomial pathogens, and possibly Candida as well, in the ICU is the colonized or infected patient. Most infections begin with nosocomial colonization by organisms acquired from the inadequately cleaned hands of noncolonized HCWs. Increasing evidence suggests that antibiotic-resistant organisms, particularly MRSA, resistant enterococci, and C. difficile, may also be acquired from the inanimate environment immediately surrounding the patient. Some pathogens (e.g., respiratory viruses, influenza, S. pneumoniae) are spread by large droplet nuclei that travel 3 to 6 feet from the source. Other pathogens (e.g., Mycobacterium tuberculosis, varicella-zoster virus, measles), are transmitted by the airborne route.
- ICUs are uniquely conducive to the epidemic spread of nosocomial organisms of all types, especially antibiotic-resistant bacteria and even Candida; more than half of all detected hospital epidemics occur in ICUs.
- An active, visible institutional infection control program can prevent up to one-third of nosocomial infections. Surveillance of infection, whether total or focused, and education of all personnel are the most essential components of the program.
- The regular use of waterless alcohol-based handrubs or a chlorhexidine-containing agent for handwashing between patients will reduce endemic nosocomial infections in the ICU by at least 30%.
- Stringent attention to isolation precautions, especially use of disposable gloves and a gown for contacts with patients known to be infected or colonized by resistant organisms, is mandatory to minimize cross-infection and prevent outbreaks. It is essential to monitor for misuse of gloves as part of universal gloving to avoid a paradoxical increase in the risk of nosocomial infection.
- Modern-day ICUs must have adequate numbers of special negative-pressure isolation rooms for the care of patients with suspected or proven pulmonary tuberculosis and other airborne infections such as varicella-zoster virus.

- Patients who have undergone recent bone marrow transplants or who have received intensive chemotherapy and are experiencing prolonged severe granulocytopenia should receive ICU care in special HEPA-filtered positive-pressure isolation rooms to protect them from devastating deep Aspergillus and other filamentous fungal infection.
- Meticulous attention to aseptic technique and the use of maximal barrier precautions—long-sleeved sterile surgical gown, mask, and head cover, as well as sterile gloves—during the insertion of CVCs; the use of 2% chlorhexidine solutions for cutaneous antisepsis; avoiding insertion into the femoral veins when possible; and prompt removal of catheters as soon as they are no longer necessary can reduce the incidence of catheter-related BSI at least threefold.
- Several studies have demonstrated that the use of gloves for all patient contacts (i.e., universal gloving), decreases ICU infection rates, as have some studies of prophylactic use of simple barrier precautions. Universal gloving and protective isolation are more appealing ecologically than the use of SDD.
- Measures to avert needle sticks and other sharps injuries are the most important aspect of universal precautions; these measures are necessary to protect the HCWs from HIV and other bloodborne viruses.
- A crisis of antibiotic resistance exists in ICUs. The progressive increase in antibiotic resistance of nosocomial staphylococci (methicillin), gram-negative bacilli (aminoglycosides, expanded-spectrum β-lactams, and carbapenems) and enterococci (vancomycin or ampicillin), and the sixfold increase in Candida infections during the past two decades indicates that it is of highest priority to reduce antimicrobial pressure within ICUs.
- Novel technology holds the greatest promise for prevention of nosocomial infection in general, particularly the development of medical devices that are intrinsically resistant to infection.
- Identifying more effective ways to communicate knowledge of infection control to hospital personnel, especially with regard to handwashing, aseptic use of devices, and antibiotic therapy, and to apply it consistently in all hospitals would have vast immediate benefits.

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Review Questions

1. Which one of the following is most correct regarding antimicrobial stewardship?
   a. Prolonged use of broad-spectrum antimicrobials is not associated with antimicrobial resistance or Clostridium difficile infection.
   b. Only a small proportion of antimicrobial use in the intensive care unit (ICU) is either inappropriate or unnecessary.
   c. Antimicrobial stewardship programs have been shown to improve infection cure rates, reduce treatment failures, increase frequency of correct antibiotic prescribing, and decrease antibiotic resistance and C. difficile infection.
   d. Prospective audits with intervention and feedback and formulary restriction and preauthorization are not core strategies of antimicrobial stewardship.

   Answer: c. Prolonged use of broad-spectrum antimicrobial therapy is associated with antimicrobial resistance and C. difficile. It is estimated that up to 50% of antimicrobial use in U.S. acute care hospitals is either inappropriate or unnecessary. Antibiotic stewardship is defined as coordinated interventions designed to improve the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy, and route of administration. Antibiotic stewardship programs have been shown to improve infection cure rates, reduce treatment failures, increase frequency of correct antibiotic prescribing, and decrease antibiotic resistance and C. difficile infection. Prospective audits with intervention and feedback and formulary restriction and preauthorization are core strategies of antimicrobial stewardship programs.
2. Which one of the following is associated with the highest rate of device-related bloodstream infections in the ICU?
   a. Arterial catheters
   b. Central venous catheters
   c. Hemodialysis catheters
   d. Pulmonary artery catheters

   Answer: c. The highest rates of bloodstream infections are seen with the use of hemodialysis catheter (10% of patients). Arterial catheters have rates of device-related bloodstream infection in the range of only 1%. Central vein catheters in the subclavian vein or internal jugular have rates of device-related bloodstream infections in the range of 3% to 5%. Swan-Ganz pulmonary artery catheter use is associated with a 1% to 3% risk of bloodstream infections. Infection rates are associated with the use of proper sterile technique at insertion time.
3. Which of the following is a recommended strategy to reduce catheter-associated urinary tract infection (CAUTI)?
   a. Use of systemic antimicrobials to prevent CAUTI
   b. Maintaining an open drainage system
   c. Use standard precautions, including the use of gloves and gown as appropriate, during any manipulation of catheter or collecting system
   d. Keep collecting bag at level of bladder at all times

   Answer: c. Use of systemic antimicrobials are not recommended to prevent CAUTI. Maintaining a closed drainage system is key; if a break in aseptic technique, disconnection, or leakage occurs, replace the catheter and collecting system. Use of standard precautions, including the use of gloves and gown as appropriate, during any manipulation of the catheter or collecting system is recommended. It is recommended to maintain an unobstructed urine flow, including keeping the collecting bag below the level of bladder at all times, keeping the catheter and collecting tube free from kinking, and emptying the collecting bag regularly.
4. Which one of the following has the strongest causative association with ventilator-associated pneumonia (VAP)?
   a. Oropharyngeal bacteria
   b. Gastric bacteria
   c. Nasal bacteria
   d. Skin bacteria

   Answer: a. Oropharyngeal bacteria are the major source of VAP, not gastric bacteria. It does not appear that nasal bacteria independently play a significant role in the development of VAP. Other sources exist exogenously, such as bacteria brought to patients from inadequately washed hands, inadequately disinfected respiratory therapy equipment, contaminated medication vials, and inadequately disinfected nebulizers shared among patients. Aspiration of oropharyngeal bacteria into the lower respiratory tract and reduced host-defense lung mechanisms are risk factors for the development of VAP.
5. A 40-year-old male with a history of alcoholism and injection drug use presents heavily intoxicated and requires intubation for airway protection. On day 3 of mechanical ventilation he develops fever, leukocytosis, new lung infiltrates as seen on chest x-ray, and increased tracheal secretions. Which of the following is correct?
   a. He does not have VAP as he likely aspirated before intubation and has community-acquired pneumonia.
   b. The most likely organisms causing VAP at any stage are either Streptococcus pneumoniae or Haemophilus influenza.
   c. The American Thoracic Society and Society of Critical Care Medicine recommends an invasive diagnostic approach such as bronchoalveolar lavage as it has been shown to decrease mortality.
   d. If results of Gram staining of deep tracheal aspirate are negative, then the patient is unlikely to have bacterial VAP

   Answer: d. Hospital-acquired pneumonia (HAP) is defined as pneumonia that develops more than 48 hours after hospitalization. VAP is a subset of HAP and is defined as pneumonia that occurs more than 48 to 72 hours after initiating mechanical ventilation.

   Microorganisms associated with early VAP within 4 days of intubation are Streptococcus pneumoniae and Haemophilus species. The microbial spectrum shifts to nosocomial agents the longer patient is supported by mechanical ventilation and is exposed to antibiotics. Invasive diagnostic approach failed to show improved 28-day mortality and the data are inconclusive. If initial result of a Gram stain of a deep tracheal aspirate is negative, the patient is unlikely to have a bacterial VAP.
6. Which one of the following statements is most correct with regard to the use of selective digestive decontamination (SDD) in ICU patients?
   a. It increases VAPs caused by gram-positive organisms.
   b. It increases ICU mortality.
   c. It decreases the incidence of VAPs caused by gram-negative organisms.
   d. It decreases the incidence of VAPs caused by Candida species.

   Answer: b. Selective digestive decontamination (SDD) has been shown in some randomized trials to reduce the incidence of

VAP, and in one large clinical trial has shown a decrease in mortality. SDD consists of scheduled applications of non-absorbable antibiotics with activity against aerobic bacteria and yeast, such as polymyxin, tobramycin, and amphotericin B. In addition, a broad-spectrum antibiotic is administered intravenously for the first 3 days of ICU hospitalization. SDD has been shown to reduce the rate of gram-negative bacilli and in one large trial, Staphylococcus aureus infection. There has been no proven reduction in Candida species with the use of SDD.

48

Principles Governing Antimicrobial Therapy in the Intensive Care Unit

HOLLIS R. O'NEAL, CHRISTOPHER B. THOMAS, AND GEORGE H. KARAM

CHAPTER OUTLINE

Right Drug
- A Clinical Dilemma
- Clinical Responses to Multidrug Resistance
- Role of Combination Therapy
- Prevention of the Emergence of Resistance
- Increased Opportunity to Achieve Appropriate Therapy
- Properties of Antibiotics That Affect Their Usefulness in the Clinical Setting
- Penetration at the Site of Infection: Tissue-Targeted Therapy
- Special Pharmacologic Properties
- Unintended Consequences of Antibiotic Therapy

Right Time

Right Dose

Right Duration

Antibiotic Stewardship in the Intensive Care Unit

Conclusions

As medicine advances it is commonplace for older drugs to be replaced by newer ones. Often, the newer drug may have more potency, a more desirable dosing schedule, or a better side effect profile. The usual scenario is that the "old" drug still works, but the "new" ones work better. This is not always the case with antibiotics; antibiotics often evolve because the old drugs cease to work—the microorganisms targeted by these agents evolve, often through repeated exposure, to evade the effect of these medications. The result of this frequent exposure of microorganisms to antibiotics, and the ability of the microorganisms to become resistant to the effects of these medications, has created a crisis in the field of infectious diseases—we cannot keep up with the pathogens' ability to evade our weapons. Indeed, the problem is in many ways self-inflicted, caused by misuse and overuse of antimicrobials. As Dr. Art Wheeler, the late director of the Vanderbilt Medical Intensive Care Unit (ICU) and pioneer in critical care medicine, once said while conducting rounds, "There are only two classes of drugs that, when you give them, have the potential to affect not only the patient you give them to, but also all of the other patients and providers that they will contact: radiotherapeutics and antibiotics." The intent of this chapter is to help readers develop an understanding of antibiotic resistance and provide the framework for an effective, responsible process for the use of this invaluable class of medications.

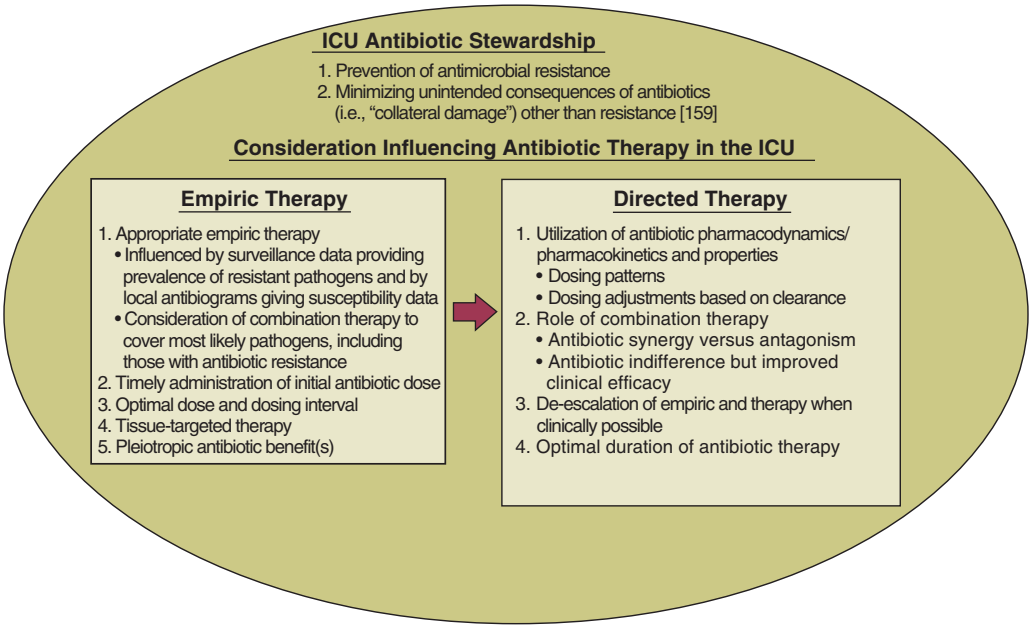
In the critical care setting, antibiotic selection typically entails a two-stage process: empiric therapy, followed by de-escalation to directed, definitive therapy upon identification of the pathogen. Fig. 48.1 illustrates this progression in antibiotic therapy and summarizes some principles that contribute to the goal of achieving optimal efficacy while attempting to preserve the antibiotic armamentarium—the components of antibiotic stewardship. A challenge for the critical care physician is to recognize that antibiotic therapy for the critically ill may ultimately affect that unit's microbiome. If antibiotic-resistant organisms or organisms with certain virulence factors are selected by a pattern of antibiotic use, those pathogens can become part of the ICU's ecology and affect other patients. The 2016 update[1] of the 2007 inaugural Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America joint guideline for the development of an institutional program to enhance antimicrobial stewardship behavior[2] reiterates the challenge of coordinating interventions to improve and measure the appropriate use of antimicrobial agents.

Four focuses of antibiotic prescribing are of primary importance in both the clinical and public health context: the right drug, the right time, the right dose, and the right duration.[3] In acknowledgment of this mandate, this chapter focuses on the elements of antibiotic stewardship that pertain to antibiotic prescription in ICUs. Practitioners must combine antibiotics with infection prevention for it to be optimally effective. Such a combination of philosophical priorities results in an approach to antimicrobial therapy that is collaborative and multidisciplinary. Awareness of such factors is important in the development of the knowledge base regarding adequate antibiotic therapy and its effect on not only morbidity and mortality but also the hospital ecology.

Right Drug

A Clinical Dilemma

Often in clinical medicine, there are life-threatening infections for which there are not definitive data to guide the selection of optimal therapy. Representative examples are hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), in which gram-negative bacteria are frequently the etiologic agents. The



• **Fig. 48.1** Considerations influencing forms of therapy in the intensive care unit *(ICU)*. Several principles influence antibiotic prescription for an individual patient, first in empiric and then in directed therapy. Antibiotic selection at all times occurs within the context of the entire intensive care unit, raising principles relevant to antibiotic stewardship that may conflict or compete with those influencing antibiotic prescription.

most recent iteration of the clinical guideline for treating HAP and VAP[4] acknowledged the varied treatment options for covering gram-negative bacteria. The authors identified 29 randomized controlled clinical trials comparing different gram-negative regimens for empiric treatment of VAP, including regimens that included carbapenems, cephalosporins, antipseudomonal penicillins, aminoglycosides, quinolones, aztreonam, and tigecycline, with these agents given either alone or in combination. Individually, none of these trials reported significant differences in clinical response or mortality rates between comparator arms with the exceptions of tigecycline[5] and doripenem,[6] which were both associated with worse outcomes. In the absence of definitive data from the trials, the authors performed a series of meta-analyses comparing each class of antibiotics against all other classes to determine whether any class of antibiotics might be superior to another. They reached no definitive conclusion about a gold standard antibiotic for the treatment of HAP or VAP. The absence of definitive data directing antibiotic therapy for these and many other serious infections in the ICU is emblematic of the challenge for the intensivist. Several variables influence decisions about selection of the "right drug," including the microbiology of antibiotic-resistant organisms and the pharmacology of the antimicrobial agents used to treat infections. A basic understanding of the mechanisms of resistance and the organisms that express them can lead to more effective empiric therapy and a more efficient de-escalation process.

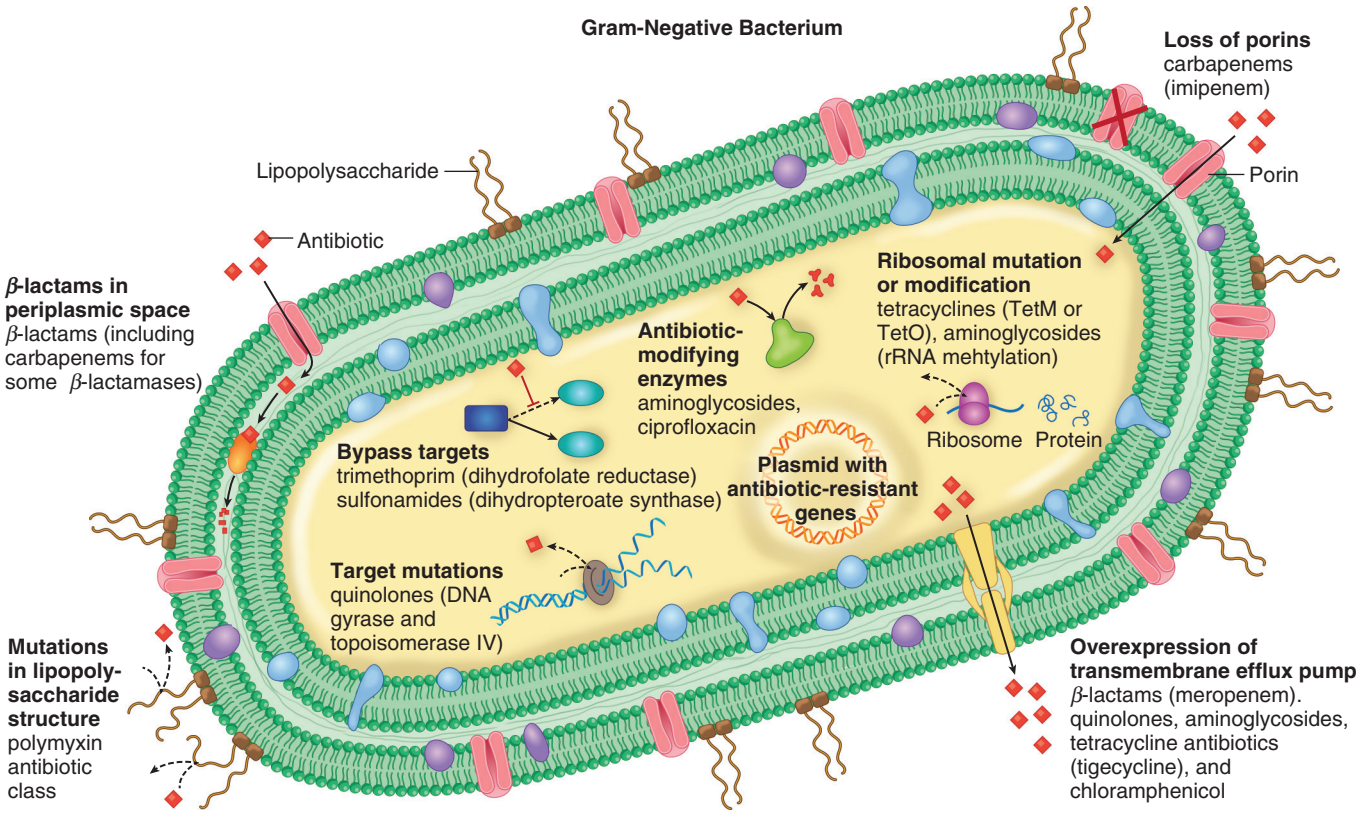
Clinical Responses to Multidrug Resistance

Antibiotic resistance leads to delays in appropriate antibiotic therapy and subsequent treatment failure.[7] Furthermore, in studies addressing increased mortality rates associated with inadequate initial antimicrobial therapy for serious infections,[8–13] antimicrobial resistance is a frequent reason for initially selecting an ineffective antibiotic. Trouillet and colleagues evaluated the risk factors for resistance in patients with VAP[14]; the most important of those were use of antibiotics within the past 15 days and mechanical ventilation of at least 7 days. When these two parameters were used in subcategories to evaluate the predisposition for selecting resistant organisms, antibiotic use was a more influential factor than was mechanical ventilation. This fact highlights the dual role that antibiotics play in the ICU: (1) treatment of infection and (2) potential selection of resistant organisms. The challenge for the clinician is to achieve the appropriate degree of balance between these two opposing effects.

The understanding of the development of clinical resistance is evolving. Research has shown that intermittent antibiotic exposures lead rapidly to the evolution of tolerance—the ability to survive under treatment without developing resistance. Using in vitro evolution experiments, investigators have shown that tolerance usually precedes resistance, with mathematical population genetics modeling showing that tolerance boosts the chances for resistance mutations to spread in the population.[15] With these experiments has come a better understanding of the sequential role that antibiotics can have to first lead to tolerance mutations that then pave the way for the rapid subsequent evolution of resistance. Such knowledge provides insight into the impact of antimicrobial exposure on bacterial ecology. Clinical implications of this include the importance of minimizing unnecessary broadness and duration of antibiotic therapy.

Mechanisms of Action and of Resistance

Fig. 48.2 depicts the mechanisms by which bacteria become resistant to antibiotics[16]; Table 48.1 summarizes these mechanisms for specific classes of antibiotics.[17] Fundamentally, an antibiotic must bind to a target site to affect its action and kill the microorganism. As examples, β-lactams, which prevent synthesis of the bacterial cell wall, bind to penicillin-binding proteins (PBPs) located on the inner membrane of the cell wall, whereas fluoroquinolones, which



• **Fig. 48.2** The mechanisms by which bacteria become resistant to antibiotics. (From Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med.* 2010;362:1804–1813.)

TABLE 48.1 Mechanisms of Resistance in Antibiotic Classes Used to Treat Resistant Pathogens

	Permeability[a]	Enzymatic Destruction	Altered Binding Sites	Efflux[b]
β-Lactams[c]	✓ (including porin channel closure with carbapenems)	β-Lactamases	Penicillin-binding proteins	✓
Fluoroquinolones[d]	✓	Described, but not a classic resistance mechanism for quinolones[e]	• Alterations in DNA gyrase and topoisomerase IV • Protection by plasmid-mediated Qnr protein	✓
Aminoglycosides[f]	✓	Adenolating and acetylating enzymes	30S ribosomal subunit	✓
Tetracyclines[g]	✓	Modification enzymes	70S ribosomal subunit	✓

[a]Delcour AH. Outer membrane permeability and antibiotic resistance. *Biochim Biophys Acta.* 2009;1794:808–816.
[b]Poole K. Efflux-mediated antimicrobial resistance. *J Antimicrob Chemother.* 2005;56:20–51.
[c]Jacoby GA, .Munoz-Price LS. The new beta-lactamases. *N Engl J Med.* 2005;352:380–391.
[d]Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. *Ann N Y Acad Sci.* 2015;1354:12–31.
[e]Jacoby GA. Mechanisms of resistance to quinolones. *Clin Infect Dis.* 2005:41(suppl 2):S120–S126.
[f]Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM, Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother.* 1999;43:727–737.
[g]Grossman TH, Starosta AL, Fyfe C, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. *Antimicrob Agents Chemother.* 201;56:2559–2564.

prevent replication of the genetic elements required for bacterial replication, bind to DNA gyrase located within the cytoplasm. To reach its target site, an antibiotic must penetrate the outermost part of the bacterial cell wall; thus impermeability precludes the drug from getting to its target site. Once an antibiotic enters the bacterial cell wall, but before it binds to its target site, there are two potential mechanisms by which the bacteria can prevent the antibiotic from achieving its effect: (1) enzymatic destruction of the antibiotic and (2) extrusion of the drug from the bacteria via efflux pumps. Because of the importance of enzymatic destruction and of efflux that leads to the drug resistance encountered in the critical care setting, these two mechanisms of action are discussed in some detail; however, it is important to consider the importance of target-site binding and of impaired penetration because both mechanisms of resistance have practical implications for the clinician.

Binding to a Target Site

Although there are multiple sites to which antibiotics bind and exert their action, probably the most relevant in clinical practice is the binding of β-lactam antibiotics to PBPs. PBPs are enzymes on the cytoplasmic membrane that play a role in the synthesis of the peptidoglycan cell wall. When bacteria have alterations in their PBPs such that antibiotics (typically a β-lactam) can no longer bind to that site, the organism demonstrates resistance to that antibiotic.

In clinical medicine, the two most important examples of resistance mediated via altered PBPs are methicillin resistance in *Staphylococcus aureus* (MRSA) and penicillin resistance in *Streptococcus pneumoniae*. The clinical significance of this mechanism is best represented by a relatively common practice. Assume that a patient has an infection presumed to be caused by *S. pneumoniae* that is unresponsive to penicillin. An uninformed practice pattern is the addition of a β-lactamase inhibitor like clavulanic acid to a drug like amoxicillin as the next agent used in an attempt to treat that infection. Because the resistance in penicillin-resistant *S. pneumoniae* is not via β-lactamase production but via altered PBPs, the β-lactamase inhibitor adds no benefit. Alternatively, a higher dose of penicillin might overcome the problem of decreased affinity of the PBPs and improve efficacy of the drug.

Although classically described with resistance in gram-positive bacteria, alterations in certain PBPs occur with some gram-negative bacteria, such as certain carbapenem-resistant strains of *Acinetobacter baumannii*.[18] The β-lactamase inhibitors (i.e., sulbactam, clavulanic acid, tazobactam, avibactam, and vaborbactam) rarely have primary activity against bacteria. The exception to this tenet is the intrinsic activity of sulbactam against *A. baumannii* that occurs on the basis of sulbactam binding to PBPs.[19] Even though the U.S. Food and Drug Administration (FDA) has not approved the compound for such use, some clinicians include sulbactam in certain antibiotic regimens in an attempt to provide coverage against resistant strains of *Acinetobacter*.

Penetration Through the Bacterial Cell Wall

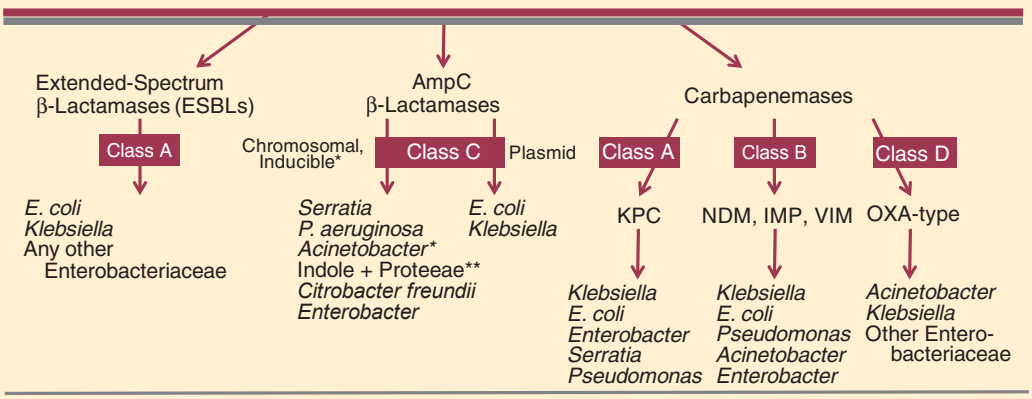
An antibiotic must penetrate the bacterial cell wall to reach its target binding site. Representative examples of resistance caused by altered permeability of the bacterial cell wall include the outer membrane impermeability of *Stenotrophomonas* to β-lactam antibiotics and the inner membrane impermeability that is the basis for aminoglycoside resistance.[20]

One route that can be used by certain antibiotics is through trimers of proteins in the cell wall referred to as porins. Normally a point of access for nutrients into the bacteria and excretory products out of the bacteria, antibiotics, most notably carbapenems, use porin channels as the route of entry. When an organism becomes deficient in these porins, the dependent antibiotics are not able to enter the bacteria, thus resulting in resistance to these agents. The most important example of resistance mediated by porin channel closure is the resistance of *Pseudomonas aeruginosa* to carbapenems.

Enzymatic Degradation

Enzymatic degradation of antibiotics is one of the most widespread and variable mechanisms of antibiotic resistance available to microorganisms. The classic example of resistance by enzymatic destruction is the cleaving—and subsequent inactivation—of β-lactam antibiotics by the β-lactamase family of enzymes. These enzymes are capable of cleaving the four-membered β-lactam ring that is common to all the β-lactam antibiotics (i.e., penicillins, cephalosporins, carbapenems and monobactams) as well as certain β-lactamase inhibitors (i.e., clavulanic acid, sulbactam, and tazobactam). This family of enzymes is large and diverse; Table 48.2 outlines a conceptual approach to this mechanism of resistance. Because countless β-lactamase enzymes exist, clinicians must use a clinically relevant classification system. The Ambler classification divides β-lactamase enzymes into four distinct classes (i.e., Ambler classes A, B, C, and D) based on their molecular structure.[21] In this scheme, classes A, C, and D have serine bases whereas class B has a metallobase. This system can be further simplified to consider three types of β-lactamases with

TABLE 48.2 A Clinical Approach to Gram-Negative Resistance Caused by β-Lactamases[a]



KPC, Kiebsiella pneumoniae carbapenemase; *NDM,* New Delhi metallo-β-lactamase; *IMP,* active on imipenem; *OXA*, oxacillinase; *VIM,* Verona integron-encoded.

[a]Based on the Ambler classification (i.e., classes A, B, C, and D) of β-lactamases and using the most likely pathogens (not an all-inclusive listing). Serine-based β-lactamas: classes A, C, and D; metallo-based β-lactamases: class B.

[b]AmpC β-lactamase of *Acinetobacter* is not inducible and therefore is less important for resistance in *Acinetobacter*.

[c]The Proteeae tribe of Enterobacteriaceae is composed of three genera of gram-negative organisms: *Proteus* (*P. mirabilis*, *P. vulgaris*, and *P. myxofaciens*); *Morganella* (*M. morganii*); and *Providencia* (*P. rettgeri*, *P. stuartii*, and *P. alcalifaciens*). Of these indole-positive organisms, *M. morganii*, *P. rettgeri*, and *P. stuartii* produce inducible, chromosomal AmpC β-lactamase and have been described as causing systemic infections, including bacteremia. From Kim BN, Kim NJ, Kim MN, et al. Bacteraemia due to tribe Proteeae: a review of 132 cases during a decade (1991–2000). *Scand J Infect Dis.* 2003;35:98–103.

relevance to clinical medicine: (1) extended-spectrum β-lactamases (ESBLs), (2) AmpC β-lactamases (which are class C β-lactamases, also referred to as a type 1 enzyme), and (3) carbapenemases.

Extended-Spectrum β-Lactamases

An increasingly common problem facing clinicians and clinical microbiologists is the presence of ESBLs produced by such pathogens as *Klebsiella*, *E. coli*, *Enterobacter*, and *Proteus*. First described in the 1980s, these enzymes may occur on the basis of a change of only one amino acid in the β-lactamases these pathogens normally produce.[22] The use of any of several classes of antibiotics, notably third-generation cephalosporins and fluoroquinolones, appears to be a risk factor for selecting ESBLs.[23,24]

ESBLs are not chromosomal; rather, they are carried on large plasmids that may contain genetic material that conveys resistance to many classes of antibiotics. For example, the resistance genes for aminoglycosides may be located on the same plasmid as those encoding an ESBL. As a result, gentamicin and tobramycin resistance often occurs in ESBL producers.[25] With fluoroquinolones, multiple mechanisms may contribute to quinolone resistance in ESBL producers. Topoisomerase mutations (i.e., target modification) may be associated with decreased binding. The *qnr* gene codes for a protein that wraps around DNA gyrase, thereby preventing quinolones from attaching to target binding sites.[26,27] In addition, ESBL-producing organisms may possess efflux pumps, and because fluoroquinolones are subject to extrusion from bacteria by means of these pumps, efflux is a potential mechanism of quinolone resistance in ESBL producers.[28]

In the early years after their discovery, ESBL-producing organisms typically occurred in either hospitalized patients or in those who had been exposed to antibiotics. The early 2000s saw ESBL infections occurring in community hospital and antibiotic-naïve, patients,[29] with about 35% of infections caused by ESBL-producing organisms occurring in patients who had no previous health care contact.[30] With the awareness of community ESBL infections came increased identification of specific types of ESBLs (e.g., the enzyme CTX-M, which refers to a cefotaximase that was initially identified in Munich, Germany) occurring predominately in isolates of *Escherichia coli* from community urinary specimens.[31] Jacoby and Munoz-Price suggested an explanation for why infection with ESBL-producing pathogens might originate in the community setting in patients without the risk factors for either selective antibiotic pressure or person-to-person spread of the organism.[25] Genes for CTX-M–type enzymes are found on the chromosome of *Kluyvera*, a genus of rarely pathogenic commensal organisms found in the gastrointestinal tract. It was postulated that pathogenic organisms such as *E. coli* obtained CTX-M–type enzymes by plasmid acquisition from these commensals with which they have close proximity in an environmental reservoir (e.g., the gastrointestinal tract). The awareness of such a trend for community-acquired resistant pathogens may influence the initial empiric therapy of patients with either a gastrointestinal or urinary tract source of infection who present ill enough to require ICU admission.

Although infection with ESBL-producing organisms has been associated with significant clinical consequences, no definitive recommendations exist for how to optimally treat such infections, and, at the time of writing this chapter, no antibiotic on the market has an FDA-approved indication specifically for treating infections caused by ESBL-producing pathogens. The reviews by Jacoby and Munoz-Price[25] and by Paterson and Bonomo[22] list carbapenem as a drug of choice for infections caused by ESBL-producing pathogens. Influencing this recommendation are the facts that ESBL-producing pathogens are often resistant to fluoroquinolones and aminoglycosides and that carbapenems, although β-lactam agents, are paradoxically stable in the presence of ESBLs.

An unanswered question is whether noncarbapenem therapy might be appropriate for some patients, such as those with severe, community-acquired infections requiring ICU admission, for both empiric and definitive therapy. A Spanish post hoc analysis addressed this question using patients from six published prospective cohorts with bloodstream infections due to ESBL-producing strains of *E. coli*,[32] with most of these infections originating from the urinary tract. These results suggested amoxicillin/clavulanic acid and piperacillin/tazobactam to be suitable alternatives to carbapenems for treating patients with bloodstream infections caused by ESBL-producing *E. coli* if the isolate was susceptible in vitro to these agents. The review did not suggest an optimal management of ESBL-producing *E. coli* bloodstream infections originating outside the urinary tract and of infections caused by ESBL-producing pathogens other than *E. coli*.

A retrospective, propensity-matched analysis of monomicrobial bacteremia caused by ESBL producers at two medical centers between May 2002 and August 2007 compared outcomes of patients who received definitive therapy with cefepime to those who received definitive therapy with a carbapenem. All patients who received cefepime had sensitive isolates based on the Clinical and Laboratory Standards Institute (CLSI) breakpoint for cefepime that was current for the time (8 μg/mL). Using that susceptibility breakpoint, investigators found definitive therapy with cefepime to be inferior to carbapenem therapy for the primary endpoint of 30-day crude mortality.[33]

In 2010, which was subsequent to the publication of this article,[33] CLSI lowered the susceptibility breakpoint for cefepime to <2 μg/mL. After the breakpoint change, a clinical analysis compared the outcomes of therapy against ESBL-producing Enterobacteriaceae based on the pharmacokinetic/pharmacodynamic properties of cefepime and piperacillin/tazobactam.[34] The authors concluded that standard-dose cefepime was a reasonable option for the definitive therapy of invasive infections resulting from ESBL-producing *E. coli* and *Klebsiella* species with minimal inhibitory concentrations of (MICs) ≤2 μg/mL or less, which now defined susceptibility.

Based on the antimicrobial stewardship principle of heterogeneity as a means of minimizing the emergence of bacterial resistance and the lack of prospective data defining optimal therapy for infections caused by ESBL-producing organisms, many experts have focused on potential alternatives to carbapenems as "a drug of choice" for such infections.

In a perspective article, Harris et al. suggested potential roles for β-lactam/β-lactamase inhibitor combinations (BLBLIs) in the treatment of ESBL infections in the following settings: in the urinary tract, in a nonurinary site if the isolate has a low MIC, and when source control has been achieved.[35]

A multinational, retrospective cohort study by Gutiérrez-Gutiérrez et al. showed that BLBLIs, if active in vitro, appear to be as effective as carbapenems for empiric and definitive bloodstream infection caused by ESBL-producing Enterobacteriaceae, regardless of source and specific species, if used at appropriate doses.[36] Bassetti et al. proposed that the best alternative to carbapenems for the treatment of ESBL infections may be BLBLIs, specifically piperacillin/tazobactam, if the MIC of the ESBL-producing pathogen is 16.4 μg/mL or less.[37]

The conclusions of these studies suggesting a potential role for a noncarbapenem regimen for the treatment of infections caused by ESBL-producing organisms are consistent with the 2016

guidelines by the IDSA and the American Thoracic Society (ATS) for the management of adults with HAP and VAP.[4] In those guidelines the authors acknowledged that their synthesis of the evidence failed to identify an agent that is clearly preferable to others in the treatment of HAP/VAP caused by ESBL-producing gram-negative bacilli; the panel therefore did not recommend a preferred antibiotic regimen for patients with confirmed HAP/VAP caused by ESBL-producing gram-negative bacilli.

A concern is whether use of agents such as a penicillin combined with a β-lactamase inhibitor might select for patterns of resistance other than ESBLs. In a matched case-control study from Singapore in which 203 cases of carbapenem-resistant Enterobacteriaceae infection or colonization were matched with 203 controls, the most common resistance enzymes were New Delhi metallo–β-lactamase 1 (NDM-1, in 44.4% of isolates), *Klebsiella pneumoniae* carbapenemase (KPC, 39.9%), and oxacillinase-48 (OXA-48, 7.8%).[38] Penicillin antibiotics were among the risk factors demonstrated by multivariate analysis to be an independent risk factor for carbapenem-resistant Enterobacteriaceae colonization or infection. With the increasing prevalence of OXA-48 β-lactamases in carbapenem-resistant *K. pneumoniae*, it is important to be aware about whether one pattern of antibiotic use (for example, use of a carbapenem-sparing regimen to treat infection by ESBL-producing bacteria) might predispose to a different pattern of resistance (such as OXA-48–producing Enterobacteriaceae infection).

The MERINO trial was an international multicenter open-label non-inferiority randomized controlled trial of piperacillin-tazobactam versus meropenem for the definitive treatment of bloodstream infections caused by third-generation cephalosporin non-susceptible Escherichia coli or Klebsiella spp. The trial enrolled 378 patients from 32 sites in 9 countries. The study, in which the primary outcome was mortality at 30 days after randomization, was prematurely terminated based after the third interim analysis by the data safety monitoring board, and the preliminary findings were reported at the 2018 European Congress for Clinical Microbiology and Infectious Diseases.[38a] More than 50% of the enrolled patients had healthcare-associated infections. The urinary tract most common site (60.9% of patients), and E. coli was the most common organism (86.5% of patients). There was a statistically significant difference in mortality rate in patients treated with piperacillin-tazobactam (23 patients, 12.3%) compared with meropenem (7 patients, 3.7%). There was no difference between the two groups regarding subsequent infections of drug-resistant bacteria or C. difficile.

An alarming trend in the worldwide epidemic of antibiotic resistance has been the increasing prevalence of carbapenem-hydrolyzing β-lactamases that coexist with ESBLs. A clinical report described a group of infections caused by *Klebsiella* spp. in which 45% of *K. pneumoniae* strains produced ESBLs, with 3.3% of the strains carrying KPC-2 carbapenem-hydrolyzing enzymes.[39] To investigate this outbreak, the investigators studied the prior antibiotic exposure in the patients from whom these KPC-2 enzymes were isolated. Most had received a β-lactam or fluoroquinolone, but only 20% had received a carbapenem. These findings have clinical relevance not only because of shared risk factors for both ESBL- and carbapenemase-producing organisms but also because of the coexistence of multiple mechanisms of bacterial resistance in the same patient.

A clinically relevant consideration in the selection of therapy for infections caused by ESBL-producing bacteria is whether the antibiotic has activity against *Pseudomonas aeruginosa*, which is not an ESBL-producing pathogen. The antimicrobial principle in such a situation is to avoid the collateral damage that may result by selecting resistant strains of *P. aeruginosa*. To pursue such a pseudomonal-sparing strategy (which is not accepted by all infectious disease specialists as a means of preventing resistance), the clinician may divide the carbapenems into two categories: those that have activity against *P. aeruginosa* (i.e., imipenem, meropenem, doripenem) and the one that does not (i.e., ertapenem). Incorporating the data from Sanders and Sanders, the selection of resistant strains of *P. aeruginosa* occurs when a spontaneously mutated antibiotic-resistant colony proliferates because the antibiotic kills sensitive, nonmutant organisms.[40] Although numerous references regarding antibiotic selective pressure leading to drug-resistant *P. aeruginosa* have been published, two publications are representative of how a process might be favored by pseudomonal-active antibiotics.

In a 2-year case-control study of 2613 patients admitted to three ICUs in a large teaching hospital in Paris, France, prolonged receipt of antibiotics with specific antipseudomonal activity, most notably ciprofloxacin, was associated with the emergence of multidrug-resistant (MDR) *P. aeruginosa*.[41] The authors concluded that if treatment with an antibiotic active against gram-negative bacteria is needed, agents with little antipseudomonal activity should be preferred over those with specific antipseudomonal activity to limit the emergence of MDR *P. aeruginosa*. Using data from 779 isolates of carbapenem-resistant *P. aeruginosa*, Carmeli and colleagues showed by univariate analysis that the risk factors for isolation of carbapenem-resistant *P. aeruginosa* were receipt of group 2 carbapenems (imipenem, meropenem) ($P < 0.0001$), aminoglycosides ($P = 0.034$), or penicillins ($P = 0.05$).[42] They found no association between group 1 carbapenem (ertapenem) use and resultant imipenem-resistant *P. aeruginosa* ($P = 0.2$).

There have been theoretical concerns that use of an agent like ertapenem might select for strains of carbapenem-resistant *P. aeruginosa*. Ecologic studies conducted over the first 9 years that ertapenem was on the market specifically addressed this concern, and Nicolau et al. published those results in a review on the topic.[43] Results from the 10 clinical studies evaluating the effect of ertapenem use on the susceptibility of *Pseudomonas* to carbapenems uniformly showed that ertapenem use did not result in decreased *Pseudomonas* susceptibility to the antipseudomonal carbapenems.

AmpC β-Lactamases (Type 1)

The clinically representative list of organisms producing AmpC β-lactamase is included in Table 48.2. Unlike the plasmid-mediated ESBL, AmpC (sometimes referred to as type 1) β-lactamases are most often chromosomally mediated, with the product of the *ampC* gene (hence the term AmpC β-lactamases) being the prototypical enzyme. On occasion, however, AmpC β-lactamase production can be plasmid mediated. As acknowledged in Table 48.2, AmpC β-lactamase production is inducible in most of the bacteria capable of producing this enzyme; however, there are some bacteria (most notably, *Acinetobacter* as a producer of chromosomally mediated AmpC enzyme and *E. coli* as an example of plasmid-mediated AmpC enzyme) in which AmpC β-lactamase production is noninducible.[44] This latter fact explains why AmpC β-lactamase is not a classic mechanism of antibiotic resistance in *Acinetobacter*. According to data from the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance system, these organisms account for 13% to 40% of nosocomial infections involving blood, surgical site, urine, and lung.[45] Even though the listed pathogens do not always produce AmpC enzymes, the potential exists and the clinician must consider it when selecting empiric therapy.[46] Because AmpC β-lactamases have an affinity for cephalosporins

(and have therefore been referred to by some authors as cephalosporinases), third-generation cephalosporins are not predictably stable in the their presence.[47] Also lacking consistent stability are the BLBLIs (i.e., sulbactam, clavulanic acid, and tazobactam).

Exposure to specific antibiotics may influence a microorganism's ability to produce AmpC β-lactamases. Two mechanisms have been described by which this occurs: (1) induction and (2) the selection of spontaneous mutant strains (previously referred to as stable de-repression). Sanders and Sanders explored the property of induction when they performed an investigation in which they incubated an organism with the potential to produce AmpC β-lactamases overnight in the presence of antibiotic.[40] After this incubation, they performed an assay for AmpC β-lactamase. If they subsequently detected the enzyme, they described the process as induction. They identified cefoxitin, imipenem, and clavulanic acid as strong inducing β-lactams. Of note, upon removal of the inducing antibiotic, the β-lactamase production ceased before the next dose of drug was due to be given. The investigators thus described induction as a reversible in vitro phenomenon. Since the description of induction as an in vitro phenomenon, no definitive evidence has accumulated demonstrating that induction in gram-negative organisms leads to clinically significant resistance in patients; however, the *ampC* gene product can lead to alarming resistance patterns through another mechanism.

The selection of spontaneous mutant strains of bacteria has been proven to occur in the clinical setting. Organisms that possess the *ampC* gene possess complex regulatory mechanisms that prevent overexpression of the gene; however, a certain number of bacteria within clinical isolates (often in the 10^{-6} to 10^{-7} range) will have spontaneous mutation(s) that can allow them to overproduce AmpC β-lactamase.[40] Upon exposure to certain broad-spectrum antibiotics, the wild-type organisms die; however, the mutant strains proliferate to become the predominant organisms, clinically manifesting as a resistant strain. Most notable of the antibiotics described to select these "stably de-repressed" mutants are the third-generation cephalosporins.[48,49]

In the overwhelming majority of instances with gram-negative organisms, antibiotics do not cause induction of resistance, but rather certain antibiotics efficiently kill susceptible organisms while leaving resistant mutants to proliferate, thereby selecting the resistant microbes to flourish. This process of selection, not induction, is the basis for most of the resistance encountered in the clinical setting. Thus when clinicians suspect infection with organisms capable of producing AmpC β-lactamase, they should avoid certain antibiotics that are not only good substrate for the product enzymes but also efficiently select these mutants. In the critical care setting, two clinical lessons regarding AmpC β-lactamases are important.

In a five-center prospective trial that evaluated the therapy of *Enterobacter* bacteremia, the development of resistance of *Enterobacter* isolates during therapy with an extended-spectrum (i.e., third-generation) cephalosporin to which the organism was initially susceptible was 19%, in contrast to no significant development of resistance of those *Enterobacter* isolates treated with other β-lactam antibiotics.[48] This example of selection of resistance during therapy is representative of the concept that in vitro susceptibility is not always predictive of in vivo outcome. Resultant from this knowledge is the practice of avoiding third-generation cephalosporins for the treatment of *Enterobacter* bloodstream infections, even when the isolate is initially susceptible, because of the propensity of these antibiotics to select for strains of *Enterobacter* that have the spontaneous mutation that allows for their expression of AmpC β-lactamase.

A second example is *P. aeruginosa,* which possesses three chromosomally mediated mechanisms of resistance: (1) AmpC β-lactamases, (2) efflux pumps, and (3) outer membrane porin alterations.[50,51] Until recently, there was no single β-lactam antibiotic stable in the presence of all three of these mechanisms of resistance. Ceftolozane is a new cephalosporin that is structurally similar to ceftazidime but differs from it by a modification that allows increased antipseudomonal activity as well as activity against some extended-spectrum β-lactamase–producing strains. Importantly, ceftolozane is stable in the presence of all three of the chromosomally mediated resistance mechanisms in *P. aeruginosa.* For clinical use, ceftolozane is combined with tazobactam. Although the addition of the β-lactamase inhibitor does not increase the antipseudomonal activity of ceftolozane, it does significantly enhance the coverage of Enterobacteriaceae isolates that produce extended-spectrum β-lactamases.[52]

The randomized, double-blind, phase II trial (ASPECT-cUTI) compared a combination of ceftolozane and tazobactam with levofloxacin in the treatment of complicated urinary tract infections, including pyelonephritis.[53] In that trial, ceftolozane/tazobactam led to better responses than high-dose levofloxacin. Of the patients in the microbiologic modified intention to treat population, *P. aeruginosa* was the pathogen in only 23 (2.9%) of the 800 patients with pyelonephritic. Another prospective, randomized, double-blind, phase III trial (ASPECT-cIAI) compared ceftolozane/tazobactam given in combination with metronidazole to meropenem in the treatment of complicated intra-abdominal infections.[54] Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem. Of the 806 patients in the microbiologic modified intention to treat population, 72 (8.9%) had infection with *P. aeruginosa*. Susceptibility rates of *P. aeruginosa* to ceftolozane/tazobactam and meropenem were 98.6% and 89.9%, respectively. At the present time, clinical trials are under way to assess the role, if any, that ceftolozane/tazobactam will have in pulmonary infections, including those that may cause critical illness.

Carbapenemases

Carbapenemase is the name used for those β-lactamases that have the ability to inactivate carbapenems, which is the broadest class of antimicrobial agents currently available. The name *carbapenemase* has the potential to be misleading. In an insightful discussion of carbapenemases, Queenan and Bush acknowledged that KPC carbapenemases hydrolyze β-lactams of all classes, with the most efficient hydrolysis observed for nitrocefin, cephalothin, cephaloridine, benzylpenicillin, ampicillin, and piperacillin.[55] The same enzyme also hydrolyzes the carbapenems imipenem and meropenem, as well as the β-lactam antibiotics cefotaxime and aztreonam, albeit 10-fold less efficiently than the penicillins and early cephalosporins. Simply stated, the carbapenemases have a broad hydrolysis spectrum that includes most β-lactam antibiotics.

The carbapenemases are as diverse in structure as they are in substrate, having members in three of the four Ambler classes of β-lactamases. An example from clinical practice of a class B metalloenzyme is the NDM found in certain Enterobacteriaceae. After the identification of metallo–β-lactamases, microbiologists began identifying serine-based β-lactamases capable of hydrolyzing carbapenems in Ambler group A (which is the same class in which the majority of ESBLs are found). These enzymes were produced by *K. pneumoniae* and were subsequently referred to as KPCs. Although there are also class D serine-based carbapenemases such as the OXA-type enzymes produced by organisms like Enterobacteriaceae and *Acinetobacter* species, the class A and class B

carbapenemases are most frequently discussed today in clinical practice. With this understanding, the clinician can begin to approach the role of antibiotics in selecting for organisms that produce carbapenemases.

A common assumption is that carbapenem antibiotics are the most likely to select for resistance owing to carbapenemase production. Although not definitively proven, multiple reports in the literature support the conclusion that several classes of antibiotics may result in subsequent infection with carbapenemase-producing bacteria. The most consistent risk factors that lead to the selection of carbapenemase-producing bacteria are not the class of antibiotics being used (since multiple classes of antibiotics other than carbapenems have been associated with the selection of carbapenemase-producing gram-negative bacteria); rather, it is the intensity of the antimicrobial therapy and the duration of therapy.[56,57]

In the absence of the identification of a specific class of antibiotics responsible for selecting carbapenemase-producing bacteria, efforts to identify other variables that contribute to the problem are underway. Two representative articles provide insight into the association between prior antimicrobial therapy and the subsequent identification of carbapenemase-producing bacteria. In a 4-year case-control study (n = 102), the only covariate independently associated with carbapenem-resistant Enterobacteriaceae in all multivariate analyses was the cumulative number of prior antibiotic exposures.[56] A study in which data were collected over 26 months in a tertiary care university hospital with an established endemicity of carbapenem-resistant ESBL-*Klebsiella pneumoniae* (ESBL-CRKP) demonstrated an interaction effect in which increased exposure to fluoroquinolones amplified the impact of exposure to carbapenems (and vice versa) on ESBL-CRKP infection risk.[58] In this study, the duration of prior treatment with fluoroquinolones was also associated with increased risk of infection with ESBL-CSKP, whereas prior receipt of carbapenems presented a protective effect against ESBL-CSKP infection. These data are consistent with previous reports that no particular class of antibiotic is the predominant predisposing factor for selection of carbapenemase production. In summary, after resistant pathogens colonize patients, any broad-spectrum antibiotic has the ability to kill the normal flora, thereby allowing the resistant strains to proliferate and to cause clinical disease.

Treating carbapenemase-producing bacteria is challenging, and there are neither definitive nor predictable recommendations that guarantee clinical success. In the absence of such data, the clinician is challenged to make clinically relevant deductions from the published literature. The findings from 15 studies and reports in treating infections caused by KPCs showed success rates of 75% with aminoglycosides, 73% with polymyxin combinations, 71% with tigecycline, 40% with carbapenems, and 14% with polymyxin monotherapy.[59] Antimicrobial agents accepted as having activity based on in vitro susceptibility are tigecycline, polymyxins, and aztreonam.[60] There are evolving data suggesting a potential role for carbapenems as a therapeutic option if the MIC of the infecting organism is 4 mg/L or less and the carbapenem is given in combination with another active agent.[61]

The response to the clinical problem of treatment for infections caused by carbapenemase-producing bacteria has included BLBLI combinations. A clinical approach to carbapenemases is represented in Table 48.2. Carbapenemases are serine-based (classes A and D) or metallo-based (class B).

In contrast to the traditional β-lactamase inhibitors (i.e., sulbactam, clavulanic acid, and tazobactam), all of which have the β-lactam ring as part of their structure, a new class of β-lactamase inhibitors that does not possess a β-lactam ring is now available. The initial member of this class of non-BLBLIs to make it to the antibiotic market in the United States is avibactam. In addition to being stable in the presence of most ESBLs and some AmpC β-lactamases, avibactam, when added to ceftazidime, has been shown to increase activity against KPCs. Of note, avibactam is unstable in the presence of metallo-based carbapenemases.[62]

Vaborbactam is a non-BLBLI that is given in combination with meropenem. Like avibactam, it is a potent inhibitor of KPCs; in contrast to relebactam, preliminary studies have not shown that it increases activity against *P. aeruginosa.*[63] Vaborbactam is not active against metallo–β-lactamases.

Relebactam is a non-BLBLI that is being studied in combination with imipenem. Like avibactam, it is active against KPC-producing gram-negative bacteria. Even though the addition of relebactam to imipenem does not increase activity against *A. baumannii,* there is enhanced activity against *P. aeruginosa*, including isolates with depressed oprD (porin) and increased AmpC (type 1) β-lactamase expression.[64] Metallo-β-lactamases are not susceptible to inhibition by relebactam.

Much more challenging than therapy for the serine-based KPCs is that for the NDM carbapenemases. Included as agents with potential activity are colistin as well as the investigational agents aztreonam/avibactam and ervacycline.[65] It is noteworthy that avibactam does nothing to enhance the efficacy of aztreonam as the active agent against NDMs. Because NDMs often occur in combination with other β-lactamases, the addition of avibactam allows the activity of aztreonam against NDMs to be detectable. As a component of combination therapy, fosfomycin may have a role.[66]

The examples of carbapenem resistance (whether on the basis of carbapenemase or other mechanism of resistance) in *Pseudomonas, Acinetobacter, Stenotrophomonas*, and *Klebsiella* underscore an important concept in antimicrobial therapy for the critical care clinician. When multidrug resistance occurs, the clinician cannot assume that such resistance results from exposure to the broadest class of antibiotic to which the organism is resistant. To accept such a flawed assessment could result in limited use of that class of antibiotic, which could then shift to increased use of the actual class of antibiotic that led to the pattern of resistance. The other clinically relevant observation in many of the recently described outbreaks is that inadequate infection control contributed to the spread of resistant strains that had been selected by antibiotics.[39,67,68]

Efflux Pumps

The importance of efflux as a mechanism of multidrug resistance in the ICU has been increasingly acknowledged.[69] Efflux pumps are three-component systems, contained within the bacterial cell wall, that allow bacteria to eliminate antibiotics that have entered the cell. Initially described in 1980 as a mechanism of resistance in tetracyclines, efflux was recognized in 1988 as a contributor to fluoroquinolone resistance.[70] In recent years, the contribution of efflux to clinical resistance has broadened, with important implications for treatment of serious infections. The composition of this system has been nicely detailed.[71,72] The pump itself (also referred to as the transporter) lies in the cytoplasmic membrane and is designated MexB, MexD, or MexF. It is attached via a linker lipoprotein (MexA, MexC, or MexE) in the periplasm to the third component, the exit portal (OprM, OprJ, or OprN), which lies in the outer membrane. These three components of the efflux pump are under repression and are therefore are not clinically active.

P. aeruginosa has several efflux systems, with MexAB-OprM and MexEF-OprN having particular clinical significance. The MexAB-OprM system contributes to both intrinsic and acquired resistance, and the MexEF-OprN system contributes only to acquired resistance.[73] The MexAB-OprM system is expressed constitutively in cells grown in standard laboratory media, where it contributes to intrinsic resistance to several antimicrobials, including fluoroquinolones, tetracyclines, piperacillin, cefepime, aztreonam, and certain carbapenems.[51] Of the β-lactams, only carbapenems appear to be poor substrates for MexAB-OprM; however, different carbapenems vary in susceptibility to efflux. Meropenem and doripenem are subject to efflux, and expression of the MexAB-OprM efflux system has been correlated with resistance to meropenem.[74] By contrast, imipenem, which is less amphipathic than meropenem, is not subject to efflux,[73] possibly owing to the need for efflux systems with MexAB-OprM to access their substrates within the cytoplasmic membrane.[74] Such a microbiologic property may explain why a gram-negative isolate may be susceptible to imipenem but resistant to meropenem.

Among the classes of antibiotics in which efflux becomes a predominant mechanism in the development of resistance, tetracyclines are noteworthy. This has clinical significance because *A. baumannii* has become a significant nosocomial pathogen, and tigecycline is one of the few therapeutic options for treating infections caused by this pathogen. To address the problem in increasingly reported tigecycline resistance, a study to assess the prevalence and characteristics of efflux-based tigecycline resistance in clinical isolates of *A. baumannii* was undertaken.[75] *A. baumannii* isolates, including 64 tigecycline-nonsusceptible *A. baumannii* and 10 tigecycline-susceptible *A. baumannii* isolates, were analyzed. The study showed that the active efflux pump AdeABC appeared to play important roles in the tigecycline resistance of *A. baumannii*.[75] Eravacycline is a fluorocycline in the tetracycline class. Compared with tigecycline, eravacycline generally has lower MICs against gram-negative organisms, including resistant pathogens such as *Acinetobacter*.[76] For *A. baumannii*, eravacycline MICs correlated with increased expression of the *adeB* efflux gene.[77]

Clinical Relevance for Understanding Antibiotic Resistance

An understanding of the mechanisms of antibiotic resistance is integral to understanding the emergence of MDR organisms. A common mistake in clinical practice is to assume that the major predisposition to a pattern of resistance is the overuse of the broadest category of antibiotic to which a pathogen is resistant; indeed, many examples illustrate that this is not the case. A classic example of multidrug resistance in gram-negative organisms is the resistance in *P. aeruginosa*. As previously noted, *P. aeruginosa* possesses three mechanisms of resistance regulated by genetic operons on the chromosome: (1) AmpC β-lactamases, efflux pumps, and outer membrane porin alterations.[50,51,78] Because the clinician will not have information at the time of empiric therapy regarding which of these mechanisms might be present in the *P. aeruginosa* being targeted, regimens for infections such as HAP often target more than one of these mechanisms of pseudomonal resistance.[79] For infections such as HAP and VAP, in which *P. aeruginosa* is a pathogen targeted with empiric therapy and for which fluoroquinolones are offered as an option in the initial regimen,[79–81] data on the risk of fluoroquinolones leading to multidrug resistance via efflux mechanisms become especially noteworthy. The fluoroquinolones may select certain *nfxc (mexT)* mutants.[50,71] In addition to resistance to fluoroquinolones, these mutants may have decreased susceptibility and even clinical resistance to carbapenems (e.g., imipenem, meropenem) that occurs on the basis of either closure of porin channels in the outer membrane of the bacterial cell wall or upregulation of an efflux pump. Such information may help explain patterns of carbapenem resistance in health care institutions with low rates of carbapenem usage.

The experience with carbapenem-resistant *A. baumannii* in Brooklyn, New York, provides another important insight into the problem of selection of resistance by one class of antibiotic to an entirely different class. In a study to evaluate the endemicity of *A. baumannii*, all unique patient isolates of this pathogen were collected from 15 Brooklyn hospitals over a 3-month period.[67] Antibiotic susceptibilities, ribotyping, and the relationship between antibiotic use and resistance rates were determined. Among the 224 carbapenem-resistant strains of *A. baumannii*, ribotyping demonstrated that one strain accounted for two-thirds of the isolates and was present in all 15 participating hospitals. The strongest predisposition to selection for this pathogen was cephalosporin use. Known *A. baumannii* resistance mechanisms include chromosomally associated β-lactamases and porin protein mutations,[82] so it can be assumed that this represents selection of carbapenem-resistant mutant strains by the cephalosporins.

A study in which the investigators collected data over 26 months in a tertiary care university hospital with an established endemicity of carbapenem-resistant ESBL-CRKP demonstrated an interaction effect in which increased exposure to fluoroquinolones amplified the impact of exposure to carbapenems (and vice versa) on ESBL-CRKP infection risk. In this study, the duration of prior treatment with fluoroquinolones was also associated with increased risk of infection with ESBL-CSKP, whereas prior receipt of carbapenems presented a protective effect against ESBL-CSKP infection.[57]

The evolving data about risk factors for the selection of organisms that produce carbapenemases suggest that the most important variables are not the class of antibiotics being used (since multiple classes of antibiotics other than carbapenems have been associated with the selection of carbapenemase-producing gram-negative bacteria) but rather the intensity and the duration of the antimicrobial therapy.[56,57]

Based on these examples, a principle of antibiotic therapy in the ICU should be that resistance may be selected by a class of antibiotics other than the agent to which the resistance is being reported (e.g., carbapenem resistance being selected by noncarbapenem antibiotics).

A second principle is that antibiotics without activity against certain pathogens may provide less risk of selecting for resistant strains than do antibiotics that do cover such pathogens. An important example might be *P. aeruginosa.* Because of the ability of *P. aeruginosa* to express multiple mechanisms of resistance, many experts recommend avoiding the use of traditional antipseudomonal agents (i.e., a pseudomonal-sparing regimen) when treating infections in which *Pseudomonas* is not a suspected pathogen, as the use of overuse these agents may result in the development of multidrug resistance in *Pseudomonas* isolates.[41]

Role of Combination Therapy

Synergy

The concept of synergy, in which antimicrobial combinations are assumed to be more effective than single agents, is one of the most frequently cited justifications for combination therapy. The best-recognized example of synergistic antimicrobial therapy is in treatment of enterococcal endocarditis, where treatment with

penicillin or ampicillin monotherapy has been associated with a high rate of relapse compared with combined therapy using penicillin or ampicillin plus streptomycin or gentamicin.[83,84] Discussions of combination therapy have raised the question of whether the use of multiple drugs in the treatment of an infection may result in improved clinical outcomes. One example is the treatment of bacteremia with *S. aureus* in which some clinicians advocate using a semisynthetic penicillinase-resistant penicillin (e.g., nafcillin or oxacillin) in combination with a brief course (3 to 5 days) of an aminoglycoside. This is based on data demonstrating more rapid clearing of bacteremia.[85] Unfortunately, clearance of organism was not correlated with a mortality reduction in nonaddicts with primarily left-sided endocarditis caused by *S. aureus* when compared to monotherapy nafcillin. The mechanism of synergy between antipseudomonal penicillins and aminoglycosides in *P. aeruginosa* infections is similar to aforementioned enterococci.[86] Despite this microbiologic observation, the presence or absence of synergy received less priority in an alternate trial assessing outcomes in patients with *P. aeruginosa* bacteremia; rather, combination therapy to prevent the emergence of resistance was explored.[87]

In contrast with the beneficial effect of synergy, a combination regimen may result in the detrimental effect of antagonism. The treatment of pneumococcal meningitis in the 1950s serves as the preeminent example. The mortality rate in patients who received penicillin alone was 21%, whereas combination therapy with penicillin (a bactericidal agent) plus chlortetracycline (a bacteriostatic agent) resulted in a staggering mortality rate of 79%.[88]

The clinical importance of antagonism has increased in the era of community-associated methicillin-resistant *S. aureus* (CA-MRSA). MRSA infection is an independent predictor of mortality, ICU length of stay, and overall cost of care.[89–92] Efforts have been made to identify the in vitro activity of antibiotic combinations with potential clinical benefit. A study using 10 different strains of *S. aureus* found an overall pattern of antibiotic indifference (no combination effect) in combinations of linezolid with fusidic acid, rifampin, or gentamicin. On the other hand, the combination of linezolid with ciprofloxacin or vancomycin resulted in slight antagonism and reduced bactericidal effect when investigators used these combinations against the same strains of staphylococci.[93] A subsequent study using the checkerboard broth microdilution method tested linezolid in combination with 28 different antimicrobial agents (including vancomycin and several fluoroquinolones) did not confirm the antagonistic effect.[94] Sahuquillo and colleagues reproduced the effect of antibiotic indifference with vancomycin, but they noted antagonism with levofloxacin in two of the five *S. aureus* isolates tested.[95]

Further investigations have evaluated 5-day treatment regimens of linezolid monotherapy, vancomycin monotherapy, and linezolid in combination with vancomycin in 40 rabbits with MRSA aortic valve endocarditis.[96] Treatment with vancomycin alone achieved the largest mean reductions in valvular vegetation bacterial counts ($P = 0.05$) as well as sterilization of aortic valve vegetations in three subjects. Linezolid monotherapy resulted in zero sterilized vegetations. In addition, combination therapy with linezolid and vancomycin resulted in a lower peak serum linezolid level than linezolid alone. Even though in vitro synergy testing revealed additive or indifferent activity between the two drugs, the rabbit model revealed in vivo antagonism. A potential explanation offered by the investigators for the observed antagonism was the effect of combining a bacteriostatic (linezolid) with a bactericidal drug (vancomycin). The observed reduction in peak serum linezolid levels suggests a role for additional mechanisms in the interaction between the two antibiotics. Unfortunately, the clinical significance of these findings is not yet known.

Several studies have evaluated the use of the semisynthetic penicillins (e.g., nafcillin) in combination regimens to treat infection with MRSA. In a pharmacokinetic/pharmacodynamic model evaluating the combination of nafcillin and vancomycin, Leonard found evidence of synergy in the treatment of heterogeneously vancomycin-intermediate *Staphylococcus aureus*, MRSA, and methicillin-sensitive *S. aureus*.[97] Subsequently, Leonard and Rolek found evidence of synergy between daptomycin and nafcillin for the treatment of VISA.[98] Interestingly, they noted a more pronounced synergistic effect as the daptomycin susceptibility decreased. Despite these findings, no clinical trials exist that have proven this in vitro phenomenon translates to the clinical setting.

In the absence of definitive data on optimal management of *S. aureus* infections in seriously ill patients, a pattern has emerged in some health care systems to prescribe combination therapy for this pathogen. The overall assessment of the data is that antibiotic indifference appears to best characterize the drug interaction profile of linezolid with vancomycin. Because some data, albeit unsubstantiated in controlled clinical trials, suggest caution in combination administration of linezolid with vancomycin[93] and the fluoroquinolones,[95] it is important for the intensivist to be aware of the potential unintended consequences. In summation, the role of combination therapy in the overall treatment of serious MRSA infection remains unclear.[99]

Enhanced Efficacy Against a Pathogen

The potential for combination therapy to result in increased efficacy against a pathogen via a mechanism other than synergy remains a common clinical question. In an attempt to decipher the answer, Paul et al. conducted a meta-analysis of 64 trials with 7586 patients comparing β-lactam monotherapy versus β-lactam plus an aminoglycoside in immunocompetent patients with sepsis.[100] No statistically significant advantage of combination therapy was identified among the 1835 patients with gram-negative infections for whom the data were analyzed. In contrast with the prior results,[87] the investigators observed no improvement in survival for the 426 patients who had infection caused by *P. aeruginosa*. Rates of resistance development did not differ between the two treatment groups; however, nephrotoxicity developed significantly more often with combination therapy.

Prevention of the Emergence of Resistance

Clinicians frequently use combination therapy for *P. aeruginosa* to prevent the emergence of resistance. Results of some clinical trials[101] and fear of the emergence of resistance have provided the basis for this practice habit. Despite the importance of this subject, no definitive data are available to prove that combination therapy will prevent the emergence of *Pseudomonas* resistance.[102]

In an effort to determine the impact of combination therapy on the risk of the overall emergence of antibiotic resistance, a meta-analysis of eight randomized controlled clinical trials comparing β-lactam monotherapy to β-lactam plus aminoglycoside combination therapy was performed.[103] Among initially antimicrobial-susceptible isolates in this analysis, combination therapy did not affect the development of antimicrobial resistance. Subsequently, a larger meta-analysis of 64 trials comparing β-lactam monotherapy versus β-lactam plus aminoglycoside combination therapy in immunocompetent patients with sepsis also failed to demonstrate a difference in the rate of development of resistance.[100]

Increased Opportunity to Achieve Appropriate Therapy

Even though clinicians frequently invoke the issues of synergy and of reduction in the emergence of resistance in discussions of combination therapy, the relevant data do not prove consistent benefits. In patients in the intensive care setting, an important advantage of combination therapy is that it provides the clinician with broader antibacterial coverage for potentially MDR microorganisms.[104] Additionally, because inappropriate initial therapy may result in increased mortality, a combination of antibiotics has the potential benefit of providing coverage against a pathogen that may not be the most likely on a statistical basis but is a reasonable consideration in life-threatening clinical settings confronting the critical care physician. The use of antibiotic combinations for empiric therapy increases the probability that at least one of the agents will have activity against the causative organism; however, once the clinician identifies the organisms, de-escalation to monotherapy, where possible, should become a priority.

Properties of Antibiotics That Affect Their Usefulness in the Clinical Setting

Immunomodulating Effect of Antibiotics

Although most classification schema group antibiotics by their chemical structure and spectrum of coverage, certain antibiotics may possess additional properties that have important clinical implications. The interaction of antibiotics with host immune response, bacterial population kinetics, and bacterial gene expression for exotoxin production are examples of the pleiotropic, or "off-target," properties of antibiotics. This is especially relevant in the treatment of life-threatening infections caused by gram-positive cocci and may provide a basis for combination therapy in the treatment of these infections.

Streptococcal toxic shock syndrome is a clinical infection in which bacteria produce exotoxins that act as host superantigens, precipitating shock, multiple organ failure, and death. Although *Streptococcus pyogenes* demonstrates exquisite in vitro sensitivity to penicillin, experimental studies of infection by this pathogen have demonstrated reduced efficacy against organisms in the stationary phase of bacterial growth. This phenomenon has been termed the Eagle effect, whereby high organism population density and slow organism division make treatment with an antibiotic dependent on cell wall synthesis ineffective.[105] Some cite the Eagle effect as a justification for use of the bacteriostatic antibiotic clindamycin in the treatment of toxic shock syndrome. Clindamycin inhibits bacterial protein synthesis independent of the stage of bacterial growth, resulting in the inhibition of bacterial exotoxin production. Finally, clindamycin facilitates the phagocytosis of *S. pyogenes* by inhibiting M protein synthesis and suppresses the production of PBPs.[106] In addition to its effects on microbes, evidence demonstrates that clindamycin has immunomodulatory effects, suppressing monocyte synthesis of tumor necrosis factor-α.[107,108] All of these pleiotropic qualities have resulted in the recommendation for clindamycin use in necrotizing skin or soft tissue infections and toxic shock syndrome caused by *S. pyogenes*.[106]

The dramatic increase in the worldwide incidence of highly virulent, community-acquired infection with CA-MRSA has resulted in increasing reports of necrotizing skin and soft tissue infections as well as necrotizing pneumonia confronting the critical care physician.[109–111] CA-MRSA virulence has been attributed to expression of several virulence factors: α-hemolysins, toxic shock syndrome toxin-1 (TSST-1), staphylococcal enterotoxin B, and Panton-Valentine leukocidin (PVL). The association of staphylococcal virulence with the current CA-MRSA epidemic prompted Stevens and colleagues to investigate the impact of antibiotics on the expression of virulence-associated exotoxin genes.[112] Both clindamycin and linezolid demonstrated markedly suppressed in vitro production of staphylococcal toxin genes. In fact, no PVL production up to 12 hours after antibiotic administration was observed. In contrast, subinhibitory concentrations of nafcillin resulted in increased toxin production. These findings led the investigators to conclude that the inhibition of protein synthesis is an important consideration in the selection of antimicrobial agents for treatment of serious infections caused by toxin-producing gram-positive cocci.[112]

The inflammatory response to pneumococci is one of the most potent in medicine.[113] Macrolides induce an immunomodulatory effect that attenuates the production of inflammatory cytokines,[114] including suppression of harmful interleukin host responses and inhibition of neutrophil oxidant burst and degranulation.[115–117] A growing body of evidence exists to support the benefit of macrolide therapy for bacteremic pneumonia caused by *S. pneumoniae*.[115–123] Although there are multiple proposed explanations, efficacy appears to extend beyond the drug's spectrum of antimicrobial activity. In a review of critical illness in asplenic patients, it was acknowledged that macrolide therapy has not been specifically studied in the splenectomy population; however, consideration for use of empiric macrolide therapy in combination with a β-lactam antibiotic owing to the pleiotropic antiinflammatory effects was raised.[124] Such pleiotropic effects have received an increasing focus of attention and further illustrate how immune modulation influences recommendations for therapy in the intensive care setting.

Penetration at the Site of Infection: Tissue-Targeted Therapy

Clinicians now understand the importance of pharmacokinetic properties of antibiotics in the treatment of pneumonia caused by MDR gram-positive cocci. Understanding the relevance of pharmacokinetic properties will also assist the critical care physician navigate through the recent published literature for these infections.

Pulmonary pharmacokinetics specifically address the tissue penetration and distribution of antibiotics within the lung.[125] Early studies investigating antibiotic penetration in pulmonary infections in the critically ill included aminoglycosides and fluoroquinolones. Although aminoglycosides reach acceptable levels in the interstitium of the lung, levels in pulmonary secretions reach a mean of only about 20% of the concomitant serum level.[126] By contrast, the concentrations of quinolones in lung tissue and bronchial secretions exceed the concomitant serum concentrations.[127] Even though quinolones have better penetration into bronchopulmonary secretions and less potential for nephrotoxicity than aminoglycosides, available data show a trend toward improved survival in patients with VAP treated with an aminoglycoside-containing combination as opposed to one containing a quinolone.[128] A concern with fluoroquinolones in combination therapy directed against gram-negative organisms is the selection of resistance. This is of particular importance in treatment of *P. aeruginosa* where the resultant resistance may involve multiple classes of antibiotics.[129] To maximize clinical efficacy and limit nephrotoxicity with aminoglycosides,

some investigators have suggested, based on clinical trials, discontinuation of the aminoglycoside after 5 days if the patient's condition is improving.[130]

Existing pharmacokinetic evidence highlights the extremely poor lung tissue penetration of vancomycin. Cruciani and associates investigated vancomycin pharmacokinetics in 30 human lung tissue sections after administration of a 1-g dose over 1 hour.[131] They used a comparison of serum-to-tissue concentration over the dosing interval to generate a graph to determine a concentration ratio. Overall, the lung tissue concentration reaches 21% of serum levels. Not surprisingly, investigation has confirmed even poorer penetration into epithelial lining fluid.[132] These data raise concern that the traditional dosing regimens of vancomycin (1 g given intravenously every 12 hours) and low target serum trough concentrations (5–10 μg/mL) will generate lung tissue concentrations below the MIC for *S. aureus*. The issues surrounding suboptimal vancomycin dosing are reflected in the 2005 published ATS/IDSA guidelines for treatment for adults with HAP, VAP, and health care–associated pneumonia, which noted that retrospective pharmacokinetic modeling suggested that vancomycin failures may be related to inadequate dosing. Because of these concerns the authors recommended achieving trough levels for vancomycin of 15 to 20 μg/mL.[79] A joint vancomycin clinical guideline for the treatment of all complicated infections caused by MRSA recommended intensified vancomycin dosing.[133]

In contrast to the poor pulmonary pharmacokinetic properties of vancomycin, several studies of linezolid confirm excellent lung penetration in healthy volunteer subjects and in vitro modeling.[134–136] These improved levels appear to correlate with observed improved clinical outcomes with linezolid over vancomycin.[137–140] Boselli and coworkers investigated the steady-state plasma pharmacokinetic variables and epithelial lining fluid concentrations of linezolid administered to critically ill patients with VAP.[141] Epithelial lining fluid concentrations of linezolid approximated 100% of corresponding plasma values, with drug concentrations that exceeded the susceptibility breakpoint (4 μg/mL) for *S. aureus* throughout a majority of the dosing interval.

A retrospective analysis of two multinational, double-blind, randomized studies suggested linezolid to be superior to vancomycin in traditional dosing regimens for treating MRSA pneumonia.[140] A subsequent randomized, controlled clinical trial of linezolid versus vancomycin in the treatment of nosocomial pneumonia favored linezolid; furthermore, a subgroup analysis of this investigation did not suggest a benefit in those patients with vancomycin troughs of 15 μg/L or higher on day 3.[142] In patients with HAP and VAP, there is a lack of data to inform the definitive choice for optimal therapy between different agents active against MRSA. Vancomycin and linezolid have been best studied. In the most current iteration of the HAP and VAP guideline,[4] variability in individual studies comparing vancomycin and linezolid are noted. This led the authors to conduct meta-analyses of the four trials, in which no difference in mortality was found when the data were analyzed using an intention-to-treat strategy or a modified intention-to-treat strategy. They also found no difference in the clinical cure rate in an intention-to-treat analysis; however, there was improvement of the clinical cure rate among patients who received linezolid in a modified intention-to-treat analysis. Linezolid and vancomycin appeared to confer no clear difference in nephrotoxicity, thrombocytopenia, serious adverse events, or need for treatment discontinuation owing to an adverse event. The authors subsequently concluded that "The choice between vancomycin and linezolid may be guided by patient-specific factor such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function, and cost."[4]

Because of the difficulty in achieving adequate drug levels in pulmonary tissue and secretions, many clinicians consider the use of topical, aerosolized antibiotics to deliver drug directly to the site of infection.[143] For patients receiving mechanical ventilation, aerosolized antibiotics delivered via an efficient system may achieve airway-drug concentrations 100- to 300-fold higher than the MIC of most bacteria, including MDR pathogens. Potential theoretical benefits include both reduced systemic toxicity and reduced pressure for selection of resistant organisms.[144,145] In a double-blind, placebo-controlled study in 42 ICU patients requiring prolonged mechanical ventilation who were colonized and/or infected with potentially difficult-to-treat pathogens (e.g., MRSA and nonfermenting gram-negative bacteria), aerosolized antibiotics successfully eradicated the existing MDR organisms and reduced the pressure for new resistance.[146] Technical issues associated with the adequate delivery of nebulized antibiotics have been reviewed.[147]

Despite studies of several antibiotics administered as aerosolized agents, none has established efficacy and dosing. Most of the evidence supporting nebulized tobramycin originates from small studies and meta-analyses assessing its utility in the management of chronic respiratory disease such as cystic fibrosis, not in the treatment of acute infection.[148] Although the risk of toxicity appears lower with the administration of nebulized (rather than intravenous) tobramycin, certain populations, such as those with renal insufficiency, may be at risk.[149] A meta-analysis of 12 studies using nebulized antibiotics showed improved clinical cure rates in VAP, but this effect did not persist after trial sequential analysis. There was no effect on microbiological cure, lengths of stay, or mortality.[150] Owing to the increasing prevalence of MDR gram-negative organisms such as *A. baumannii* and *P. aeruginosa*, clinicians increasingly face the need to administer colistimethate via intravenous (IV) infusion,[151] with some giving consideration to aerosolization,[152,153] as therapy for VAP and HAP. Although the quality of the evidence was considered poor, a recent meta-analysis of studies suggested that addition of aerosolized colistin in VAP was associated with improved clinical and microbiologic response rates but had no effect on mortality.[154]

Special Pharmacologic Properties

As the focus of antibiotic research has expanded beyond the in vitro properties, the importance of antibiotic performance at the in vivo target tissue level is becoming increasingly recognized. With the 2003 introduction of daptomycin for treatment of infections caused by resistant gram-positive cocci the concept of "organ-specific deactivation" arose.[155] Daptomycin is an IV cyclic lipopeptide with rapid, concentration-dependent killing and bactericidal activity against a broad spectrum of gram-positive cocci.[156–158] It demonstrates a unique mechanism of action, with calcium-dependent insertion into the phospholipid bacterial cell membrane. This results in cell depolarization via potassium efflux, causing disruption of DNA, ribonucleic acid (RNA), and protein synthesis.[159]

As a result of two multicenter, randomized, controlled trials comparing it with penicillinase-resistant penicillin or vancomycin,[160] daptomycin, at a daily dose of 4 mg/kg (for patients with creatinine clearance greater than 30 mL/min), received FDA approval for the treatment of complicated skin and soft tissue infections. A subsequent randomized, open-label trial investigated the use of daptomycin in *S. aureus* bacteremia and endocarditis.[161] This trial

prompted FDA approval of daptomycin for treatment of *S. aureus* bacteremia, including right-sided endocarditis, at a daily IV dose of 6 mg/kg.

Phase III clinical trials explored treatment of community-acquired pneumonia in hospitalized patients. Despite daptomycin's potent in vitro bactericidal activity against *S. pneumoniae*, clinical outcomes were disappointing and inferior to those with the comparator, ceftriaxone. Although daptomycin is known to exhibit poor penetration into epithelial lining fluid, the reason for treatment failure was not fully elucidated until Silverman and colleagues described a unique organ-specific inactivation process.[155] Investigators linked daptomycin's inactivation to its mechanism of bactericidal action: calcium-dependent membrane lipid binding.[155,159,162,163] Using a mouse model, they demonstrated drug sequestration and inactivation by binding to phospholipid vesicles that are found in pulmonary surfactant.[155] Because of the presence of surfactant in the target tissue, daptomycin is not an appropriate therapeutic agent for treatment of pneumonia. This phenomenon appears to be unique to daptomycin,[155] but it does raise the question of unrecognized organ-specific inactivation for other classes of antibiotics and other target organs.

Unintended Consequences of Antibiotic Therapy

Traditional teaching about antibiotics focused on three classic parameters: efficacy, safety, and cost-effectiveness. With respect to safety, the major considerations were allergic reactions and adverse effects. Within the pandemic of antibiotic resistance, clinicians must consider an important safety issue: unintended consequences of antibiotic therapy. An insightful report termed such unintended consequences as the "collateral damage" of antibiotics encompassing the selection of drug-resistant organisms and development of colonization or infection with MDR organisms.[164]

The increasing prevalence of MRSA infections in critically ill patients has required an ongoing evaluation of factors that propagate and sustain this pattern of resistance. The role of inadequate handwashing in the spread of nosocomial MRSA in hospitals has been well known for many years.[165] As rates of MRSA have increased in infections such as HAP,[166] other variables that may serve as risk factors for MRSA infection are targeted.

Infection by strains of *Clostridium difficile* with increased levels of toxin production and the resultant complications of toxic megacolon, bowel perforation, and death is a problem that has gained attention in recent years.[167] A postulated cause for this increase in toxin production is hypermutation. Spontaneous mutations that lead to bacterial resistance typically occur with a frequency of 10^{-6} to 10^{-8}. Hypermutation refers to a situation in which the mutation rate exceeds the rate of spontaneous mutations.[168] Certain factors may lead to an increase in the potential for a mutation that can lead to resistance. Antibiotics that have an effect on DNA have been shown with in vitro experiments to contribute to this predisposition to resistance.[168]

To better understand outbreaks of clinical disease caused by toxin-producing strains of *C. difficile*, researchers explored the genetics of epidemic strains.[169,170] In these studies, investigators noted an 18-base-pair deletion in the *tcdC* gene, which normally downregulates production of toxins A and B. The presence of binary toxin genes was an additional finding. Investigators postulated that these contribute to the hyperproduction of toxin expressed in clinical outbreaks. The epidemiologic analysis of these outbreaks identified fluoroquinolone therapy as a risk factor in some *C. difficile* outbreaks.[169–171] These observations challenge the critical care clinician to consider the potential of unintended antibiotic consequences in the selection of empiric antibiotic therapy in seriously ill patients.

In addition to *C. difficile,* the effect of antibiotics on toxin production has been studied in gram-positive organisms. In a study investigating the effects that cell wall–active antibiotics and protein synthesis inhibitors have on transcription and translation of genes for PVL, α-hemolysin, and TSST-1, Miller et al. demonstrated that subinhibitory concentrations of nafcillin both induced and prolonged messenger RNA (mRNA) expression for PVL, α-hemolysin, and TSST-1.[111] The investigators suggested that inadvertent use of β-lactam antibiotics to treat MRSA infections may contribute to worse outcomes.

When approved for clinical use in 1958 as the first glycopeptide antibiotic, impurities in vancomycin, often referred to as "Mississippi Mud," resulted in nephrotoxicity. Since that time, the incidence of all vancomycin toxicities has reduced owing to the improvement in vancomycin purity from 70% to almost 95% with improved fermentation methods.[172] After three decades of use, the issue of vancomycin and kidney injury was addressed by Moellering with the following editorial comment:

> Although vancomycin was originally thought to be ototoxic and nephrotoxic, recent studies of animals have failed to confirm either the ototoxicity or the nephrotoxicity of vancomycin administered alone. Definitive data proving that vancomycin is ototoxic or nephrotoxic in humans are likewise difficult to find in the literature. One area in which considerable controversy remains, however, relates to the possibility that vancomycin may produce synergistic or enhanced nephrotoxicity in patients receiving concomitant aminoglycosides.[173]

A consensus review of therapeutic monitoring of vancomycin in adult patients by the American Society of Health-System Pharmacists, the IDSA, and the Society of Infectious Diseases Pharmacists noted that data derived from more recent studies appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages (e.g., 1 g every 12 hours [15 mg/kg every 12 hours]), unless it is used concomitantly with known nephrotoxic drugs or at very high dosages.[133] The authors suggested a case definition of vancomycin-induced nephrotoxicity to be multiple (at least two or three consecutive) high serum creatinine concentrations (increase of 0.5 mg/dL or 50% or higher increase from baseline, whichever is greater) documented after several days of vancomycin therapy in the absence of an alternative explanation.

Over the ensuing two decades since the Moellering editorial, research has identified several contributing factors to the development of vancomycin-associated nephrotoxicity, including patients who receive daily doses in excess of 4 g, where toxicity rates may be as high as 34.6%.[174] Other risk factors for vancomycin-associated nephrotoxicity include increased body weight, extended duration of therapy, history of kidney disease, higher severity of illness, hypotension, elevated trough concentrations, and receipt of concomitant nephrotoxic medications including other antimicrobials.[172,175–177]

Certain β-lactam antibiotics may also contribute to nephrotoxicity owing to acute interstitial nephritis.[178] Because of the high frequency combination therapy in the ICU, one of the important considerations for synergistic nephrotoxicity is the concomitant use of vancomycin with piperacillin/tazobactam.

A retrospective, matched, cohort study of 558 patients compared the risk of acute kidney injury in patients receiving concomitant vancomycin plus piperacillin/tazobactam versus those using vancomycin and cefepime.[179] The investigators matched subjects for severity of illness, ICU status, duration of combination therapy, vancomycin dose, and number of concomitant nephrotoxins. In multivariate analysis, therapy with vancomycin plus piperacillin/tazobactam was an independent predictor of acute kidney injury (hazard ratio 4.27; 95% confidence interval [CI] 2.73–6.68). Among patients who developed acute kidney injury, the median onset was more rapid in the group receiving vancomycin plus piperacillin/tazobactam compared with the vancomycin plus cefepime group (3 vs. 5 days $P \leq 0.0001$).

In a registered meta-analysis (PROSPERO: CRD42016041646) using 14 observational studies with a total of 3549 patients, concomitant vancomycin and piperacillin/tazobactam was associated with acute kidney injury in unadjusted odds ratio (OR 3.12; 95% CI 2.04–4.78) and in adjusted odds ratio (OR 3.11; 95% CI 1.77–5.47) analyses.[180] The clinical observation of increased development of acute kidney injury owing to synergistic nephrotoxicity with dual-therapy vancomycin and piperacillin/tazobactam should be taken into consideration when determining either empiric or definitive therapy in ICU patients at risk for renal dysfunction. Identification of risk that prevents homogenous prescribing habits may eventually lead to a goal of antibiotic stewardship: greater heterogeneity in antibiotic choices in ICU medicine.

Right Time

The adequacy of initial empiric antibiotic therapy influences outcomes of clinical infections in the critically ill. For many years, clinicians adjusted antibiotic therapy on hospital day 2 or 3 after either bacterial susceptibility was known or the clinical course of the patient had been defined. This practice was based on the assumption that neither morbidity nor mortality would be negatively affected by such delays. The 1990s saw the publication of several reports challenging this tenet in the infectious disease processes of sepsis and VAP.[8–13,181] In these reports, investigators used the term *inadequate* to describe situations in which the organism causing an infection was not sensitive to antibiotic therapy as indicated by in vitro susceptibility. The published studies exhibited variability in sample size, inconclusiveness regarding whether isolated organisms were pathogens or colonizers, and lack of consistent identification of confounders that contributed to mortality; thus it was not possible to prove that such inadequate therapy affected mortality. Nevertheless, the consensus of multiple studies was that initial inadequate therapy had the potential to contribute to mortality.[182]

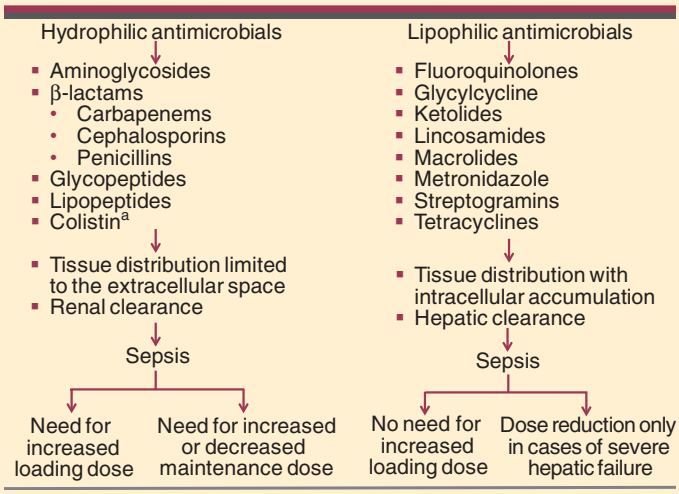
Shortly after the reports emphasizing the importance of initial, adequate therapy, there was a growing awareness of other important variables that influenced clinical outcomes in the critically ill. In a 2005 joint guideline for management of patients with HAP, VAP, and health care–associated pneumonia, the ATS and the IDSA modified definitions for the terms used in the selection of antibiotic therapy.[79] *Inappropriate* replaced the term *inadequate;* furthermore, the authors adopted *adequate* to refer to therapy that included not only the correct antibiotic based on the susceptibility of the organism but also optimal dose, correct route of administration, and use, if necessary, of combination therapy.[79] A contemporary definition of adequate therapy has now evolved to include that antimicrobial therapy (1) should be initiated as soon as possible after the onset of sepsis (with this usually occurring before the causative pathogen is known), (2) should be broad enough when given empirically to cover the potential causative microorganisms, and (3) embody appropriate antimicrobial dosing to maximize microbial killing, minimize the development of multidrug antimicrobial resistance, and avoid concentration-related adverse drug reactions.[183]

Multiple studies have addressed the impact of the timing of antibiotic therapy for patients in the ICU. In an analysis based on 107 consecutive patients receiving mechanical ventilation and antibiotic treatment for VAP, Iregui and colleagues noted that 30.8% (33 of 107) received antibiotic treatment that was delayed for 24 hours or more after initially meeting diagnostic criteria for VAP. These patients were classified as having initially delayed appropriate antibiotic therapy (IDAAT).[184] Two major variables were identified in these patients with IDAAT: (1) a delay in writing an antibiotic order (in 75.8% of the cases), and (2) the presence of a bacterial species resistant to the initially prescribed antibiotic regimen (in 18.2%). The investigators found that the hospital mortality rate was 69.7% for the patients with IDAAT, in contrast to only 28.4% for the patients without IDAAT ($P < 0.01$). An earlier study noted that modification of the antibiotic regimen to cover pathogens based on the susceptibility report did not eliminate the increased mortality associated with inadequate empiric therapy in patients with VAP.[11] This finding formed the basis for the statement that secondary modifications of an initially failing antibiotic regimen do not substantially improve the outcome for critically ill patients.[185] These results challenge the clinician to promptly order antibiotics that cover the involved pathogens even before culture results are available.

The IDSA practice guidelines for management of adult patients with meningitis note the lack of prospective clinical data on the relationship of the timing of administration of antimicrobial agents to clinical outcome in patients with bacterial meningitis.[186] Data from a retrospective cohort study of 269 adult patients with community-acquired bacterial meningitis provide some insights into the timing of antibiotic therapy in the absence of definitive recommendations.[187] Using these and other data, the IDSA acknowledged that evidence for definitive recommendations is inadequate and concluded that a reasonable assumption is to administer treatment for bacterial meningitis before the infection advances to a high level of clinical severity.[186] Referring to meningitis as a "neurologic emergency," the guideline recommended that appropriate therapy for meningitis be initiated as soon as possible after the diagnosis is considered to be likely. In support of the importance of prompt timing, this document also noted the potential in certain patients for administration of antibiotics before hospital admission if the patient initially presents outside the hospital.

For the critical care clinician, sepsis is a clinical entity in which appropriate timing of antibiotic therapy has been associated with improved clinical outcomes.[8,9,13,104,181] A sentinel retrospective cohort study of 2731 patients with septic shock–related recurrent or persistent hypotension in 14 North American ICUs demonstrated an associated increase in mortality rates with delayed antibiotic delivery. Survival rates decreased from 79.9% to 70.5% if administration of antibiotics administration was delayed from within the first hour to the second hour after hypotension development. In the 6 hours after onset of hypotension, the survival rate decreased by an average of 7.6% for each hourly delay in drug delivery.[188] A later larger study in 165 international ICUs involving 28,150 patients with sepsis and septic shock further evaluated the link between antibiotic timing and outcomes. Results demonstrated a positive relationship between the earlier administration of antibiotics and mortality in patients with severe sepsis and septic shock, even

TABLE 48.3 Effects of Pathophysiology on Pharmacokinetics in Critically Ill Patients



[a]Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med.* 2009;37:840–851.

Adapted from Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. *Adv Drug Deliv Rev.* 2014;77:3–11.

when stratified by location of sepsis diagnosis.[189] Although a more recent meta-analysis has questioned the validity of the initial observations[190] regarding mortality benefit, the meta-analysis suffered from inclusion of studies with negative results with significant flaws characterized by small study sample sizes and large variations in index timing. Thus the 2016 Surviving Sepsis Campaign guidelines continued to recognize the importance of prompt therapy in influencing clinical outcomes. The guidelines specifically provide a strong recommendation citing a moderate quality of evidence to initiate administration of IV antimicrobials as soon as possible after recognition of sepsis and septic shock and within 1 hour.[191] Consistent with the 2008 guidelines, appropriate routine microbiologic cultures, including blood cultures, should be obtained before initiating antibiotic therapy but should not prevent prompt administration of antimicrobial therapy.[192]

Right Dose

As the literature regarding the treatment of infections in the ICU has evolved over the years, studies have identified several elements that influence the optimal dose of an antibiotic. The manner in which antibiotics kill bacteria varies among different classes of drugs, but the two major pharmacodynamic categories of killing are *time-dependent* killing and *concentration-dependent* killing.[193] In time-dependent killing, also referred to as *concentration-independent* killing, maximum bacterial killing occurs when the drug concentration remains above the MIC. Examples of antibiotics that demonstrate time-dependent killing include β-lactam antibiotics (i.e., penicillins, cephalosporins, carbapenems, and monobactams) and vancomycin. Conversely, in concentration-dependent killing, maximum bacterial killing occurs when the peak drug concentration is approximately 10 times the MIC. Examples of agents with concentration-dependent killing are fluoroquinolones and aminoglycosides. Several studies have demonstrated the relevance of these properties in the management of patients with serious infections.

In recent years, the focus on discussing antibiotic properties has moved toward the characterization of antimicrobial agents as being either hydrophilic or lipophilic. The knowledge of these properties may affect dosing strategies. A summary of these physicochemical properties of antibiotics and their effects on dosing strategy is included in Table 48.3.[183,194] Noteworthy is the lack of uniform consistency between time-dependency and hydrophilicity and between concentration-dependency and lipophilicity (e.g., aminoglycosides and lipopeptides [daptomycin], which are hydrophilic but concentration dependent). It is important to understand these pharmacologic properties and the variations that occur with hydrophilic antibiotics in the presence of sepsis. Most relevant are (1) the significant antibiotic dilution that might occur with hydrophilic antibiotics when intravascular fluid escapes into tissues and (2) the fluctuations of renal function that often occur in patients with sepsis and result in increasing or decreasing elimination rates. In contrast to hydrophilic antibiotics, lipophilic antimicrobials are less affected in their pharmacokinetic behavior by the pathophysiology of sepsis, as they are normally distributed in the intracellular and extracellular spaces.[183] This distribution means that retrodiffusion from the intracellular reservoir to the extracellular space may prevent antibiotic dilution whenever intravascular fluid escapes into tissues. Also, most of these agents are cleared through the liver, whose function is often less significantly compromised during sepsis, with the result that elimination rates are frequently similar to those observed in stable patients.

Ultimately, hydrophilic antibiotics often need higher loading dosages and increased or decreased maintenance dosages in critically ill patients with sepsis compared with noncritical stable patients. On the contrary, similar concentration-time profiles are observed for lipophilic agents in critically ill as well as noncritically ill patients.

As summarized by Blot and colleagues,[183] the following characterizations of antibiotics are relevant: (1) time-dependent

antibiotics (i.e., cumulative percentage of time over a 24-hour time [i.e., T] period that the free [*f*, or unbound] antimicrobial concentration exceeds the MIC [*f*T > MIC]: β-lactam antimicrobials); (2) concentration-dependent antibiotics (i.e., peak concentration in a dosing interval divided by the MIC), with the usual maximum concentration (C_{MAX}/MIC target exceeding 8–10): aminoglycosides and daptomycin; and (3) concentration-dependent with time-dependence (i.e., defined by the area under the curve over a 24-hour period [$AUC_{0–24h}$] divided by the MIC [$AUC_{0–24h}$/MIC]): fluoroquinolones, tigecycline, linezolid, and glycopeptides.

An unresolved issue is whether vancomycin is only time-dependent[195] or whether it is a combination of concentration-dependent with time dependence.[183] Because vancomycin exhibits time-dependent killing,[195] the length of time that concentrations of vancomycin stay above the pathogen's MIC is important to bacterial eradication. As drug levels decline, organisms have the potential to regrow, increasing the chance of clinical failure. This pharmacologic principle is influential in the practice patterns of more frequent (every 6 hours) or of continuous infusion vancomycin dosing for infections like pneumonia in which vancomycin penetration to the target site may not be optimal. Those who embrace vancomycin as having concentration-dependent with time-dependence properties do not usually advocate for continuous infusion.

Because a goal with time-dependent antibiotics such as β-lactams is to maintain antibiotic levels above the MIC of the organism for as long as possible during the dosing cycle, it is important to be aware of inadequate concentrations of these agents in patients with sepsis when standard dosage regimens are administered. This is particularly noteworthy when infection is caused by difficult-to-treat organisms such as *P. aeruginosa*.[196,197] On a theoretical basis, administration of β-lactams at increased doses, with increased frequency, or by an extended or continuous infusion can result in improvement in obtaining pharmacodynamic target attainment. Among these options, clinicians have used continuous infusions in critically ill patients, and this strategy achieves higher steady-state β-lactam concentrations compared with trough concentrations with standard intermittent regimens.[198] Despite such an advantage, continuous infusion β-lactam therapy may still result in concentrations below the MIC for difficult-to-treat pathogens, especially in patients with a high creatinine clearance and high renal drug elimination.[199] Because of such variables, enhanced clinical efficacy of continuous infusions of β-lactam antibiotics has not been consistently demonstrated.[194] As research explores new approaches to drug administration, it is important to be aware of the potential for neurotoxicity such as progressive neurologic deterioration with high-concentration β-lactam antibiotics.[147]

The postantibiotic effect, in which microbial killing persists despite clearance to undetectable serum levels, complements the concentration-dependent killing of gram-negative bacilli exhibited by aminoglycosides. These two properties may serve as the basis for once-daily aminoglycoside therapy.[200] Giving the same total dose in larger concentration less often may result in better killing, longer postantibiotic effect period, and reduced aminoglycoside toxicity.

In such a dosing schedule, clinicians administer single doses of gentamicin or tobramycin of 5 mg per kg to 7 mg per kg of body weight. Nicolau et al. reported their experience with once-daily therapy using 7 mg per kg in 2184 adult patients.[201] After exclusion of patients with end-stage liver disease with ascites, burns involving greater than 20% total body surface area, pregnancy, end-stage renal disease requiring dialysis, and enterococcal endocarditis, it was deemed unnecessary to draw standard peak and trough samples. Monitoring was completed by obtaining a single random blood sample between 6 and 14 hours after the start of an aminoglycoside infusion. The treating clinician could subsequently adjust the dosing interval in accordance with a provided nomogram. The authors made several important observations in this large group of patients. (1) Despite the prolonged drug-free period, bacterial regrowth was not clinically evident. (2) No increase in either ototoxicity or nephrotoxicity was found. (3) Efficacy was promoted in a cost-effective manner.[201] Supporting this strategy, a meta-analysis evaluating the safety and efficacy of once-daily aminoglycosides in 1200 patients from 16 trials found no difference concerning efficacy and safety between single-dose and multiple-dose regimens.[202]

Despite the role that colistin plays in the treatment of infections caused by carbapenemase-producing bacteria, there are no consistent recommendations regarding the dosing of this antibiotic. A comparison of U.S. FDA and European Medicines Agency colistin dosing strategies used pharmacokinetic data from 162 adult critically ill patients with creatinine clearances ranging from 5.4 to 211 mL/min to determine the average steady-state plasma colistin concentration.[203] In this study, there was variability in susceptibility breakpoints for *P.* and *Acinetobacter*, with the Clinical Laboratory Standards Institute breakpoints of 2 mg/L or less and 2 mg/L less, respectively, and with the European Committee on Antimicrobial Susceptibility Testing breakpoints of 4 mg/L or less and 2 mg/L or less, respectively. Based on these analyses, there has been variability in colistin dosing. The FDA recommended body weight–adjusted doses, whereas the European Medicines Agency recommends dosing in million international units.

To achieve optimal clinical benefits while minimizing the unintended consequences of selecting resistant bacteria, clinicians must simultaneously consider multiple variables when using concentration-dependent drugs in the treatment of serious infections. In a study of lower respiratory tract infections caused by *P. aeruginosa*, clinicians administered ciprofloxacin intravenously at a dose of 200 to 300 mg every 12 hours.[204] Resistance emerged at a rate greater than 70% during therapy, similar to the 75% rate predicted by a pharmacodynamic study.[205] By contrast, a randomized comparison of imipenem and ciprofloxacin for treatment of nosocomial pneumonia used a ciprofloxacin regimen of 400 mg given intravenously every 8 hours and noted emergence of resistance during therapy in 33% of cases in which *Pseudomonas* was the causative pathogen.[101] This rate was similar to the 38% predicted by the pharmacodynamic study previously cited.[205] These data emphasize the importance of considering not only the dosing interval but also the dose of antibiotic administered when using concentration-dependent antibiotics to treat infections in the critically ill.

In addition to dose and interval, antibiotic clearance plays an integral role in adequacy of antibiotic therapy. While it is routinely accepted that reductions in antibiotic dosing are appropriate in advancing acute kidney injury,[206] clinicians may fail to escalate drug administration in the increasingly reported clinical phenomenon of augmented renal clearance (ARC).[207] ARC is defined as the enhanced renal elimination of circulating solutes owing to an increased creatinine clearance (CrCl >130 mL/min per 1.73 m^2). Prevalence of ARC is higher in burn,[208] major trauma,[209] traumatic brain injury,[210] and febrile neutropenic[211] ICU patients; however,

it is difficult to traditionally recognize as derived estimates of glomerular filtration, such as the modification of diet in renal disease equation and Cockcroft-Gault formula are less accurate than direct measurement.[212] In 48 ICU patients with measured CrCl, Udy and colleagues demonstrated that CrCl values greater than or equal to 130 mL/min per 1.73 m^2 were associated with initial trough concentrations of β-lactams less than MIC in 82% ($P < 0.001$). Moreover, CrCl remained a significant predictor of subtherapeutic concentrations after multivariate analysis.[213] ARC has importance in vancomycin dosing as well. Baptista et al. performed a prospective, single-center, observational cohort study of 93 consecutive septic patients in the ICU treated with vancomycin by continuous infusion after a weight-based loading dose. Investigators compared patients with and without ARC. A statistically significant correlation between subtherapeutic vancomycin serum concentration and ARC was observed in the first 3 days of treatment.[214]

An interaction between renal clearance and hypoalbuminemia also plays a prominent role in pharmacokinetics. Ulldemolins and colleagues demonstrated that in critically ill patients with hypoalbuminemia, unbound flucloxacillin concentrations fell below concentrations necessary for treatment of methicillin-susceptible *S. aureus* 4 hours after standard bolus infusions.[215] The combination of increased volume of distribution owing to hypoalbuminemia combined with ARC presents a daily situation where lower achieved antibacterial exposures could result in subtherapeutic dosing, particularly for time-dependent antibiotics.[216] Because accurate and timely drug exposure is necessary for optimal clinical benefit,[9] clinicians must identify ARC and associated factors like hypoalbuminemia to prevent subtherapeutic pharmacologic treatment.

Right Duration

Given that antibiotic exposure may be a risk factor for resistance,[14] it is important in the process of antibiotic stewardship to identify opportunities to minimize exposure to these therapeutic agents. The concept of de-escalation therapy incorporates the dual goals of (1) initially attempting to decrease mortality by selecting the appropriate antibiotic for empiric therapy but (2) decreasing the time that a patient is exposed to the broad-spectrum therapy that might be necessary to correctly obtain administration of initial therapy.

Classically there have been three ways that de-escalation can occur. The most intuitively understood is changing from a broad-spectrum agent to a narrower-spectrum agent based on culture and sensitivity data. As is well known to those who practice in the intensive care setting, culture data are often negative in the sickest patients and the option of de-escalating based on culture data is often not available.

The de-escalation process becomes less clear when diagnostic studies do not yield an obvious pathogen. Perhaps an appropriate manner of using the information gained by a negative culture is to allow the nonrecovery of certain organisms to influence the alteration of an existing regimen. HAP, including VAP, provides a clinically applicable example of this concept. To minimize mortality, patients with HAP typically receive a three-drug empiric regimen that includes coverage against MRSA and *P. aeruginosa*. ATS/IDSA guidelines for HAP have suggested that clinically improving patients not receiving antibiotics when cultures are obtained may have therapy against MRSA and *P. aeruginosa* stopped if sputum cultures are negative for these pathogens.[79]

The third possibility for achieving de-escalation therapy is by decreasing the duration of therapy to the shortest time length necessary to achieve an optimal clinical outcome.[217] Often the decisions regarding traditional durations of therapy find their basis not in controlled trials or prospective studies, but rather in expert opinion. Although certain infections, such as *S. aureus* bacteremia, require well-defined and often prolonged durations of IV therapy,[218,219] trials in VAP have challenged some of the classic tenets and resulted in recommendations for shorter durations of therapy.

Dennesen and coworkers[220] evaluated the response to antimicrobial therapy administered according to ATS guidelines in 27 patients diagnosed with VAP. The diagnosis was made via bronchoalveolar lavage in conjunction with clinical parameters to confirm the diagnosis of VAP. Semiquantitative tracheal aspirates were used for subsequent microbiologic surveillance and all patients received appropriate antibiotic therapy. After initiation of antimicrobials, T_{max} (maximal temperature over a 24-hour period), partial pressure of arterial oxygen/fraction of inspired oxygen (the ratio used to quantify impairment of oxygen gas exchange in the lung), white blood cell count, and semiquantitative cultures of endotracheal aspirate were monitored. Resolution of clinical parameters occurred primarily within the first 6 days of therapy. Using cultures of endotracheal aspirates, the investigators found that colonization with *P. aeruginosa* persisted throughout the duration of treatment, whereas colonization with *S. aureus, Haemophlius influenzae*, and *S. pneumoniae* resolved shortly after initiation of therapy. Acquired colonization, predominantly with resistant pathogens such as *P. aeruginosa* or members of the Enterobacteriaceae family, usually occurred in week 2 and frequently preceded a recurrent episode of pneumonia. Based on these data, 7 days were suggested to be an appropriate duration of therapy for patients with VAP.

Ibrahim and colleagues evaluated a clinical guideline for the treatment of VAP using 7 days of therapy.[221] A total of 102 patients were prospectively evaluated, 50 before institution of the guidelines and 52 after institution. In addition to more frequent choice of adequate initial antibiotic treatment after implementation of the clinical guideline, patients also had shorter antibiotic courses when treated under the guideline. Investigators noted no mortality difference between the two groups. As was the case with the study by Dennesen and coworkers,[220] a second episode of VAP was more likely to occur in the patients receiving the longer, traditional duration of therapy.

Chastre and associates conducted a prospective, multicenter, randomized, double-blind study of 401 patients with VAP confirmed by quantitative cultures obtained by bronchoscopic protected specimen brush, bronchoalveolar lavage, or both.[222] Only patients who had received initial appropriate antibiotic therapy were included. Investigators divided therapy into two categories: short course, which was given for 8 days in 197 patients, versus long course, which was given for 15 days in 204 patients. Clinical efficacy was similar between the short course and long course groups. Because slightly more patients with nonfermenting gram-negative bacilli (e.g., *P. aeruginosa* and *A. baumannii*) assigned to the 8-day regimen had pulmonary infection recurrences, the investigators were unable to demonstrate the noninferiority of the 8-day regimen for infection by such pathogens compared to the 15-day course of therapy. Multiresistant pathogens more frequently caused recurrences in patients who received the 15-day regimen. Even though the findings from this study do not definitively prove that therapy for HAP or VAP can be limited to 7 days, they lend support to the findings by Dennesen[220] and Ibrahim[221] and their colleagues.

The previously cited trials formed the initial basis for the move to shorter durations of therapy for both HAP and VAP. There have been several additional trials along with meta-analyses and systemic reviews of the topic that have been nicely summarized in the 2016 guidelines by the ISDA and the ATS for the management of adults with HAP and VAP.[4] These guidelines recommend that therapy both for HAP (non-VAP) and for VAP is a 7-day course of antimicrobial therapy, with the acknowledgement that there exist situations in which a shorter or longer duration of antibiotics may be indicated depending on the rate of improvement of clinical, radiologic, and laboratory parameters.

The option for a shorter duration of therapy extends beyond pneumonia. In a randomized clinical trial of 518 patients with complicated intra-abdominal infection who had undergone an adequate source-control procedure, the outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days) that extended until after the resolution of the physiologic abnormalities of fever, leukocytosis, and ileus.[223] The IDSA and European Society for Microbiology and Infectious Diseases collaborated in the development of an international clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women.[224] Those guidelines recommend the option of a 7-day course of oral fluoroquinolone therapy in women with uncomplicated pyelonephritis. Unfortunately, at the present time, there are no guideline recommendations for the duration of therapy in complicated urinary tract infection.

Adding to the decision-making process for reducing duration are advances in biomarker technology. The Stop Antibiotics on Procalcitonin (PCT) Guidance Study (SAPS)[225] was a prospective multicenter, randomized control trial open-label trial in 15 medical centers in the Netherlands involving 1546 ICU patients. Patients were randomly assigned to PCT-guided or standard of care antibiotic discontinuation strategies. Nonbinding advice was provided to the PCT-guided group to discontinue antimicrobial therapy if the PCT concentration had reduced by at least 80% of its maximum value or to less than 0.5 mg/L. The median duration of treatment was shorter in the PCT-guided group. Another interesting result of the trial was the associated reduction in 28-day mortality from 25% in the standard group to 20% in the PCT group. Given improving results in serial measurements of biomarkers, clinicians in ICUs with suboptimal culture collection results or techniques may consider the use of PCT to assist in safely discontinuing antibiotic therapy.

Antibiotic Stewardship in the Intensive Care Unit

To protect the finite resource of antibiotics that are available in clinical practice, it is important for the clinician to use antibiotics judiciously so that currently available agents are active for as long as possible. Several approaches toward achieving this goal have been described.

In a study of international collaboration by five different countries (United States, South Africa, Colombia, Australia, and the United Kingdom), it was shown that individual efforts can positively affect local and national antimicrobial stewardship programs. Based on this finding, the collaborative recommended that antibiotic stewardship models evolve from infection specialist–based teams to those that use cadres of health care professionals, including pharmacists, nurses, and community health workers, to meet the needs of the global population.[226] An implication from this study is that ICU-specific stewardship programs may have merit.

For many years, the standard approach to antibiotic prescribing occurred in a homogeneous manner in which a single or limited numbers of antibiotics were used as the "workhorse" agent(s) in empiric therapy.[227] Such an approach to antibiotic prescribing often resulted in restricted formularies, in the hope that limiting broad-spectrum agents might prevent the emergence of resistance. Unfortunately, this approach did not take into consideration that inadequate therapy in seriously ill patients might not be reversible when clinicians changed initial antibiotics to the correct agents once susceptibilities returned. In addition, it was during this era of restricted formularies that the proliferation of bacterial resistance began to occur. Because an inherent risk with homogeneous antibiotic use is the selective pressure that can lead to resistance, clinicians must consider other approaches.

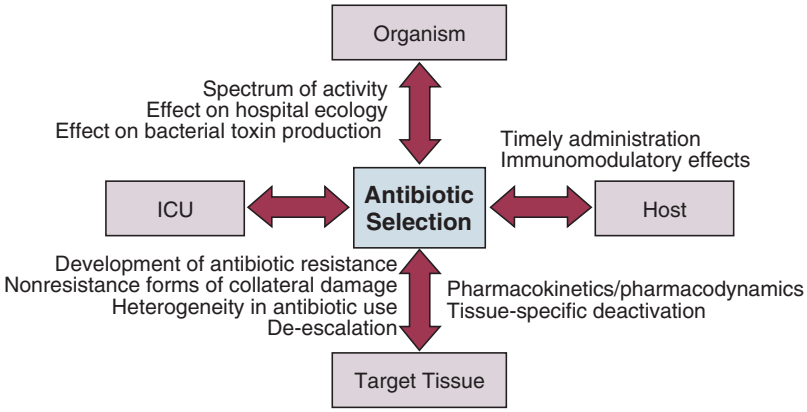
Heterogeneous antibiotic use, in which antibiotic selection is based not on hospital mandates but rather on issues related both to the patient and the pathogens involved in the infectious process, may decrease selective pressure.[228] Clinicians can achieve heterogeneity in any of several ways. A strategy by which multiple or all classes of antibiotics are available for use (i.e., antibiotic heterogeneity) has been suggested as part of a broader effort aimed at curtailing antibiotic resistance within ICUs. A mathematical model was developed to compare antibiotic cycling to the process of mixing, in which antibiotic variation is random as opposed to the regulation that occurs with a process like antibiotic cycling.[229] The premise for such a comparison is that mixing imposes greater fluctuation in selective conditions, thereby yielding greater heterogeneity than occurs with cycling. A simple ecologic explanation led to the conclusion that cycling is unlikely to be effective and may even hinder resistance control. Mixing may yield more favorable results toward the goal of preserving antibiotic susceptibility.

In contrast with homogeneous antibiotic use, which was developed to control resistance, heterogeneous use is aimed at managing resistance.[228] Because resistance at some level is an inevitable part of medical practice, the latter approach seems more insightful.

Conclusions

At a time when bacterial resistance is becoming more prevalent and antibiotic development is not as robust and rapid as necessary, the critical care clinician is faced with the daunting challenge of achieving clinical efficacy without compromising the antibiotic armamentarium that exists at present. For this to be accomplished, the interplay of several important concepts drives the decision process. As depicted in Fig. 48.3, these considerations include the organism, the host, and the targeted tissue, as well as specific issues related to the ICU itself.

Armed with the knowledge of these variables, health care providers now have the foundation for achieving a major goal of antibiotic stewardship: education.[1,2] As noted in the initial guideline for antibiotic stewardship, it was acknowledged that education alone, without incorporation of active intervention, is only marginally effective at changing antimicrobial prescribing practices and has not demonstrated a sustained effect.[2] An understanding of the principles governing antimicrobial selection in the ICU should better position critical care clinicians for practicing the art of antibiotic prescribing in a manner that both achieves efficacy for optimal outcome and preserves the integrity of the antibiotics available for this task.



• **Fig. 48.3** The interplay of antibiotic selection with principles relevant to host, organism, intensive care unit *(ICU)*, and target tissue. Adequate antibiotic therapy is dictated by more than matching the spectrum of antibiotic activity with a pathogen's in vitro susceptibility.

Key Points

- Initial appropriate antibiotic therapy (defined as matching antibiotic to pathogen susceptibility), with early dose administration, reduces mortality in the treatment of serious infections.
- Optimal antibiotic therapy takes into consideration more than the spectrum of activity and also includes dose optimization, ensuring target tissue penetration, and consideration of combination therapy.
- Empiric and directed antibiotic regimens for the individual patient also are influenced by factors that the critical care physician must recognize: time-dependent versus concentration-dependent killing, synergy versus antagonism, immunomodulatory antibiotic properties, inhibition of bacterial protein synthesis, and organ-specific deactivation.
- In selecting antibiotics for serious infections, the clinician should consider not only the individual therapeutic efficacy but also the potential for unintended antibiotic consequences, such as selection of resistant microorganisms.
- Antibiotic therapy is a risk factor for selecting resistant microorganisms and should not be broader in coverage, or given longer in duration, than necessary in clinically stable patients.
- Stratification based on severity of illness plays an important role in clinical decisions about how broad initial antibiotic therapy should be.
- When possible, initial broad and aggressive antibiotic therapy should be rapidly de-escalated as soon as the clinical situation might allow.
- It is important to recognize that resistance to a class of antibiotics may be selected by therapy with an entirely different class of antibiotics.
- With the increasing prevalence of community-acquired mechanisms of resistance such as ESBL production, it is important to stratify initial therapeutic options based on severity of illness.
- Informed decisions concerning initial antibiotic selection must take into consideration surveillance data that reveal patterns of resistance that occur within a practice setting. Timely antibiograms, which when possible are unit-specific, increase the ability to make strategic decisions about initial antibiotic therapy.
- Knowledge of the mechanisms by which antibiotic-resistant bacteria are selected can lead to more judicious patterns of antibiotic use that may ultimately help to manage the evolving global patterns of resistance.

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Review Questions

1. For optimal clinical outcome when selecting empiric antimicrobial therapy, which of the following choices is correct?
- **a.** The clinician should adjust antimicrobial therapy on day 2 or 3 of the clinical course.
- **b.** Timing of initial dosing is key.
- **c.** Optimal dose and dosing interval do not make a difference in outcome.
- **d.** Tissue-targeted therapy has no role in managing infection.

Answer: b. Intensive care unit (ICU) antibiotic stewardship focuses on prevention of antimicrobial resistance and unintended consequences of antibiotics other than resistance. Empiric therapy should be adequate not only for the correct antibiotic based on susceptibility of the organism but also for optimal dose/dose interval, correct route of administration, and use of combination therapy if needed. Other variables playing a role in optimal clinical outcome include time of administration and pharmacologic properties of the agent (i.e., suppressed toxin production with clindamycin in group A streptococcus infection). Another point to consider is the potential for selection of antibiotic resistance (i.e., quinolones and multidrug-resistant *Pseudomonas*).

2. Which one of the following antibiotics would be effective in treating an infection caused by an extended-spectrum β-lactamase–producing strain of *Klebsiella* species?
- **a.** Piperacillin/tazobactam
- **b.** Meropenem
- **c.** Ampicillin/sulbactam
- **d.** Ceftazidime

Answer: b. The resistance that occurs with extended-spectrum β-lactamase (ESBL) producers is of importance in initial antibiotic selection in two regards. Even antibiotics that are stable in the presence of β-lactamases may not have a predictable activity. Inferior outcomes have been seen with cefepime and piperacillin/tazobactam. There is no antibiotic presently on the market with FDA approval to treat infections caused by an ESBL-producing organism. The data extrapolated from medical literature suggest that carbapenems are the drug of choice to treat such infections.

3. Which antibiotic should be avoided while treating an *Enterobacter* infection if laboratory data suggest susceptibility?
- **a.** Levofloxacin
- **b.** Bactrim
- **c.** Ceftriaxone
- **d.** Cefepime

Answer: c. Type 1 β-lactamases (ampCs) are chromosomally mediated product from *ampC* genes. Common β-lactamase–expressing organisms are SPICE or SPACE organisms (*Serratia*, *Pseudomonas aeruginosa*, indole-positive Proteeae, *Citrobacter*, *Enterobacter*) with some authors replacing the "I" for "A" of *Acinetobacter*. Those pathogens do not always express *ampC* genes but they have the potential of doing so. As type 1 β-lactamases have affinity for cephalosporins, third-generation cephalosporins are not predictably stable.

4. The concept of synergy is best described in which of the following?
- **a.** Use of penicillin or ampicillin with gentamicin in enterococcal endocarditis
- **b.** Combination of linezolid and vancomycin to treat methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis
- **c.** Use of β-lactam and an aminoglycoside as empiric therapy for sepsis
- **d.** Combination of ciprofloxacin and linezolid to increase the in vitro bactericidal effect of ciprofloxacin against MRSA

Answer: a. The role of combination therapy has received increased interest. The most frequently cited effect is synergy, which has been well described with penicillin and ampicillin with gentamicin in treatment of enteroccocal endocarditis. In vitro studies of combinations of linezolid and vancomycin or ciprofloxacin with MRSA revealed some slight antagonism with decreased bactericidal activity. Data failed to show that combination of a β-lactam with aminoglycoside has a clinical advantage over monotherapy. Combination therapy has failed to show an advantage in prevention of resistance when treating *Pseudomonas* infection. In the intensive care unit an important advantage of using combination therapy is that it increases the chance of adequate therapy when dealing with multidrug-resistant organisms.

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Antifungal and Antiviral Therapy

LUIS OSTROSKY-ZEICHNER AND MOHANAD AL-OBAIDI

CHAPTER OUTLINE

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- Cidofovir
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- Other Antivirals

Specific Indications and Uses for Antivirals
- Herpes Simplex Virus and Varicella-Zoster
- Cytomegalovirus
- Influenza
- Other Viruses

Over the past two decades, fungal and viral diseases have become progressively more important to the critical care specialist. Increasing populations of immunocompromised hosts with serious fungal and viral infections often require critical care, and patients hospitalized in critical care units are also susceptible to these infections. Effective management of these conditions not only requires use of the appropriate anti-infective agents, but in-depth knowledge of their pharmacodynamic/pharmacokinetic properties, as well as awareness of their physiologic effects, toxicities, and drug interactions. Recent years have also brought important antifungal and antiviral drug developments, giving the clinician an ever-increasing arsenal of therapeutic choices.

Systemic Antifungal Agents

This chapter focuses on systemic antifungal therapy as it is relevant to the critical care setting. Topical therapy of candidiasis and therapy of other systemic fungal infections are omitted or only briefly reviewed. The interested reader is referred to the Infectious Diseases Society of America guidelines on the topic.[1]

Polyenes

Polyenes act by binding to ergosterol in the fungal cytoplasmic membrane, forming pores that causes ionic leakage and osmotic unstability.[2,3] In addition, they were found to cause oxidative damage to *Candia albicans*.[2] Polyenes are fungicidal in most settings and the most prominent members of the family are amphotericin B and nystatin. Both drugs have important toxic effects that often limit their use in patients with organ/system failure. Newer formulations of the drugs have been developed to reduce this limitation.

Amphotericin B and Its Lipid Formulations

Amphotericin B is produced by *Streptomyces nodosus* and is one of the oldest and most widely used antifungal agents. There is much

experience with its use in mycoses and hosts, and it is usually the comparison standard for new therapies.[3] Because of significant acute and chronic toxicities, there is an extensive anecdotal literature describing ways to ameliorate these toxicities, as well as limitations of all these strategies.[4] The advent of lipid-based formulations of amphotericin B has enhanced our ability to limit toxicities and provide adequate courses of therapy.[5]

Amphotericin B has in vitro and vivo activity against most isolates of *Candida* spp., *Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Mucorales, Coccidioides immitis, Paracoccidioides brasiliensis, Aspergillus* spp., *Fusarium* spp., and *Sporothrix schenckii.*[6] The activity of amphotericin B is so broad that it is almost easier to think of this in terms of the few species that are consistently less susceptible or actually resistant to amphotericin B: *Aspergillus terreus,*[7] *Trichosporon* spp.,[8] and *Pseudallescheria boydii (Scedosporium prolificans).*[9] One species of *Candida, C. lusitaniae*, readily becomes resistant to the polyenes.[10] Resistance among isolates of *Candida* is otherwise rare.[11,12]

Amphotericin B is hydrophobic and combined with deoxycholate to permit intravenous (IV) administration in an aqueous solvent. Once in the bloodstream, it dissociates and binds to plasma proteins and lipoproteins. It is stored in the liver and other organs and slowly eliminated. Drug metabolism is complex and not affected by renal or liver failure.[3] Neither hemodialysis nor peritoneal dialysis removes the drug. Measuring drug levels is possible[13] but not of obvious clinical relevance. Cerebrospinal fluid (CSF) penetration is poor. Although amphotericin B is primarily used in IV infusions, it can also be used topically for localized gastrointestinal or urinary infections or instilled directly to treat central nervous system (CNS) infections.

The most common toxicity is the systemic reaction associated with IV infusion, thought to be caused by release of inflammatory mediators from monocytes and macrophages and producing fever, hypotension, and on occasion severe dyspnea. Two forms of renal toxicity are seen. First, a very acute form of renal dysfunction appears to be related to amphotericin B–induced renal arteriolar constriction.[14] Second, cumulative dose-dependent tubular damage is almost invariably seen if significant doses are given. The tubular injury is characterized by potassium/magnesium wasting and azotemia. It is generally reversible when the drug is stopped but it is also particularly aggravated if the patient is volume depleted or given other nephrotoxic drugs. The renal injury also reduces erythropoietin production[15] and thus causes a mild anemia during chronic therapy (the hematocrit typically falls to about 30%). Finally, amphotericin B may precipitate cardiac arrhythmias, especially if the patient is already hypokalemic and hypomagnesemic.[16–19] The deoxycholate formulation of amphotericin B is given intravenously at 0.5 to 1.0 mg/kg per day, but it can also be administered every other day by doubling the dose. To avoid producing a precipitate, it must be diluted in an electrolyte-free solution at no more than 0.1 mg/mL. It should be administered over no less than 1 hour and most authorities prefer a 2- to 3-hour infusion.[20] Because the occasional patient reacts violently to the drug, an initial test dose of 1 mg of the drug may be given before infusing the entire first dose; however we prefer just starting a slow infusion of the first dose. Premedication with acetaminophen, diphenhydramine, and steroids may be used if the patient develops reactions to the infusion. Volume loading appears to reduce nephrotoxicity, and many authorities give (if possible) 500 to 1000 mL normal saline solution just before each dose of amphotericin B. Administration via a central line is advisable as peripherally given amphotericin B often produces phlebitis.

Treatment goals have been traditionally and arbitrarily cumulative (such as 1 or 2 total g), but a time-based approach is increasingly used for some diseases (e.g., for candidemia, where 2 weeks of therapy at 0.6 to 0.7 mg/kg after the last positive blood culture has been shown to produce a late relapse rate of about 1%).[21] Although the importance of therapy in the typical patient is unclear,[22,23] candiduria is sometimes treated with amphotericin B bladder washes. A typical dose is 50 mg of amphotericin B diluted in 1000 mL of water and irrigated over 24 hours. A small number of intracranial fungal infections benefit from intrathecal dosing at 0.1 to 0.5 mg 3 times per week, but expert advice should be sought if this therapy is considered. Intraperitoneal amphotericin B is contraindicated, as it may cause excruciating pain and peritoneal fibrosis.

There are three lipid-based formulations of the drug: amphotericin B colloidal dispersion (ABCD, marketed as Amphotec and Amphocil), amphotericin B lipid complex (ABLC, marketed as Abelcet), and liposomal amphotericin (L-AmB, marketed as AmBisome). The names of these compounds are often confusing. Only one of the drugs (L-AmB) is a true liposome. However, it is not uncommon for physicians to refer to therapy with these compounds in general as therapy with "liposomal amphotericin B." The preferred terminology is "lipid-associated formulation of amphotericin B" (LFAB).[5] When speaking of specific compounds, we find that use of the names ABCD, ABLC, and AmBisome minimizes confusion.

All three LFABs have comparable efficacy among themselves and when compared to regular amphotericin B, but significantly less nephrotoxicity.[5,24] They are also thought to be concentrated and distributed in the reticuloendothelial system, theoretically achieving higher tissue delivery and concentration. The lipid carrier does, however, dramatically change the pharmacology and delivery of these compounds and higher doses than is typical for amphotericin B are both safe and necessary for optimal activity: the licensed doses are 5 mg/kg per day (ABLC), 3 to 6 mg/kg per day (ABCD), and 3 to 5 mg/kg per day (AmBisome). The optimal dose of these compounds is unclear and the agents appear generally equipotent. Dosages of ~3 mg/kg per day would appear suitable for treatment of most serious *Candida* infections. Doses of at least 5 mg/kg per day are used for mold infections, with some authors recommending even higher doses.[25–27] However, it was shown no advantage to using 10 mg/kg per day over 3 mg/kg per day for invasive aspergillosis and other invasive mold infections.[28]

All three LFABs appear active against the same range of fungal infections that can be treated with amphotericin B. The compounds do differ in their relative toxicities.[24] ABCD appears to have significant administration-related toxicity and is not often used. AmBisome and ABLC are both well tolerated, but AmBisome has been associated with somewhat less nephrotoxicity in some patient settings.[29] Some patients will tolerate one formulation better than another.[30,31]

Because of the cost of the LFABs, there has been great interest in the concept of making a pseudo-LFAB by suspending amphotericin B deoxycholate in commercially available lipid emulsions.[32–34] This practice does not, however, consistently reduce toxicity.[35] This may be due to preparation-dependent precipitation of the amphotericin B noted by some[36,37] but not all[38] authors. Most authorities have concluded that further work with this approach should be undertaken as part of a controlled clinical trial that addresses these issues.[39] A meta-analysis on the use of these formulations has been published, but because of heterogeneity, the results are inconclusive.[40]

The cost of the LFABs is significant, but the counterbalancing reduction in nephrotoxicity is also valuable and should be considered when choosing an LFAB versus a conventional amphotericin B.[41] A recent study of the impact of nephrotoxicity of amphotericin B deoxycholate in patients with invasive aspergillosis suggested that this patient population had significant morbidity owing to the amphotericin B itself.[42] Use of amphotericin B deoxycholate produces significant nephrotoxicity in about 30% of patients, increasing hospital length of stay and hospitalization costs by nearly $30,000.[43,44] Nevertheless, the context of amphotericin B–induced toxicity should also be considered. A rise of the creatinine to 3 mg/dL in an otherwise well patient who is being treated with amphotericin B for (say) osteoarticular sporotrichosis may be clinically imperceptible because the patient has no other acute medical problems. On the other hand, a rise in creatinine from 1 mg/dL to 2 mg/dL may be disastrous in a surgical patient who also has nosocomial pneumonia and cardiac insufficiency. No firm guidelines in this area have yet to emerge. We currently believe that an LFAB are the formulations of choice when available.

Flucytosine

Flucytosine (also known as 5-fluorocytosine [5-FC]) is the fluorine analog of cytosine.[45] It was originally synthesized as an antineoplastic agent, but poor antitumor activity and discovery of its antifungal properties led to its further development as an antifungal agent. It acts by deamination to 5-fluorouracil and then conversion to a noncompetitive inhibitor of thymidylate synthetase that interferes with fungal DNA and ribonucleic acid synthesis. It has been demonstrated to be effective in cryptococcosis, candidiasis, and chromomycosis. Drug resistance in vivo develops quickly, so the standard practice is to combine it with another agent.[46,47] 5-FC is water-soluble and has high bioavailability. Protein binding is negligible and approximately 90% is excreted in urine. CSF penetration is good, and both hemodialysis and peritoneal dialysis remove it. It is teratogenic in rats and therefore is contraindicated in pregnancy. Adverse effects include rash, diarrhea, and hepatic dysfunction. High blood levels (>100 μg/mL) are associated with profound leukopenia and thrombocytopenia.[48] This has prompted the recommendation of monitoring drug levels, renal/liver function, and blood counts in patients receiving 5-FC. Doses of 150 mg/kg per day divided in four doses have usually been suggested, but in vivo[49] and human experience[50] suggest that doses of 100 mg/kg per day (again, divided into four doses) may be as effective and better tolerated. Renal failure requires dose adjustment to half the dose if creatinine clearance (CrCl) is 25 to 50 mL/min and a quarter of dose if it falls below 25 mL/min. Patients receiving hemodialysis should be given the latter dose above after dialysis. Combination with amphotericin requires constant monitoring of toxicity parameters and dose adjustment. The target blood level is approximately 50 μg/mL. Most experts would discontinue use of this agent if blood counts start dropping, regardless of the blood levels. The use of 5-FC is currently limited as availability has become extremely limited in certain regions of the world.

The Azole Antifungal Agents

The introduction of this class of drugs was a major advance in antifungal therapy, because they offer both IV and oral (PO) formulations for the treatment of systemic mycosis. Their widespread use has also prompted the emergence of resistance. Azoles act by blocking the activity of lanosterol demethylase, a cytochrome enzyme in both fungal and mammalian cells. Fungal cell membrane synthesis of ergosterol is inhibited and other sterol intermediates are substituted in the membrane, resulting in a nonviable cell. This effect is much slower than that of amphotericin, so these drugs are generally regarded as fungistatic. Because these drugs reduce production of the ergosterol to which polyenes must bind to produce their effect, there is a potential for the azoles and polyenes to appear antagonistic. However, these effects are drug-, organism-, and model-dependent and a range of effects may be seen. This area is complex and has recently been reviewed.[51,52] All of the azoles have the ability to interfere with mammalian sterol synthesis. This was most notable with ketoconazole, which can produce gynecomastia and adrenal insufficiency.[53,54] Subsequent azoles have been selected for lack of such effects. All of the azoles can, however, produce hepatic dysfunction. The most common pattern is that of increased transaminases. However, any form of dysfunction may be seen. This can be life-threatening if not recognized. The hepatic dysfunction is usually reversible upon discontinuation of the offending azole.

Another concern with azoles is drug interactions. This becomes particularly important in the critical care setting where many drugs are being used concomitantly. Table 49.1 summarizes the most important drug interactions that have been reported. The critical interactions are generally related to drugs cleared by the liver. Some agents (e.g., rifampin and phenobarbital) induce the enzymes that clear the azoles. In other cases, the azole interferes with clearance of another agent (e.g., the azoles predictably increase blood levels of cyclosporine). It is not possible to list all of the known interactions. Consultation with a pharmacy specialist is suggested when using azoles in the setting of polypharmacy, particularly in the critical care setting and when caring for patients with multiple comorbidities.

Fluconazole

Fluconazole is a triazole with in vitro and in vivo activity mainly against yeast, such as *Candida* spp. and *C. neoformans*. It also has efficacy against *C. immitis*, *H. capsulatum, and B. dermatitidis.* Unfortunately, resistance (mediated by increased production of target enzymes, efflux pumps, and mutations in the target enzyme) has become a problem, particularly in *C. albicans* (mutation to resistance is seen), *C. glabrata* (has intrinsically lower susceptibility and may become highly resistant), and *krusei* (intrinsically highly resistant).[55,56] Nevertheless, fluconazole is still very active against most strains causing invasive candidiasis and higher doses can be used for organisms that have "dose-dependent susceptibility." Fluconazole is water-soluble and is available in oral and IV preparations that can achieve similar blood levels as it has excellent bioavailability and it is well absorbed regardless of the gastric contents. It has a long half-life and can be administered in a single daily dose. It exhibits little binding to serum proteins and is widely distributed in all body fluids. CSF penetration is particularly high, making it very useful in the treatment of CNS infections such as cryptococcosis and coccidioidomycosis. Fluconazole is excreted by the kidneys and dosing should be adjusted in proportion to the CrCl. The most common adverse effects are nausea and vomiting; skin rash is infrequent but can be severe and hepatitis has also been reported. The usual dose is 400 to 800 mg (or 6–8 mg/kg) per day PO or IV, but doses as high as 2 g/day have been tolerated.[57]

Itraconazole

Itraconazole is a triazole antifungal agent with a wider spectrum than fluconazole. It has in vitro and in vivo activity against *Candida*

TABLE 49.1 Selected Azole-Drug Interactions[a]

Azole Drug	Azole Alters Levels of:	Azole Levels Altered by:
Fluconazole	Cisapride Cyclosporine Diazepam Glipizide Glyburide Midazolam Phenytoin Rifabutin Sulfonylureas Tacrolimus Terfenadine Warfarins and coumarins Amitriptyline, nortriptyline Carbamazepine Celecoxib Fentanyl HMG-CoA reductase inhibitors Saquinavir Quinidine	Rifampin
Itraconazole	Astemizole Cisapride Cyclosporine Diazepam Digoxin Dihydropyridines Lovastatin Methylprednisolone Midazolam Phenytoin Quinidine Ritonavir Sulfonylureas Terfenadine Vinca alkaloids Warfarins and coumarins	Carbamazepine DDI H2-blockers Phenobarbital Phenytoin Proton pump inhibitors Rifabutin Rifampin Sucralfate Ritonavir
Voriconazole	Sirolimus Rifabutin Efavirenz Ritonavir Terfenadine Astemizole Cisapride Pimozide Quinidine Cyclosporine Methadone Tacrolimus Phenytoin Warfarin Omeprazole Fentanyl Oxycodone Oral contraceptives (containing ethinyl estradiol and norethindrone)	Rifampin Efavirenz Rifabutin Ritonavir Carbamazepine Phenytoin
Posaconazole	Sirolimus Tacrolimus Cyclosporine Pimozide Quinidine Simvastatin Ergot alkaloids Midazolam Ritonavir Atazanavir Vinca alkaloids Calcium channel blockers Digoxin Glipizide HMG-CoA Reductase inhibitors	Efavirenz Rifabutin Phenytoin Cimetidine Esomeprazole Metoclopramide
Isavuconazole	Bupropion Lopinavir/ritonavir Sirolimus Tacrolimus Cyclosporine Mycophenolate mofetil Digoxin Atorvastatin Midazolam Colchicine Dabigatran	Lopinavir/ritonavir Rifampin Carbamazepine Long-acting barbiturates St. John's wort

[a]Generally, azoles tend to increase the levels of other drugs, whereas other drugs tend to decrease the level of the azole. This list is not meant to be comprehensive and the prescriber should consult the full prescribing information. Consultation with a pharmacy specialist is recommended when azoles are to be used in complex polypharmacy situations.

spp., *Aspergillus* spp., *Histoplasma* spp., *B. dermatitidis, S. schenckii, Trichophyton* spp., *C. neoformans, C. immitis,* and *P. brasiliensis*.[58,59] The resistance issues observed for fluconazole are also an issue with itraconazole.[56] Itraconazole was initially available only in a capsule form with unpredictable bioavailability. Absorption of the capsule formulation is optimized by ingestion with food.[60] Two formulations were later introduced. First, there is the cyclodextrin solution formulation for oral administration that significantly enhances bioavailability and is now preferred over the capsule for producing maximal blood levels.[61] Second, an IV formulation (in a cyclodextrin carrier) was developed and it has been shown to quickly and reliably produce significant blood levels.[62–64] However, the IV formulation later became unavailable in the United States.[65] Itraconazole is highly protein-bound and has a prolonged half-life. CSF penetration is negligible, so it is not generally used for CNS infections. Itraconazole is metabolized by the liver and dosing does not need to be modified in renal failure. However, the cyclodextrin carrier used in the IV formulation is cleared by the kidneys and its behavior in patients with renal dysfunction is not known. Thus this formulation of itraconazole should not be used in patients with a CrCl below 25 mL/h. IV itraconazole was shown to cause transient decrease in cardiac contractility in experiments involving dogs and is contraindicated in patients with congestive heart failure.[65]

Adverse effects are mainly gastrointestinal, with nausea, vomiting, and abdominal pain occurring in up to 10% of patients. Hepatitis is uncommon but liver enzyme monitoring is recommended. Because

itraconazole and its major metabolite hydroxyitraconazole are inhibitors of cytochrome P450 3A4 (CYP 3A4), drug interactions are a major issue and the most common ones are summarized in Table 49.1.[65]

The usual oral dose is 100 to 400 mg/day and the oral solution formulation is now preferred. Giving the daily oral dose as two divided doses appears to maximize blood levels. IV dosing is 200 mg twice a day for 2 days and then 200 mg IV daily for a maximum of 14 days. Efficacy is plasma concentration-related and serum levels can be obtained from national reference laboratories. Such testing is warranted if oral itraconazole is being used to treat a serious fungal infection. Although minimal efficacious blood levels have not been defined, the point of testing is to ensure that at least some level is being obtained. Levels of at least 250 ng/mL are desirable.[61,65,66]

Voriconazole

Voriconazole is licensed for the treatment of invasive candidiasis and invasive aspergillosis, as well as for the treatment of *Fusarium* and *Scedosporium* infections. It is considered the treatment of choice for invasive aspergillosis.[67] Voriconazole was not inferior to amphotericin B followed by fluconazole in a large clinical trial, but it is unknown if it has any advantages over fluconazole or the echinocandins for treating infections by fluconazole-resistant *C. glabrata*.[68,69] Although it has activity against the endemic mycoses, data are limited at this point, so it is not recommended for routine use in these infections at this time.[70,71]

A relevant gap in its activity is for the Zygomycetes (such as *Mucor* spp., *Absidia* spp., and *Rhizopus* spp.). Moreover, there have been multiple reports of breakthrough Zygomycetes infections in patients receiving voriconazole prophylaxis or treatment, but a causal relationship has not been established.[72,73] Nevertheless, clinicians should be aware that this drug does not have activity against these organisms; thus it should not be used for empirical therapy of mold infections if Zygomycetes are in the differential diagnosis.

Voriconazole is available in oral (tablets and suspension) and IV formulations, with 96% bioavailability. The usual dosing is 4 to 6 mg/kg IV every 12 hours or 200 to 400 mg PO every 12 hours. Voriconazole has nonlinear pharmacokinetics; thus increasing the dose does not necessarily increase blood levels. Routine blood level measurement to document absorption is now recommended, although blood levels associated with specific efficacy and safety margins have not been established. In addition, voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP 2C19, CYP 2C9, and CYP 3A4, and has extensive drug interactions with many drugs commonly used in the critical care setting. Certain patients were identified as rapid metabolizers and others as slow metabolizers (15% of Asian descent), and proper levels monitoring is warranted.[66] Consultation with a pharmacy specialist is recommended for patients receiving multiple drugs. Like itraconazole, the IV formulation is prepared in a cyclodextrin-based formulation; thus it is not recommended for use in patients with CrCl below 50 mL/min. In contrast, in this patient population, the oral formulation may be safely used. Adverse events include self-limited visual disturbances and hallucinations (usually in higher levels >5.5 μg/mL), infrequent reports of hepatic insufficiency, skin photosensitivity, increased incidence of skin cancers with long term use,[74,75] painful periostitis,[76,77] and as with the other azoles, rare reports of arrhythmias and QT prolongation. Also to be kept in mind is that monitoring of liver enzymes is recommended during voriconazole therapy.[78–80] Trough levels above 0.5 μg/mL are recommended for prophylaxis, whereas levels below 1 to 2 μg/mL achieve therapeutic effect.[66]

Posaconazole

Posaconazole is a triazole licensed primarily for prophylaxis of fungal infections in high-risk patients,[81,82] and has promising activity against mold infections, particularly infections by the Zygomycetes and *Fusarium*.[83] It has also shown excellent in vitro and in vivo activity against *Candida* spp. with demonstrated efficacy in esophageal disease. Posaconazole has high protein binding (~99%). It is available in an oral formulation and recently in IV form.[84–86] A new formulation of tablets (delayed-release) has a better profile with regard to achieving steady-state levels at faster rates compared to the oral solution; it can be given without food and once daily in cases of antifungal prophylaxis.[86] Similar to other triazoles, posaconazole can lead to adverse effects such as elevated liver enzymes, gastrointestinal symptoms, and QT prolongation. There is no dose adjustment in renal failure except for the IV formulation (cyclodextrin-based formulation), which is not recommended to be given to patients with CrCl below 50 mL/min. The goal level of prophylaxis is above 0.7 mg/L with levels above 1 mg/L for therapy.[87]

Isavuconazole

Isavuconazonium sulfate is the most recent U.S. Food and Drug Administration (FDA)-approved triazole for the treatment of invasive aspergillosis and mucormycosis. Isavuconazonium sulfate is the prodrug for isavuconazole; we refer to it by the latter. Isavuconazole acts by inhibiting CYP 450–dependent enzyme lanosterol 14-α-demethylase and leads to the accumulation of methylated sterol precursors and depletion of ergosterol from the fungal cell wall.[88]

Isavuconazole comes in oral and IV formulations. Both have excellent tissue distribution; however, they are 99% bound to serum proteins, mainly albumin. The oral formulation has great bioavailability (98%). No dosage adjustment is needed in patients with renal or hepatic dysfunction.

Isavuconazole has been shown to affect L-type calcium (Ca^{++}) cardiac channels, and in contrast to other triazoles, it has been shown to cause QT shortening. Although no serious arrhythmogenic effect has been linked to QT interval shortening, it is advisable to avoid isavuconazole in cases of a familial short QT period.[89–91] In a noninferiority trial comparing voriconazole to isavuconazole in immunocompromised patients with invasive aspergillosis (IA), isavuconazole was shown to be as effective as voriconazole with lower rates of adverse events (elevated hepatic enzymes, visual disturbance, and skin reactions).[90] In a limited study, isavuconazole was also shown to be effective in patients with mucormycosis who could not tolerate primary amphotericin B–based therapy or in those in whom such therapy failed when compared to historical controls.[91] Isavuconazole dosage is 372 mg IV or PO every 8 hours for 2 days (loading dose) and then daily.

Echinocandins

The echinocandin antifungal agents represent an entirely new class of antifungal drugs. There are three echinocandins on the market at this time: caspofungin, micafungin, and anidulafungin. These agents are cyclic lipohexapeptides that act via inhibition of glucan synthesis.[92] Preclinical studies have shown efficacy against all species of *Candida*, *Aspergillus* spp., and selected other fungi.[93,94] Although the target enzyme is present in most fungi, the echinocandins are not active against *C. neoformans* and molds other than *Aspergillus*.

The echinocandins appear to be rapidly fungicidal for *Candida* spp., but their activity against *Aspergillus* may be better described as fungistatic.[95] Nonetheless, they are quite active in animal models of both candidiasis and aspergillosis.[96,97] The drugs have a long half-life, permitting once-daily dosing, and are excreted in the liver. They do not interfere with the cytochrome system and are not known to be nephrotoxic, having otherwise remarkable safety profiles. At this time, differences between the three drugs appear to be subtle, requiring further study. Echinocandins are found to have better survival benefit in patients with invasive candidiasis and they should be considered as the first-line therapy for this disease.[98,99]

Caspofungin

Caspofungin was the first candin in the market. It has excellent in vitro and in vivo activity against *Aspergillus* and *Candida* spp. It has demonstrated efficacy for the treatment of invasive candidiasis, invasive aspergillosis, and empirical therapy of fungal infections in the setting of febrile neutropenia.[100–102] The usual dosing includes loading with 70 mg IV, followed by 50 mg IV every 24 hours. The safety profile is good with mild elevation of liver enzymes. Patients with hepatic insufficiency (Child-Pugh class B or C) require dosage adjustment to 35 mg/kg IV every 24 hours.[71,103,104] Drug interactions are infrequent, but monitoring cyclosporine levels in patients receiving caspofungin is recommended.[105] In a clinical trial, higher doses of caspofungin (100 mg/day) are well tolerated but do not necessarily translate into additional clinical benefits.[106]

Micafungin

Micafungin is approved by the FDA for the treatment of esophageal candidiasis, prophylaxis of *Candida* infections in stem cell transplant patients, and treatment of candidemia. Although micafungin has excellent in vitro and in vivo activity against *Aspergillus* and *Candida* spp., clinical data on invasive aspergillosis is limited.[107–109] Micafungin has demonstrated efficacy both for the treatment of invasive candidiasis and as a prophylactic agent for fungal infections in allogeneic stem cell transplant recipients.[109–111] The prophylactic dose is 50 mg IV every 24 hours, and the therapeutic dose for invasive candidiasis is 100 IV every 24 hours. As with the other echinocandins, the most frequent adverse event is mild elevation of liver enzymes. No dosage adjustment is required in the setting of renal insufficiency or moderate hepatic insufficiency. The European package insert for this drug mentions an increased incidence in hepatic tumors in animals with very prolonged high-dose exposure.[112] This finding has not been observed in humans. Mild drug interactions have been reported with concomitant use of sirolimus and nifedipine.

Anidulafungin

As with the other candins, anidulafungin has excellent in vitro and in vivo activity against *Aspergillus* and *Candida* spp.[113] It is currently indicated for the treatment of invasive candidiasis, having demonstrated noninferiority, and perhaps superiority, in a clinical trial versus fluconazole.[114] The usual dosing includes a loading dose of 200 mg IV followed by 100 mg IV every 24 hours. Anidulafungin does not require dosage adjustment for patients with renal or hepatic failure and no significant drug interactions are reported.[113,115,116]

Specific Indications and Uses for Antifungals

Although the precise diagnosis of a fungal infection may be laborious, time-consuming, and delayed, therapy should never be withheld in a critically ill patient with suspected or confirmed fungal infection. Empirical therapy is often started with an echinocandin or amphotericin B (typically one of its lipid preparations) and then tailored according to the final identification of the organism. This section presents generally accepted treatment recommendations for the most commonly encountered fungal infections in the critical care setting. Infections by less common fungi may be particularly severe and rapidly progressive and require consultation with an infectious diseases specialist for appropriate treatment. Table 49.2 summarizes the most often encountered fungal diseases in the critical care setting with their generally accepted treatment options. Fig. 49.1 presents our approach for the critically ill patient with fungemia.

Candida Infections

Although *C. albicans* remains the most common pathogen in oropharyngeal and cutaneous candidiasis, non-*albicans* species of *Candida* are increasingly frequent causes of invasive candidiasis.[117] Guidelines and reviews for therapy of candidiasis in the intensive care setting have recently been published.[99] These guidelines are extensive and are not repeated in detail. Rather, the text focuses on several clinical situations in which candidal infections are particularly challenging for the critical care specialist.

Candidemia and Disseminated Candidiasis

The diagnosis of disseminated candidiasis is always a challenge.[118] There is no single tool that conclusively makes this diagnosis. Isolation of *Candida* from the bloodstream is simply the most obvious form of disseminated candidiasis, but clinical experience makes it obvious that disseminated candidiasis can occur in the absence of detectable fungemia.

Candidemia may be treated initially with echinocandins, fluconazole, voriconazole, or amphotericin B (or its lipid preparations). In the critically ill and unstable patient, echinocandins are preferred because of their broader spectrum of activity and more rapid onset of action.[119,120] Both the anidulafungin study and recent patient-level meta-analysis of the candidemia clinical trials suggest that initial therapy with echinocandins may be superior to initial therapy with azoles.[98,114]

The susceptibility of *Candida* to the currently available antifungal agents can generally be predicted if the species of the infecting isolate is known.[10,12,117,121–129] Bloodstream isolates of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* are generally susceptible to fluconazole and amphotericin B. Isolates of *C. glabrata* and *C. krusei* are often (if not always, as is the case with *C. krusei*) resistant to fluconazole. Isolates of *C. lusitaniae* may be resistant to amphotericin B. Antifungal susceptibility testing is becoming increasingly important as a guide in the treatment of these infections.[130] In particular, detection of fluconazole resistance is very valuable, as it provides support for continued use of candins or polyenes. An emergent pathogen in intensive care units (ICUs) throughout the world, *C. auris*, may exhibit multidrug resistance, including nonsusceptibility to azoles, echinocandins, and amphotericin B.[131,132]

Although all *Candida* spp. are generally considered to be susceptible to echinocandins, *C. parapsilosis* has higher minimal inhibitory concentrations than the other *Candida* spp. This, however, has not translated into reduced activity in clinical trials.[100,133] Once the organism is identified, or if the prevalence of more resistant species is low, therapy may be switched to fluconazole 5 to 7 days after initiation of an echinocandin. Fluconazole has been demonstrated to be as effective as amphotericin B in clearing candidemia in immunocompetent hosts. The duration of treatment is 14 days after the last positive culture,[21] and if a central line is present removal is highly recommended.[98] Patients with candidemia are at risk of developing *Candida* endophthalmitis (1%–5%)[134,135]; thus performing

TABLE 49.2 Summary of Therapeutic Choices for Fungal Diseases Most Commonly Encountered in the Critical Care Setting

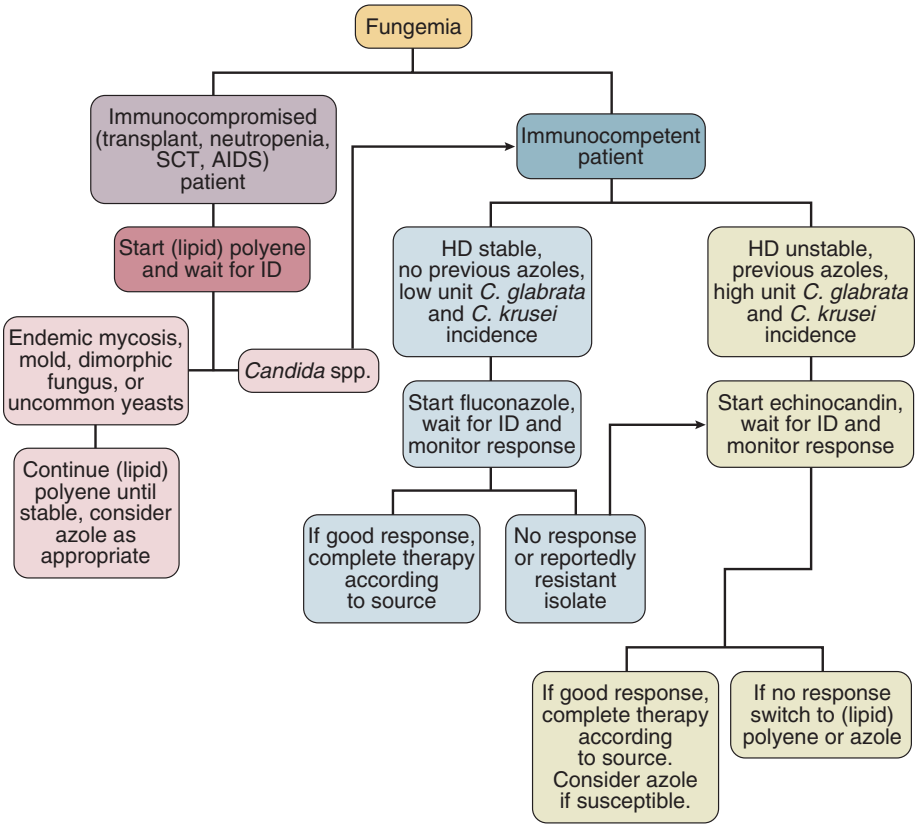
Fungal Disease	Therapy of Choice	Alternative Therapy	Duration of Treatment	Comments
Candidiasis				
Oral candidiasis	Fluconazole 200 mg single dose or 100 mg PO per day	Nystatin 200,000-U lozenges qid or 500,000-U swish and swallow qid	7–14 days	
Mucosal nonoral candidiasis	Fluconazole 200 mg first dose and continue 100 mg/day		7–14 days	
Candidemia and most forms of disseminated candidiasis	Caspofungin 50 mg/day (loading dose with 70 mg on day one); anidulafungin 100 mg/day (loading dose with 200 mg on day one); or micafungin 100 mg/day; fluconazole 400 mg qd, voriconazole 4–6 mg/kg/q12 hr, amphotericin B 0.5–0.6 mg/kg per day, lipid preparation of amphotericin B 3 mg/kg per day,		14 days after bloodstream clearance for uncomplicated candidemia; until resolution of sites of infection if disseminated	Central line removal is recommended. Assess for dissemination. An echocandin or lipid amphotericin B is usually preferred as initial therapy if the patient is unstable or infected with a non–*albicans* species. Loading doses recommended for caspofungin and anidulafungin
Urinary candidiasis	Fluconazole 200 mg first day and then 100 mg/day or amphotericin B 0.3 mg/kg IV single dose	Amphotericin B bladder washes, 50 mL/1000 mL H_2O in continuous irrigation for 2 days	7–14 days	Asymptomatic funguria does not require treatment. However it may be a sign of dissemination in immunocompromised hosts. Urinary catheter removal is very useful
Peritonitis	As for disseminated candidiasis			Removal of dialysis catheter is helpful. Surgical debridement if abscess present
Aspergillosis	Voriconazole 4–6 mg/kg per q12h (loading dose with 6 mg/kg IV q12hrs for 2 doses) Isavuconazole 372 mg daily (loading dose with 372 q8hrs for 6 doses)	Lipid preparation of amphotericin B 3 mg/kg per day	Until resolution of the clinical process and of any associated immunosuppression	May require surgical treatment. Isavuconazole and voriconazole can be administered orally or intravenously.
Histoplasmosis	Amphotericin B 0.5–1 mg/kg per day or liposomal amphotericin B 5 mg/kg per day	Itraconazole 200–400 mg/day 200 mg TID for 3 days then 200 mg BID	3–12 months	Lifelong suppression needed in HIV-infected patients
Cryptococcosis (in HIV-infected patients)	Amphotericin B 0.5–0.7 mg/kg per day or lipid preparation of amphotericin B 3–5 mg/kg per day + 5-FC induction 25 mg/kg q6h, fluconazole 400 mg per day during consolidation period	Induction with fluconazole 400 mg/day in stable patients	Managed very differently in HIV-infected (lifelong therapy needed) and uninfected patients (cure is possible). Expert consultation advised.	Consider frequent LP to relieve intracranial pressure. V-P shunts may be necessary.
Zygomycosis	Amphotericin B 0.8–1.5 mg/kg per day or lipid preparation of amphotericin B 5 mg/kg IV per day + surgical debridement + metabolic control	Isavuconazole or consider polyene + caspofungin. Limited experience with posaconazole		Surgical debridement is critical

5-FC, Flucytosine; *HIV,* human immunodeficiency virus; *LP,* lumbar puncture; *V-P,* ventriculoperitoneal.

a dilated eye examination is necessary to avoid catastrophic sequelae. Cases of proven *Candida* endophthalmitis should be evaluated and managed by an ophthalmologist, and systemic and topical antifungal therapy should be considered for a duration of 4 to 6 weeks. If evidence of disseminated candidiasis is found, therapy should be prolonged to at least 4 weeks to ensure proper organ clearance.[99]

The Intravenous Catheter in Patients With Candidemia

Although long an area of contention, current data strongly suggest that candidemia is often related to (if not primarily propagated by) a central venous catheter. Central venous catheters in particular



• **Fig. 49.1** Treating the critically ill patient with fungemia. *AIDS,* Acquired immunodeficiency syndrome; *HD,* hemodynamically; *ID,* identification to species level; *SCT,* stem cell transplant. (Modified from Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. *Crit Care Med.* 2006;34: 857–863.)

have been found to be both risk factors for developing candidemia[136–139] and associated with persistent fungemia.[137] Removal of the catheter has been associated with shorter duration of subsequent candidemia[140] and improved patient outcomes.[98,141,142] Unique to the species of *Candida*, candidemia with *C. parapsilosis* is almost always due to a catheter.[143,144] The situation may be different for neutropenic patients, particularly those who have permanent, lower-risk catheters such as Hickman catheters. Such catheters may of course become infected, but these patients may also have candidemia owing to gut translocation. This concept is supported by demonstrations that *Candida* can enter the bloodstream from the gut,[145] by the relative lack of effect of catheter removal in a large cohort of cancer patients,[143] and by the frequent demonstration of gut wall invasion in patients who die with disseminated candidiasis.[146,147] Unfortunately, there is no convincing way to tell if a given catheter is involved. Differential quantitative blood cultures through the line and from a peripheral site have been suggested to be one approach to resolving this problem,[148] but this technique remains controversial.[149] On a practical basis, lines should be removed if possible, and serious consideration of line removal should be given if fungemia persists for more than a few days. A recent patient level meta-analysis of the major candidemia clinical trials has confirmed a mortality and microbiologic cure benefit for this approach.[98]

Mucosal Infections and Colonization

Although there are many risk factors for development of disseminated candidiasis, colonization at one or more nonsterile sites represents an unusually strong risk factor.[150] As discussed earlier, local oral and mucosal candidiasis should thus be considered as a predictor of possible invasive disease in the critically ill or immunocompromised host.[151,152] Esophageal candidiasis does require systemic treatment. Fluconazole is generally preferred here, although amphotericin B and the echinocandins can also be used.

Candiduria

Treatment of asymptomatic candiduria produces only temporary clearing of the urine and is probably not indicated.[22,23] However, candiduria should probably be treated in symptomatic patients, immunocompromised patients, low–birth-weight infants, renal transplant patients, and patients undergoing urologic manipulation or surgery.[99] If treatment is indicated, systemic therapy with amphotericin or fluconazole is preferred and amphotericin bladder washes should be reserved for patients with renal insufficiency and low renal clearance. Removal of the urinary catheter is by itself a useful intervention and should always be considered.

Other Forms of Invasive Candidiasis

There are many other possible forms of invasive candidiasis: meningitis, endocarditis, and osteomyelitis, just to name a few. This area has recently been reviewed[99] and for most forms of this disease there are very few specific data regarding therapy. The largest body of data will always be anecdotal reports of use of amphotericin B, and for essentially every form there are at least a few reports of successful therapy with fluconazole. In general, LFABs are preferred when the infection is most acute, when data

on the nature of the infection are still being generated in the laboratory, or when the patient has previously received azole therapy. Fluconazole provides a good way to step down to an oral agent to complete therapy of infections caused by susceptible isolates. Data for the echinocandins are starting to accumulate for these chronic infections.[153] Removal of foreign body and surgical drainage are often key as well. An excellent example of the need to remove foreign bodies is found in treatment of dialysis catheter–related peritoneal candidiasis in which catheter removal is important. Surgical drainage is of course important in candidal peritonitis related to gut injury and fecal spillage.

Cryptococcosis

Treatment of cryptococcosis has previously been reviewed.[154,155] Cryptococcal meningitis in non–human immunodeficiency virus (HIV)-infected adults continues to be seen sporadically. The majority of the published experience on treatment is with amphotericin B given for 4 to 6 weeks.[156,157] This therapy is curative in approximately two-thirds of patients; thus this approach is warranted. Expert consultation is also appropriate for this relatively uncommon infection.[158,159]

On the other hand, cryptococcal meningitis in the HIV-infected patient is a well-established and common problem. Meningeal cryptococcosis in this setting should be treated with a 2-week course of IV amphotericin or its lipid preparations,[155,160,161] followed by suppression with fluconazole until CD4 cells recover.[162,163] Current trends favor also using 5-FC unless there is a contraindication to same.[50] High-dose fluconazole (up to 1200 mg/day) combined with 5-FC has shown to be effective in cryptococcal meningitis in HIV patients when amphotericin B is not available or not tolerated.[164] Although itraconazole does not penetrate the CSF, anecdotal evidence reported that it may be useful in treating CNS disease; however, it is apparently less potent as a long-term therapy.[165]

For all forms of cryptococcal meningitis, intracranial hypertension should be aggressively treated with repeated lumbar punctures or a CSF shunt.[166,167] The addition of steroids and other immune-modulating agents to antifungal therapy has shown promising results in animal models[168] and clinical trials are being conducted. The immune reconstitution syndrome plays a major role in cryptococcal-related morbidity in HIV patients and the current recommendation is to delay antiretroviral therapy for a few weeks after treatment for cryptococcosis is started.[155]

Aspergillosis

Treatment of aspergillosis has been extensively reviewed.[169–171] Invasive aspergillosis should be considered in any severely immunocompromised patient with an unexplained pulmonary or sinonasal process. Biopsy is normally required for definitive diagnosis, although a new generation of galactomannan-based serodiagnostic tests may prove useful as adjuncts to diagnosis.[172,173] Although amphotericin B has classically been the initial treatment of choice for invasive aspergillosis, the current treatment of choice is voriconazole,[67,80] isavuconazole,[90] or a lipid preparation of amphotericin B.[170] Aggressive surgical management is necessary and curative in some cases.[118,174] Itraconazole is also approved for the treatment of aspergillosis in patients who are intolerant or refractory to amphotericin B.[175] Overall, the outlook for invasive aspergillosis is critically dependent on recovery of immune function. Without this, the prognosis is usually dismal. Of note, recent studies have documented an increase in the incidence of invasive aspergillosis in nonhematology, nontransplant patients seen in the ICU such as chronic obstructive pulmonary disease and autoimmune diseases,[176,177] and in hospitalized ICU patients with influenza.[178] This trend should be monitored and the critical care specialist should be suspicious when cultures *Aspergillus* from a bronchoalveolar lavage or diagnostic markers such as galactomannan are positive.[179]

Histoplasmosis

The initial treatment of choice for severe acute histoplasmosis is an amphotericin B preparation.[180,181] Noncritical cases may be treated with itraconazole 200 to 400 mg/day. Fluconazole is only moderately effective and should not be used as primary therapy.[182] Successful treatment results in a decrease of serum and urine *Histoplasma* antigen.[183] The duration of therapy is a function of disease form and underlying immune status. HIV-infected patients with disseminated disease should be treated as acute histoplasmosis and maintained with lifelong suppression with itraconazole. Liposomal amphotericin B has shown excellent efficacy in this setting.[184] Non–HIV-infected patients may require from 3 to 12 months of therapy, and expert consultation is generally advised.

Mucormycosis

The treatment of choice for mucormycosis (infections typically caused by *Mucor* spp., *Rhizopus* spp., and *Absidia* spp.) is aggressive surgical debridement and prompt start of high-dose amphotericin B or a lipid preparation.[185] Follow-up therapy with active triazole therapy may be warranted, and expert consultation is advised. Isavuconazole has been recently approved for mucormycosis therapy for patients unable to tolerate amphotericin B therapy or those in whom such therapy has failed.[91] Posaconazole has also shown efficacy in this setting.[85] Meanwhile, despite the in vitro lack of activity of echinocandins against these agents, investigators have shown in vitro synergy and excellent clinical outcomes with the combination of amphotericin B and caspofungin.[186] Correction of metabolic abnormalities (acidosis, iron overload, and hyperglycemia) should also be pursued aggressively.

Other Fungal Infections

Other fungal infections, such as blastomycosis, fusariosis, and infections by *Trichosporon* spp., *C. immitis, Malassezia furfur,* and *Penicillium* spp., may be occasionally encountered in the critical care setting, particularly when caring for immunocompromised hosts. Although amphotericin B or an LFAB is probably the best empirical drug for any uncharacterized suspected fungal infection, it is not very effective against some of these pathogens. Guidelines for treating some of these infections have recently been published.[1] Expert consultation should be promptly obtained.

Areas of Controversy in Antifungal Therapy

Empirical Antifungal Therapy for the Febrile ICU Patient

Fever in the ICU patient is a complex problem that requires prompt evaluation for many possible sources, including infection, atelectasis, pulmonary embolism, drug fever, thermoregulatory dysfunction, and many more.[187] Infection by *Candida* should be suspected when the patient has risk factors such as immunocompromised,

broad-spectrum antibiotic therapy, central venous line, mechanical ventilation, parenteral nutrition, steroids, surgery (especially if the gut wall is compromised), urinary catheters, and burns.[188–191]

Unfortunately, making a diagnosis of invasive candidiasis is difficult. In the most straightforward scenario, the patient is febrile and has positive blood cultures for *Candida*. On other occasions, biopsy or aspiration is used to make a clear-cut diagnosis of a localized abscess caused by *Candida*. These situations are, however, the exception. Far more common is the scenario of a persistently febrile ICU patient with a combination of the above-mentioned risk factors. The presence of *Candida* colonization in different nonsterile body parts has been implemented in some ICU risk assessment scoring systems.[192,193] Positive cultures from the urine are also considered in this context (even though that is normally a sterile site). Candiduria in the afebrile patient is generally a clinical non-event that does not require therapy,[22,23] but candiduria in the febrile ICU patient at the very least represents colonization and increased risk of invasive disease and at the worse represents actual upper urinary tract infection. A similar logic applies to *Candida* in the sputum. Pneumonia caused by *Candida* occurs but is generally clinically inapparent.[194] The presence of *Candida* in the sputum more often originates from the gut, and thus the patient is colonized. This, in turn, is a risk factor as discussed earlier. Such a risk factor was devised as part of a scoring system, the Candida colonization index, which requires culturing several nonsterile sites to calculate. However, its benefits are controversial.[191,195]

It has been shown that the delay in starting appropriate antifungal therapy in ICU patients with invasive candidiasis is associated with increased mortality.[196] Infectious Diseases Society of America guidelines recommend empirical antifungal therapy in critically ill patients who are deemed to be high risk for the infection based on a variety of recently available risk scoring assessment strategies and scores.[99,191,197,198] However, there is a multicenter study with negative results that failed to show a benefit to fluconazole in this setting.[199]

Antifungal Prophylaxis in the ICU

Prevention is always preferred to therapy, and this is certainly true for invasive candidiasis. Although prevention of mucosal disease can be achieved with almost any regimen, prevention of invasive disease has consistently required systemic therapy. Both fluconazole and amphotericin B are effective in the right setting. The key is to select patient populations with a meaningful chance of contracting invasive candidiasis. The value of prophylaxis has been shown convincingly for bone marrow transplantation patients[200,201] and selected liver transplant patients.[202–205] Studies of patients receiving standard chemotherapy for leukemia have shown a trend favoring prophylaxis,[206,207] but the lower rates of disease in the control group reduced the statistical power of the studies. To further confuse matters, even a group that sounds homogeneous (e.g., allogeneic bone marrow transplant recipients) really is not—different forms of chemotherapy and degrees of graft-versus-host disease produce different levels of risk. This point was driven home in an editorial emphasizing the range of variation within the category of "neutropenic patient."[208]

In practical terms, multiple studies have demonstrated benefits to prophylaxis of invasive candidiasis in the ICU. [209–212] Although survival benefit is shown in one meta-analysis in surgical ICU patients,[213] most studies and meta-analyses have shown no benefits in terms of mortality.[214–218] Most experts would agree with the fact that routine use of antifungal prophylaxis should be reserved for units with a high incidence of invasive candidiasis (>5%–10%) or for carefully selected patients at the highest risk.[99,219]

Measurement of Drug Levels

Drug level monitoring is theoretically justified to ensure efficacy and avoid toxicity. However, drug level monitoring during antifungal therapy is relatively new and should not be carried out routinely because there is a lack of information on its clinical correlation and meaning. Situations in which drug level monitoring has proven useful are itraconazole levels to verify adequate absorption when using the oral forms of this compound, 5-FC levels to watch for possible myelotoxicity, and voriconazole/posaconazole levels to document absorption of the drugs when given orally.[220–222]

Susceptibility Testing

The Clinical Laboratory Standards Institute has published a guideline for standardized antifungal susceptibility testing that has been widely adopted[223] and subsequently revised. This methodology is recommended for testing *Candida* and *Cryptococcus* spp., and breakpoints as well as epidemiologic cutoff values have been developed.[224] Antifungal susceptibility testing is now widely available and should be considered when treating serious *Candida* infections, when treatment failure occurs, or when toxicity or side effects limit the use of a particular drug. It should also be remembered that pharmacology, safety, published experience, and drug interactions must be considered along with susceptibility when selecting a therapy.[99] Mold susceptibility has also been standardized, but is not routinely recommended.

Antiviral Agents

Antiviral chemotherapy has made great advances in the past two decades. Before then a diagnosis of a life-threatening viral infection meant mostly supportive therapy and patience. Although still limited, today we have a host of several treatment options for herpetic infections; upper and lower respiratory tract illness by influenza, cytomegalovirus (CMV), and respiratory syncytial virus (RSV); and some relatively exotic systemic diseases. Therapy for HIV, hepatitis B, and hepatitis C infection has also made gigantic leaps, but it is usually not undertaken in the critical care setting and is therefore beyond the scope of this chapter. Table 49.3 summarizes the currently available non–HIV-specific antiviral drugs and their general spectrum.

Acyclovir, Famciclovir, and Valacyclovir

Acyclovir is a nucleoside analog of guanine that has in vitro and in vivo activity against several viruses in the herpes virus family, particularly against herpes simplex virus type 1 (HSV-1), HSV-2, varicella-zoster virus (VZV), and Epstein-Barr virus. High concentrations also inhibit CMV. It inhibits DNA polymerase, causing DNA chain termination.[225–227] Acyclovir is the treatment of choice for severe herpetic infections in immunocompetent and immunocompromised host. Resistance owing to viral thymidine kinase mutations or, less often, DNA polymerase mutations, may emerge in severely immunocompromised patients such as transplant recipients and those with advanced HIV infection during treatment of HSV and VZV infections.[228–230] Acyclovir has also been used for CMV prophylaxis in transplant patients.[231,232] Acyclovir is

TABLE 49.3 Spectrum of Antiviral Agents

Susceptible Virus	Acyclovir/Valacyclovir/ Famciclovir	Ganciclovir/ Valganciclovir	Foscarnet	Cidofovir	Amantadine/ Rimantadine	Ribavirin	Oseltamivir/Zanamivir/ Peramivir
HSV-1	++[a]	++	++	++	0	0	0
HSV-2	++[a]	++	++	++	0	0	0
VZV	++[a]	++	++	++	0	0	0
CMV	±[a]	++[a]	++	++	0	0	0
EBV	+	++	++	++	0	0	0
Influenza A	0	0	0	0	++[a]	+	++[a]
Influenza B	0	0	0	0	0	+	++[a]

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *VZV,* varicella-zoster virus.
Notes: 0, no known activity; ±, active under specific circumstances; +, active; ++, very active.
[a]Resistant strains reported.

available in oral, IV, and topical forms. Bioavailability of the oral form is poor (15%–21%), thus the requirement of high/frequent doses. Protein binding is less than 20%. CSF penetration is low, but acyclovir is active for CNS infections. The topical form is virtually unabsorbed. The half-life is short and the drug is cleared by the kidneys, so dosage adjustment in renal failure and hemodialysis is required. Supplementation is not needed in peritoneal dialysis. Side effects are uncommon.[233] The main concern with acyclovir therapy is the crystallization of the drug in the renal tubules, leading to renal failure, which fortunately is reversible. Aggressive hydration and monitoring of renal function are recommended during IV acyclovir therapy. Oral acyclovir may cause nausea and vomiting. The usual oral dose is 200 to 800 mg q4h. The IV dosing range for severe infections is 8 to 12 mg/kg IV every 8 hours. Proven encephalitis is treated with 10 to 12 mg/kg every 8 hours for 14 to 21 days. Doses of up to 20 mg/kg may be more effective in premature infants.[234]

Famciclovir, the prodrug of penciclovir (a guanosine analog),[235,236] is a well-absorbed oral agent that has shown excellent activity against first-episode or recurrent genital herpes and HSV/VZV infection in both HIV and immunocompetent hosts.[237–239] A dose of 500 mg PO three times a day was shown to be as effective as acyclovir for treatment of herpes zoster.[240]

Valacyclovir, an analog of acyclovir with a similar profile of side effects, is available in oral formulations with the advantage of longer dosing intervals. It appears comparable to acyclovir for treatment of mucocutaneous HSV infections, but it is more effective in herpes zoster. It is also effective orally for prophylaxis of CMV in renal transplant patients.[241] The dosing range is 500 to 1000 mg PO two to three times a day.[242–245] Although absorption is excellent, there are few data to support treating invasive disease, such as CNS disease, with this drug. It is currently the drug of choice to treat patients who can be treated with oral regimens.

Ganciclovir and Valganciclovir

Ganciclovir is another nucleoside analog of guanine with a slightly wider antiviral spectrum than acyclovir. It is highly active against CMV, as well as HSV-1, HSV-2, and Epstein-Barr virus. Like acyclovir it acts by interference with DNA polymerase, but it is not an obligate chain terminator. Resistance to ganciclovir by CMV and HSV is increasingly reported. HSV isolates that are thymidine kinase–deficient and thus resistant to acyclovir will be also resistant to ganciclovir.[229,245] It is mainly indicated in prophylaxis, treatment, and suppression of CMV syndromes in immunocompromised patients.[232,246–250] Ganciclovir is available in oral, intraocular, and IV forms; the first two are useful in chronic suppression of CMV disease. Once ganciclovir reaches the bloodstream it has body-wide distribution, low protein binding, and low CNS penetration. Excretion is renal and dosage adjustment is required in renal failure. Ganciclovir is removed by hemodialysis; therefore it should be administered after dialysis. Side effects of IV ganciclovir include severe neutropenia (40%), thrombocytopenia (20%), phlebitis, rash, increased liver enzymes, and azotemia. The nephrotoxicity is potentiated by concomitant use of nephrotoxic agents and acyclovir. Ganciclovir should not be used in pregnant women because it is known to be teratogenic. The usual dose in acute infection is 5 mg/kg every 12 hours. Maintenance therapy at 5 mg/kg IV daily should be continued as long as the patient is immunocompromised. Discontinuation of therapy in AIDS patients appears feasible after immune reconstitution.[232,246,251,252] An intraocular delivery system is also available as an adjunct to the treatment of CMV retinitis.

Valganciclovir is an L-valyl ester of ganciclovir with significantly increased bioavailability over previous oral formulations of ganciclovir, resulting in levels previously unattainable with the traditional formulations. It allows for prophylaxis and treatment of CMV infections with an oral alternative. The usual dose for prophylaxis is 900 mg PO every 24 hours, and for treatment the recommended induction dose is 900 mg PO every 12 hours, followed by a maintenance dose of 900 mg PO every 24 hours. This drug requires adjustment for patients with renal impairment.[253,254]

Cidofovir

Cidofovir is a nucleotide analog with activity against most herpesviruses. Its activation is not virus enzyme–dependent, and thus it has activity against most acyclovir-resistant HSV and ganciclovir-resistant CMV. Resistant strains have also been reported and synergy with ganciclovir and foscarnet has been reported. Oral bioavailability

is very low. It is 6% protein bound and is excreted by the kidneys.[255,256] Its side effects include neutropenia and nephrotoxicity, which can manifest as proteinuria, azotemia, and a Fanconi-like renal syndrome. It has been shown to be teratogenic and mutagenic and is contraindicated in pregnancy. It is currently licensed for CMV retinitis in HIV but has also shown activity against acyclovir-resistant HSV.[257,258] The usual dose is 5 mg/kg every week for 2 weeks, then 5 mg/kg every other week.

Foscarnet

Foscarnet is a pyrophosphate analog with antiviral activity against the herpesviruses, HIV, and hepatitis B virus. Its mechanism of action is interference with DNA polymerase or reverse transcriptase to block effective viral replication. Viral isolates that are resistant to ganciclovir or acyclovir are often susceptible to foscarnet, but primary resistance to foscarnet has also been described, particularly in HIV-infected patients.[228,230,259–261] The main therapeutic indication of foscarnet is ganciclovir-resistant CMV disease. Foscarnet is only available in IV formulations and has body-wide distribution. Protein binding is 15% and it has good CNS and retinal penetration. The drug is excreted almost intact by the kidneys and requires very careful dosage adjustment in renal failure. Foscarnet is removed by hemodialysis but should be avoided in patients with severe renal dysfunction. Its main side effect is nephrotoxicity, which occurs in most patients but is reversible when therapy is stopped.[262,263] Dosage adjustment should be made by following the creatinine clearance closely. Hypocalcemia and hypercalcemia as well as phosphate abnormalities are common, so monitoring of electrolytes is also recommended. The usual dose is 60 mg/kg every 8 hours for CMV infections and 40 mg/kg every 8 hours for treating acyclovir-resistant HSV infections.

Amantadine and Rimantadine

Amantadine is a tricyclic amine inhibitor of influenza A virus. Its mechanism of action involves inhibition of the transmembrane domain of the viral M2 protein, thus preventing viral uncoating during early stages of replication. It has activity against influenza A but no clinical activity against influenza B.[264–267] Resistant strains can be developed in vitro and are also seen in household and nursing home contacts exposed to persons treated for acute influenza. It is indicated in influenza A prophylaxis and treatment and also for management of Parkinson disease and drug-induced extrapyramidal reactions. It is well absorbed orally and has body-wide distribution. It is 67% bound to plasma proteins and excreted unchanged in the urine by glomerular filtration and tubular secretion. The usual adult dosage for both prophylaxis and treatment is 100 mg twice a day. The dosage must be reduced in elderly patients and patients with renal insufficiency. In individuals 65 years of age or older, the dose should be reduced to 100 mg every day. The dose for a CrCl less than 10 mL/min is 200 mg/week. The most common adverse events are related to the CNS and correlate directly with high levels. Patients may present with confusion, seizures, hallucinations, and coma. Amantadine also causes gastrointestinal upset.

Rimantadine is another tricyclic amine with similar properties, spectrum, and indications as amantadine.[268,269] The main difference lies in its extensive metabolism by the liver and its minimal renal clearance, but it also requires dosage adjustment in advanced liver and kidney insufficiency (CrCl <10 mL/min) as well as in the elderly. Its major advantage is less frequent CNS toxicity. Dosage is 100 mg twice a day.

Ribavirin

Ribavirin is a triazole nucleoside analog with broad-spectrum antiviral activity. It is effective in vitro against RSV, influenza A and B, HSV, HIV, HCV, and viruses causing hemorrhagic fevers.[238,270–272] Its currently approved clinical indications are treatment of pediatric patients with severe RSV infection and in combination with injected interferon alfa and ribavirin capsules is approved for treatment of chronic hepatitis C.[273,274] The IV form has been shown to reduce mortality in Korean/Asian hemorrhagic fever with renal syndrome.[275] Its mechanism of action is not fully understood and intrinsic resistance has not been reported. It is available in oral, aerosolized, and IV formulations. It has high bioavailability through the oral or aerosolized forms and it is metabolized by the liver. Toxicity in the aerosolized formulation consists primarily of severe bronchospasm and cardiac rhythm abnormalities. The IV formulation also causes hemolytic anemia. Use in ventilated patients requires experienced personnel because environmental leaking and diffusion are common.[276] The recommended dosage is 6 g of ribavirin administered by continuous aerosolization for 18 hours/day for 3 to 7 days, which is FDA approved for pediatric patients. However, it was found effective in RSV-infected hematopoietic stem cell transplant recipients as it is also studied in a different dosage of 2 g aerosolized over 3 hours every 8 hours for 5 to 10 days; interestingly the latter intermittent dosing showed better outcome and ease to use in such a population.[277]

Aerosolized ribavirin should not be combined with other aerosolized medications. Induction of bronchospasm is common, and scheduled use of a bronchodilator may be required during ribarvirin therapy. It is also teratogenic and pregnant women should avoid exposure.

Oseltamivir

Oseltamivir is a sialic acid neuraminidase inhibitor that has recently become available for the treatment of both influenza A and B.[278–280] Its mechanism of action is inhibition of the viral neuraminidase, causing in turn inhibition of virus release from infected cells and spread in the respiratory tract. Drug resistance has already been reported in vitro in strains with mutations that cause changes in the viral neuraminidase or hemagglutinin. In clinical studies of adults, only 1% to 2% of posttreatment strains showed evidence of mutations with decreased neuraminidase susceptibility. Recent reports have mentioned infrequent resistance in avian-influenza and H1N1 strains.[281–283] Cross-resistance between oseltamivir and zanamivir, the other member of the class, has also been observed in vitro. It is indicated for the prevention and early treatment of uncomplicated acute influenza A and B.[284] Major clinical trials have demonstrated that oseltamivir reduces the duration, severity, and rate of complications requiring antibiotic use.[279] Its role in complicated cases such as those seen in the critical care setting is unclear at this time; however, the 2009 H1N1 epidemic contributed a wealth of data related to the use in critically ill patients.[285,286] Oseltamivir is available in an oral form, which has greater than 75% bioavailability. Protein binding is 3% to 42%. The drug is converted to oseltamivir carboxylate that is eliminated unchanged in the urine. Less than 20% of the dose is eliminated in feces. Dose adjustment is recommended for renal failure and geriatric patients when CrCl is less than 60 mL/min.[287] If CrCl 30 to 60 mL/min dose is 75 mg PO daily, CrCl 10 to 30 mL/min 30 mg PO daily, and in hemodialysis first dose of 30 mg then give one

dose after dialysis. Clinically relevant drug interactions have not been identified. Side effects include nausea, vomiting, and abdominal pain, which are usually mild. The recommended dosage is 75 mg PO twice a day for 5 days and it is recommended that treatment is begun within 2 days of symptom onset.

Zanamivir

Zanamivir is another sialic acid analog neuraminidase inhibitor that is also approved for the treatment of both influenza A and B.[288,289] Much like oseltamivir, its mechanism of action is by neuraminidase inhibition with subsequent inhibition of viral release and spread. Resistant strains have also been identified in vitro, and a resistant strain was also recovered from an immunocompromised patient with influenza B after 2 weeks of nebulized treatment.[290,291] It is indicated in acute cases of influenza with early onset of treatment.[278,284,292,293] Trials in patients with more severe disease are ongoing.[294,295] Experience is also building with its use in prophylaxis.[264,296,297] Zanamivir is available in a powder form for oral inhalation. It is also available as an IV investigational forumation.[298,299] Approximately 4% to 17% of the dose is absorbed and less than 10% of the drug is protein bound. It is excreted unchanged in the urine and unabsorbed drug is cleared in the feces. No dosage adjustment in renal or hepatic failure is recommended at this time but experience is limited. Zanamivir does not have significant drug interactions.[300,301] Bronchospasm may be precipitated. particularly in patients with underlying lung disease.[302] The recommended dose is 10 mg (two inhalations) twice a day for 5 days.

Peramivir

Peramivir is a neuraminidase inhibitor approved for the treatment of acute mild to moderate influenza A. It is also been shown to have activity against influenza B. It is available in IV formulation as one dose of 600-mg (CrCl >50 mL/min), 200-mg (CrCl 30–49 mL/min), or 100-mg (CrCl <30 mL/min) therapy. In a randomized clinical trial that recruited healthy nonpregnant adults older than 18 years with mild to moderate influenza, peramivir showed better efficacy compared with placebo by decreasing the median time to alleviation of symptoms.[303] In a Japanese multinational, randomized, double-blinded trial, peramivir was shown to be noninferior compared to oral oseltamivir.[304] However, benefits of IV peramivir have not been clearly established in hospitalized patients.[305,306]

Other Antivirals

Palivizumab is a monoclonal antibody that inhibits respiratory syncytial virus F protein. It is currently FDA approved for the prevention of RSV infection in children.[307] There are no data to support its use in adults.

Brincidofovir is a lipid conjugate of cidofovir that is available in IV and oral formulations. It has broad-spectrum activity against adenovirus, CMV, HSV, and other double-stranded DNA viruses. Although it has shown virologic efficacy, it had a significant gastrointestinal adverse effect profile. Nonetheless, it has lesser nephrotoxicity than cidofovir.[308,309]

Letermovir, a novel antiviral that interferes with the viral pUL56, has been shown effective for CMV prophylaxis in stem cell transplant patients, but it has not been explored as a therapeutic agent or for prophylaxis in other populations such as solid organ transplant patients.[310,311]

Specific Indications and Uses for Antivirals

Herpes Simplex Virus and Varicella-Zoster

Acyclovir, famciclovir, and valacyclovir are the treatment of choice for virtually all severe herpetic infections.[225,226,238,312–319] The greater oral bioavailability of famciclovir and valacyclovir makes these agents very attractive, especially for treatment of VZV. Although primary HSV-1 and HSV-2 infections can be treated orally, immunocompromised patients or severely ill patients will require IV therapy. A high index of suspicion for dissemination should be maintained in immunocompromised patients—mild, localized, or atypical disease may progress to fulminant disease. Duration of therapy in this setting is usually 7 to 14 days.

Herpetic encephalitis has had a substantial decrease in morbidity and mortality since acyclovir was introduced. As one of the few forms of viral encephalitis for which there is a treatment, empirical use of the drug is justified when viral disease is suspected and until it is ruled out. HSV polymerase chain reaction of CSF is a very sensitive and specific test for the diagnosis of this disease. The usual dose is 10 to 12 mg/kg every 8 hours for 14 to 21 days. Visceral infections, including esophagitis, hepatitis, pneumonia, and disseminated disease, are frequent in immunocompromised patients and should be treated with 5 to 10 mg/kg every 8 hours for 14 to 21 days. HSV may also cause aseptic meningitis without encephalitis in the setting of primary or recurrent genital HSV infection. Unlike the focal necrotizing disease seen with HSV encephalitis, this form of the disease is a mild, self-limited aseptic meningitis with a good prognosis.

Finally, acyclovir-resistant HSV infections, which are an increasing problem in the immunocompromised population,[229,230,320,321] can be treated with foscarnet or cidofovir.

Primary VZV infection (chickenpox) should be treated in all adults, especially in the immunocompromised.[312,315,319,322,323] Reactivation (shingles) should be treated because treatment has been shown to decrease duration and intensity of symptoms.[324,325] Mild cases may be treated with oral famciclovir or valacyclovir. Severe cases (disseminated, immunocompromised patients with involvement of more than one dermatome, or ophthalmic involvement) should be treated with IV acyclovir. It is important to remember that these patients are contagious and should be suitably isolated using airborne precautions. As with HSV, resistant strains may be treated with foscarnet.[326,327]

Cytomegalovirus

CMV infections require treatment in immunocompromised patients. Populations at increased risk of the disease are HIV-infected patients and transplant recipients. In HIV patients, both retinal and visceral involvement are initially treated with IV ganciclovir at 5 mg/kg every 12 hours for 2 weeks.[232,246,247] Valganciclovir is a suitable PO formulation for the treatment of this infection. Various maintenance options are increasingly available (including ganciclovir ocular implants) but are beyond the scope of this chapter. Resistant cases may be treated with foscarnet 60 mg/kg every 8 hours for 2 weeks[251,259] or cidofovir 5 mg/kg once weekly. Clinical and laboratory monitoring while either of these drugs is used is essential to avoid therapy-related complications. Refractory cases may be treated with cidofovir.

In the transplant patient, the combination of ganciclovir and IV immunoglobulin is now the treatment of choice for CMV pneumonia.[246,328–330] High doses of acyclovir are useful as prophylaxis

of CMV in the transplant patient but not in the HIV setting. Ganciclovir-resistant strains should be treated with foscarnet.[331]

Influenza

Clear benefit in the treatment of influenza is consistently seen only when patients are treated early in the course of the disease.[289,332–335] Therapeutic options (which can also be used prophylactically) include oseltamivir, peramivir, zanamivir, and amantadine/rimantadine.[289,306,336–340] In patients who present later in the course of the disease, the benefits of therapy are unstudied. Prevention of complications has not been clearly demonstrated. Further trials are required to demonstrate whether one class of drugs is superior to the other and whether they have a role in the critically ill patient. Rapid diagnosis of influenza is now available through different techniques that detect viral components in upper respiratory tract samples. These techniques are useful in detecting and treating infected hospitalized patients early and in regional surveillance of influenza. However, a negative test result does not completely rule out influenza and empirical therapy of ambulatory patients with a clinical syndrome strongly suggesting influenza is probably appropriate.

Avian and pandemic influenzas have received much attention from the scientific community and the media in the past 2 years. Considerable efforts are being carried out for surveillance, prompt detection, and containment of these diseases.[341–344] Critical care specialists should have increased awareness and involve infection control and public health authorities in patients with particularly severe forms of influenza with the appropriate epidemiologic background. Airborne precautions should be used in suspected and confirmed cases. As mentioned earlier, although there are few reports of neuraminidase inhibitor resistance in some avian influenza strains, these viruses appear to be generally susceptible to oseltamivir and zanamivir.[281,282]

The 2009 H1N1 epidemic virtually changed how we manage influenza in critically ill patients. During this epidemic oseltamivir and zanamivir were frequently used late in the disease and at high doses, also in the setting of extracorporeal membrane oxygenation, with variable results.[285,295,345–347] At this point the true value of these agents is still unknown, although most experts agree that at the very least they may decrease viral shedding and transmission. In retrospective studies survival rates are shown to be higher in critically ill patients with influenza infections who received neuraminidase inhibitors up to 5 days of start of symptoms; the survival rate is the highest with earlier therapy.[348,349]

An important consideration is vaccination and postexposure prophylaxis in health care personnel working in acute and chronic care facilities. Appropriate vaccination and influenza control measures in both health care personnel and patients have proven effective in decreasing disease and even mortality in patients.[350–352]

Other Viruses

Other potentially treatable viral infections that may be encountered in the critical care setting include parvovirus, for which treatment with IV immunoglobulin has shown some beneficial effects[353–355]; enterovirus, for which a new drug called pleconaril showed only marginal benefits in the setting of meningitis[356,357]; and hemorrhagic fevers and hantavirus, for which ribavirin may be considered despite definitive proof of efficacy.[270] Dengue and yellow fever can be particularly severe and are most effectively managed with aggressive supportive care. The Ebola epidemic accelerated the development and investigational use of several antivirals and monoclonal antibodies.

Key Points

- Amphotericin B and its lipid preparations are the treatment of choice for all critically ill patients with an undiagnosed fungal infection. Once diagnosis is made, other therapeutic options may be considered.
- Fluconazole has excellent antifungal activity, mainly against most yeasts, but resistance is possible and clinically relevant.
- Echinocandins comprise a class of antifungal agents with activity against *Candida* and *Aspergillus* with proven efficacy and remarkable safety profiles. They are now considered the treatment of choice for candidemia in critically ill patients.
- Combinations of antifungals should be approached carefully as they are clearly beneficial only in selected entities such as CNS disease and endocarditis.
- Empirical antifungal use and antifungal prophylaxis in the ICU setting remain controversial and should be reserved for carefully selected units and patients.
- Uncommon and serious mycoses require expert consultation.
- Acyclovir or its analogs are the drugs of choice for treatment of HSV and VZV infections. The new oral formulations (famciclovir and valacyclovir) have greater bioavailability and are preferred in ambulatory patients.
- Ganciclovir is the drug of choice for treatment of CMV disease in immunocompromised hosts. Immunoglobulin therapy is added to this in transplant patients with pneumonia.
- Critical care specialists should have a high index of suspicion for avian and pandemic influenza. Suspected or confirmed cases should have airborne precautions in place and be treated with neuraminidase inhibitors.
- Resistance is an increasingly real problem in both antifungal and antiviral therapy.

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Review Questions

1. A 45-year-old female with a history of newly diagnosed rheumatoid arthritis has been taking 20 mg oral prednisone for the past 30 weeks. She is admitted to the intensive care unit (ICU) for necrotizing pancreatitis, which is thought to be secondary to biliary calculus. She underwent surgical debridement and placement of multiple intraabdominal drains. She started intravenous (IV) antibiotics empirically. The patient began IV caspofungin empirically as she continued to have fever and leukocytosis even though she has been taking vancomycin and meropenem for 12 days. Steroids therapy was continued during her ICU stay. On day 17, the laboratory reported that the blood culture is growing yeast. What is the most appropriate measure to do next?

a. Exchange the central line, and switch caspofungin to micafungin.
b. Exchange central venous lines, and switch caspofungin to fluconazole.
c. Switch caspofungin to liposomal amphotericin B.
d. Continue same management and consider the culture is a contaminant.

Answer: c. Answer a is incorrect because the spectrum of antifungal activity is the same among the currently approved echinocandins (caspofungin, anidulafungin, and micafungin). Although answer b is considered correct in cases of line-related *Candida* infection, given that breakthrough fungemia is worrisome for resistant *Candida*, and most likely in this case cryptoccocal infection, which we will need to rule out meningitis. Answer d is clearly incorrect. Answer c is correct because breakthrough fungemia while the patient is receiving echinocandin should make us think of mainly *Cryptococcus*, *Malassezia*, or *Trichosporon* spp. Once identification is completed, a line exchange is warranted for the latter two organisms and switching to triazole therapy. This case shows a patient with the risk factor of cryptococcal infection and liposomal amphotericin B is warranted until meningitis is ruled out.

2. A 61-year-old male with a history of refractory acute myeloid leukemia status multiple chemotherapy regimens and prolonged neutropenia. The patient has started ciprofloxacin, acyclovir, and voriconazole as a prophylaxis regimen for prolonged neutropenia. The patient is known to have multiple lung nodules that are thought to represent invasive pulmonary aspergillosis per a galactomannan-positive test result from bronchoalveolar lavage. The patient is admitted to the ICU for septic shock and on the second day, blood cultures grow gram-negative rods. The patient had already started empiric antibiotic therapy with meropenem and vancomycin with good response as he is not receiving IV vasopressors. The patient now has acute kidney injury with creatinine clearance of 18 mL/min. He is receiving only IV therapy because of ileus and decreased gastrointestinal absorption. What is the next step to consider?

a. Switch meropenem to cefepime and discontinue vancomycin.
b. Start liposomal amphotericin B and continue vancomycin and cefepime.
c. Discontinue meropenem and vancomycin and continue prophylaxis.
d. Switch voriconazole to isavuconazole and continue meropenem.

Answer: d. The patient's blood culture has gram-negative rods and vancomycin can be discontinued; however, switching meropenem to cefepime should not be done until the final organism and susceptibilities are known; that is why answer a is incorrect. There is no need to start AmBisome as there are no signs of a breakthrough fungal infection, so answer b is not correct. Answer c is clearly incorrect. The patient has decreased creatinine clearance and IV voriconazole is contraindicated as it has a sulfobutylether-β-cyclodextrin component that will accumulate given declining renal function, whereas IV isavuconazole does not have this formulation and does not need dose adjustment per renal function.

3. A 72-year-old male with a history of congestive heart failure, hypertension, and diabetes mellitus presents during the month of December with a 3-day history of cough, fever, and body aches. On examination, the patient's oral temperature is 100.9°F (38.2°C), blood pressure is 95/43 mm Hg, and his pulse rate is 103 beats/min with a pulse oximetry reading of 83% on room air. The patient's respiratory status worsened in the emergency department (ED), requiring him to be intubated. Chest x-ray showed bilateral diffuse ground glass opacities. What is the next step in his management?

a. Start empirical antibiotic therapy and send blood samples for cultures and bronchoalveolar lavage for gram stain and cultures.
b. Start empirical antibiotic therapy and send blood samples for cultures, bronchoalveolar lavage for gram stain and cultures, and conduct influenza rapid antigen test.
c. Start empirical antibiotic therapy and send blood samples for cultures, start oseltamivir, obtain an influenza reverse transcription polymerase chain reaction (RT-PCR) test, and send bronchoalveolar lavage specimen for gram stain and cultures.
d. Start empirical antibiotic therapy, give one dose of peramivir, and send blood samples for cultures, bronchoalveolar lavage specimen for gram stain and cultures, and obtain influenza RT-PCR test.

Answer: c. The patient has a high risk of influenza pneumonia. Although the onset of his symptoms has passed the 48 hours of the recommended time to start oseltamivir, the patient is critically ill and neuraminidase inhibitors can be effective up to 5 days of symptom onset. Answers a, b, and d are incorrect because the patient should start empirical influenza therapy. Also, when there is a high clinical suspicion of influenza infection, therapy should not be delayed until the results of influenza tests are available.

4. A 24-year-old Caucasian female presented to the emergency department with altered mental status. Her boyfriend is with her and states the patient does not have any prior medical history. They recently returned from a vacation trip to Miami, Florida. He does not recall having any sick contacts or that she had any febrile illness during or before the trip. He recalls that her symptoms started with a headache and fever a day ago, and she took two ibuprofen pills. The emergency physician ordered a computed tomographic scan of the head without contrast, which did not suggest any pathologic process. In the ED the patient was febrile, and because of depressed mental status she was intubated and was given one dose of IV vancomycin (2 g) and one dose of ceftriaxone (2 g). Otherwise, the rest of her vital signs were normal. She underwent lumbar puncture with a normal opening pressure. Cerebral spinal fluid (CSF) showed pleocytosis (lymphocytes predominant) and elevated protein. The patient started IV acyclovir 10 mg/kg every 8 hours for suspected herpetic encephalitis. On day 2 of admission the

results of her CSF herpes simplex 1 polymerase chain reaction (HSV-1 PCR) came back positive, and magnetic resonance imaging of the brain showed left temporal encephalitis. On day 3, she developed an 20% increase in her serum creatinine. What is the underlying pathophysiology behind her acute kidney injury (AKI)?

a. Acute tubular necrosis induced by iodinated contrast
b. Acyclovir crystalline precipitation in the renal tubules
c. Vancomycin-induced nephrotoxicity
d. Acute interstitial nephritis secondary to use of nonsteroidal antiinflammatory drugs

Answer: b. The patient's creatinine has changed, which is explained by the use of acyclovir, which tends to precipitate in the renal tubules. The process is usually mild and can be avoided or reversed with IV hydration. However sometimes it may require the discontinuation of medication and the use of hemodialysis. The patient did receive vancomycin but it was only a one-time dose and is not considered the cause of her AKI, so answer c is incorrect. Although the patient received ibuprofen before coming to the hospital, it is not thought to be the cause of her AKI in this occasion as it was a low dose and as such answer d is incorrect. Answer a is incorrect because the patient did not receive iodinated contrast.

5. A 37-year-old Hispanic male has acute myeloblastic leukemia who is receiving Cytarabine and Idarubicin with prolonged neutropenia. He was admitted to the ICU for febrile illness and was found to have invasive sinusitis secondary to mucormycosis. He began a regimen of 5 mg/kg IV AmBisome and underwent debridement of the lesion. The patient was given IV fluid hydration to avoid renal injury induced by AmBisome. What is the likely mechanism behind the risk of developing cardiac arrhythmia?

a. AmBisome affects L-type Ca^{++} cardiac channels.
b. Amphotericin releases inflammatory mediators from monocytes and macrophages.
c. Electrolyte disturbance (magnesium/potassium) occurs through tubular membrane wasting.
d. Human herpesvirus 6 (HHV-6) induces myocarditis.

Answer: c. The use of amphotericin B is associated with frequent renal tubular injury that results in low magnesium and potassium levels through renal tubular leaking of electrolytes. Thus close monitoring of serum electrolytes is necessary, and some experts recommend to preemptive supplementation of the patient with magnesium and potassium to avoid such a complication. Both answers a and b are incorrect. Isavuconazole is the drug that affects L-type Ca^{++} cardiac channels, and although amphotericin B causes the release of inflammatory mediators from monocytes and macrophages, it is not known to cause cardiac arrhythmia. Answer d is incorrect in this scenario. However, in rare cases HHV-6 can cause myocarditis in severely immunocompromised patients (e.g., after allogeneic hematopoietic stem cell transplantation).

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Critically Ill Immunosuppressed Host: Infectious Complications

HENRY MASUR

CHAPTER OUTLINE

Definition

Overview of Immune and Inflammatory Responses
- Innate Immunity
- Adaptive Immunity
- Altered Inflammatory Response: Neutropenia

General Approach to Management of Patients With Altered Immune and Inflammatory Responses

Management of Specific Patient Populations
- Cancer Patients With Neutropenia
- Solid Organ Transplant Recipients
- Patients With HIV/AIDS

Immunosuppressed patients present special management issues because (1) opportunistic infections can present subtly but then progress rapidly; (2) opportunistic infections often require special diagnostic tests that would not usually be ordered for immunologically normal patients; (3) therapy often requires the use of unfamiliar antimicrobial agents plus the manipulation of immunosuppressive regimens; and (4) drug interactions between immunosuppressive agents and antimicrobial agent can compromise the efficacy and/or safety of therapies, and the complexity of these interactions can be compounded by the polypharmacy that patients in intensive care units (ICUs) are often receiving for their other acute and chronic diseases.

This chapter emphasizes the important ways in which immunosuppressed patients differ from immunologically normal individuals in terms of infectious complications. The noninfectious complications of immunosuppression are reviewed in Chapter 80.

Definition

Patients who are at increased risk for infectious complications because of a deficiency in any of their host defense mechanisms (e.g., immunologic, inflammatory, physical, or chemical) are referred to as *compromised* hosts. Almost all patients in the ICU are compromised because of one or more of these deficiencies—for example, almost all have catheters and many have wounds and/or are receiving drugs that alter their inflammatory or immunologic responses.

Patients are termed *immunocompromised* or *immunosuppressed* if their defect, whether acquired congenitally or postpartum, specifically involves immune response. Patients who have defects in inflammatory response, such as neutrophil number or function, are also considered immunosuppressed in most reviews.

Overview of Immune and Inflammatory Responses

Innate Immunity

All humans exist in an environment with billions of microorganisms that would threaten host survival if the host did not have highly effective mechanisms for protecting the host from pathogenic organisms. The innate immune system is the first-line barrier that quickly responds to microbial invasion. The innate immune system is an inherited system, inherited from parent to child, and directed against microbial molecules that are unique to microorganisms. Knowledge is rapidly expanding about specific defects in the components of innate immunity, such as defects in Toll-like receptors, mannose binding lectin, and complement. These innate responses do not change substantially during life due to prior experience with specific organisms. The innate immune system recognizes microorganisms through pattern recognition receptors (PRRs). PRRs are receptors specific for molecular components of microorganisms. Such responses can occur within minutes rather than hours or days. Innate immunity is vital to the initial encounter of the host to a microorganism. The critical effector component of the innate immune system consists of "professional" phagocytes (neutrophils, monocytes, macrophages).[1–3]

- The innate immune system is responsible for recognizing microbial invasion and modulating the inflammatory response. Components of the innate immune response include the following:
  - Physical barriers
    - For example, tight junctions in the skin, epithelial, and mucous membrane surfaces
  - Inflammation-related serum proteins
    - For example, complement and C-reactive protein

- Antimicrobial peptides
  - For example, defensins and cathelicidins on the surfaces of cells and within white cell granules
- Cell receptors that sense microorganisms and signal a defensive response
  - For example, Toll-like receptors.
- Phagocytes (neutrophils, monocytes, macrophages)

Adaptive Immunity

T cells regulate the activities of B cells and T cells, as well as other cells. T cells provide help for antibody production by B cells. T cells are the effectors of antigen-specific cell-mediated immunity. Cell-mediated immunity is the cornerstone for elimination of cells infected with intracellular pathogens and for causing graft rejection and some allergic responses.[4–8]

T-cell responses are divided into T helper 1 (TH1) and TH2 responses. TH1 responses promote production of opsonizing antibodies and induction of cellular cytotoxicity and macrophage activation. TH1 responses are central to the defense against pathogens that replicate intracellularly, such as mycobacteria, *Toxoplasma, Histoplasma, Cryptococcus,* and *Nocardia.* TH2 responses promote production of immunoglobulin E (IgE) and immunoglobulin G4 (IgG4).

Defects in each arm of the immune system are associated with characteristic infections. Knowledge of the defect produced by the underlying disease, or by medical interventions including chemotherapy, allows the clinician to develop logical preventive and empiric therapeutic management plans.[4–8]

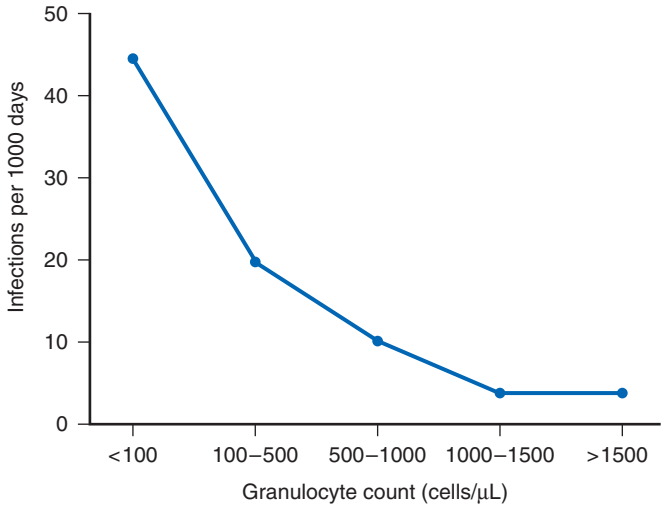
Altered Inflammatory Response: Neutropenia

Neutropenia is a well-recognized risk factor for invasive infections caused by bacteria and fungi.[9–12] The coexistence of mucosal ulcerations caused by cytotoxic therapy and neutropenia produces especially high caused by such infections.[13,14]

Patients who are neutropenic develop well-described syndromes and complications that have better outcomes if specific, evidence-based principles are followed. However, almost all neutropenic patients have mixed immunodeficiencies—that is, they have neutropenia for a variable period of time but they also have elements of cellular and/or humoral immune deficiencies owing to their underlying disease or therapies for their primary disease. These mixed immunodeficiencies make predictions of causative organisms and recommendations for optimal management more complex given the many variables involved in underlying disease, immunosuppressive regimen, and patient comorbidities.

Neutrophil counts below 1000 cells/μL—that is, an absolute neutrophil count (ANC) less than 1000/μL (the total absolute number of polymorphonuclear neutrophils plus bands) increase susceptibility to infection in a linear fashion (i.e., the lower the neutrophil count, the greater the degree of susceptibility) (Fig. 50.1).[9]

As shown in Fig. 50.1, a patient with a neutrophil count of 100 cells/μL is much more vulnerable to infection than a patient with 500 or 1000 cells/μL, and a patient with zero neutrophils is at much higher risk for fulminant infection than a patient with 50 or 100 cells/μL. The trajectory of the neutrophil count is also important: a patient with a neutrophil count of 1500 cells/μL whose neutrophil counts are dropping precipitously should best be treated like a patient with absolute neutropenia. Similarly, a patient with 500 neutrophils/μL whose counts are rising quickly



• **Fig. 50.1** Incidence of infection at declining granulocyte counts in patients with acute leukemia during induction therapy. (From Bodey GP, Buckley M, Sathe YS, et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64:328–340.)

is not nearly as vulnerable to a poor outcome as a patient with a count of 500 neutrophils/μL that is stable. The risk of life-threatening infection related to neutropenia increases as the duration of neutropenia increases. The highest-risk patients are generally defined as those with ANCs less than 500 cells/μL for longer than 7 days.[15,16]

Typical pathogens that cause bacteremias in this population include gastrointestinal flora such as *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Pseudomonas aeruginosa,* and *Candida* spp., as well as skin flora such as *Staphylococcus aureus.* In an earlier era, the majority of bacteremias in neutropenic patients were due to aerobic gram-negative bacilli. More recently, the majority of such infections are due to gram-positive cocci, in large part because of the frequent use of prophylactic regimens that include a quinolone (to prevent gram-negative bacillary infections) and trimethoprim-sulfamethoxazole (for *Pneumocystis jirovecii* pneumonia and toxoplasmosis, but which also inhibit many gram-negative bacilli as well as many non–group D streptococci).[10,11,17]

General Approach to Management of Patients With Altered Immune and Inflammatory Responses

With regard to infectious complications, effective management of immunosuppressed patients requires an understanding of several basic tenets of care, some of which are extensions of principles relevant to most patients who are in ICUs because of severe underlying diseases or acute infectious challenges.

1. Life-threatening complications often present with subtle symptoms and signs that can easily be overlooked.

   Because immunocompromised patients may lack inflammatory and immunologic mediators (e.g., because of high-dose steroids, neutropenia, or antilymphocyte antibodies), the clinical manifestations of infections are often less prominent and

less impressive than in immunocompetent patients with similar complications. Thus clinicians must recognize that even subtle changes in cognition or alertness, respiratory rate or heart rate, soft tissue tenderness or warmth, catheter site appearance, chest radiograph, or abdominal pain may warrant an aggressive diagnostic evaluation and early institution of broad-spectrum empiric therapy that is appropriate to the specific host involved.

2. Fever is not invariably present when patients have serious or life-threatening infections.

   An elevated temperature is often used as a proxy for likely infection. A temperature greater than 38.1°C twice consecutively or 38.3°C once often triggers "pan cultures" of blood, urine, and sputum, plus a chest radiograph. It should be clear to clinicians, however, that changes such as tachycardia, tachypnea, altered mental status, abdominal pain, and soft tissue tenderness may represent life-threatening, rapidly progressive infections even in the absence of an elevated temperature. Such manifestations require clinical experience and judgment to determine when aggressive diagnostic and empiric therapeutic interventions are warranted. Intensivists must also be cognizant of the potential unreliability in the methods that some health care facilities use to measure temperature, an important issue because a difference of a tenth of a degree can determine whether a fever workup is initiated and whether empiric therapy is started. Temperature elevations may be intermittent, and thus ICUs that record temperature every 1 to 2 hours or continuously are more likely to identify fevers than ICUs that measure temperature less frequently. Temperatures are measured with a wide array of temporal artery, forehead, oral, rectal, or axillary approaches, not all of which have good interdevice concordance.

   Even if temperatures are measured accurately, ICU patients have mechanical reasons (e.g., renal replacement therapy and open wounds) and pharmacologic reasons (e.g., high-dose corticosteroids) to have their fevers masked. Thus fever is only one of many parameters that should lead to a thorough evaluation for infection.

3. Immunosuppressed patients are predisposed to rapid progression of infectious complications.

   Although all ICU patients demand prompt attention and vigorous diagnostic and therapeutic management, many types of immunosuppression can be associated with especially precipitous clinical deterioration despite their innocuous presentation. Thus infected patients who are neutropenic, who are receiving high-dose corticosteroids, or who are receiving monoclonal antibodies that deplete key immunologic factors are especially likely to have a fulminant course and require expeditious diagnostic and therapeutic interventions.

4. Diagnostic evaluation needs to be prompt and definitive.

   As indicated earlier, patients with life-threatening infection may present with subtle symptoms and signs that progress rapidly to become life-threatening. These early manifestations merit aggressive attempts to define the anatomy of the lesion and the causative microbial pathogen(s). Because the spectrum of potential pathogens in such patients usually includes a wide array of viruses, fungi, protozoa, and bacteria, clinicians must be certain that appropriate specimens are obtained and the appropriate microbiologic and histologic tests are ordered to identify causative organism. Expensive or invasive tests such as magnetic resonance imaging (MRI) or invasive diagnostic techniques such as bronchoalveolar lavage (BAL) or tissue biopsies should be performed with less hesitancy than in immunologically normal patients.

   Patients often have enhanced risk factors for complications of invasive procedures, such as thrombocytopenia, coagulation factor deficiencies, hypoxemia, or renal failure. Part of the art of medicine is knowing when to be aggressive with diagnostic procedures and when to rely on empiric therapeutic approaches. However, the benefit of definitive diagnosis often outweighs these risks when the procedures are performed by experienced operators. It is also important to recognize that timing is important; delay in scheduling diagnostic procedures may result in the patient progressing and becoming too hypoxic for bronchoscopy, too unstable for computed tomography scan or MRI, or too coagulopathic for a lumbar puncture or needle aspirate of a fluid collection.

5. Prior colonization and exposures are important clues to the likely causative organisms.

   For any patient in any health care setting, a history of exposure to influenza, tuberculosis, or methicillin-resistant *S. aureus* (MRSA) would be of obvious importance in determining the likely cause of a patient's syndrome. For immunosuppressed patients, it is important to know if they have latent infections such as herpes zoster or *Toxoplasma gondii* as measured by antibodies or if they have been colonized with organisms of interest.

   Monitoring patients to determine the activity of viral, fungal and parasitic infections requires special expertise. Many transplant programs use quantitative serum polymerase chain reaction (PCR) measurements to monitor cytomegalovirus (CMV) and often Epstein-Barr virus (EBV) or BK virus as well as *Toxoplasma.* They monitor fungal pathogens with periodic serum galactomannan and β-D-glucan assays. Such information will help focus empiric therapy while the definitive cause is identified, although considerable expertise is needed to understand the sensitivity and specificity of these assays. Many oncology, transplant, and human immunodeficiency virus (HIV) programs maintain databases with such serial information that may be vital to access through the relevant consultant to optimize initial and definitive management.

6. PCR detection of an organism may identify microbes that are truly present but are not causing the patient's infectious syndrome.

   Any microbiologic test requires knowledge of the performance characteristics of the test for proper interpretation. Blood cultures are well known to occasionally reveal organisms that are contaminants rather than causative pathogens. All organisms that grow from sputum or BAL are not necessarily related to the cause of pulmonary or systemic dysfunction. However, the sensitivity of PCR tests provides a particular challenge in immunosuppressed patients who may shed organisms or nucleic acid for extended periods of time. The detection by PCR of CMV or EBV in the peripheral blood, for instance, does not necessarily indicate that a patient would benefit from treatment of the CMV or EBV. Moreover, some organisms can be detected by PCR in immunosuppressed patients for many weeks or months after an acute illness. Thus finding norovirus in the stool or influenza or RSV in a respiratory sample may represent small quantities of live organisms or residual nucleic acid acquired weeks or months earlier that

may be unrelated to the cause of the acute syndrome. They may also not reflect the patient's likelihood of transmitting the organism through another person's contact with respiratory secretions or other biologic samples.

7. Not all infections are related to the underlying disease or immunosuppression.

   Immunosuppressed patients may be admitted to the ICU with an infection related to their immunosuppression. However, they may also develop infections that occur in normal hosts, such as influenza, pneumococcal pneumonia, diverticulitis, catheter-related infection, aspiration pneumonia, or ventilator-associated pneumonia. While focusing on infections that could be related to underlying immunosuppressive disorder, the clinician should not overlook the possibility that the process is due to a more common process such as community-acquired influenza, urinary sepsis related to nephrolithiasis, aspiration pneumonia related to drugs or alcohol, or MRSA bacteremia owing to illicit drug use.

8. Empiric therapy should be started promptly.

   Time to appropriate antibiotics is an important correlate of successful outcome in any patient outcome, but time is especially important in these patients, whose conditions are prone to deteriorate rapidly. Thus the clinician must be especially vigilant that the full array of appropriate antimicrobial drugs is received by the patient and that there are no delaying factors related to pharmacy preparation, team communication, vascular access, or other factors. When multiple drugs must be given rapidly (i.e., when the differential diagnosis is broad), attention might be focused on drugs that can be given by rapid infusion such as daptomycin and meropenem.

9. Empiric therapy should be broad spectrum.

   For life-threatening infections in any patient population, it is an axiom of both critical care and infectious disease that the initial antimicrobial regimen should cover all likely pathogens, and that the regimen can be narrowed or targeted as additional information about the illness emerges. For immunosuppressed patients with a broad range of potential opportunistic, community-acquired, and hospital-acquired pathogens, such empiric regimens may include three to six antibacterial, antifungal, and antiviral agents. Although antibiotic stewardship is an important aspect of responsible resource and patient management, the first 24 to 72 hours of therapy for a life-threatening process is not the proper place to limit the number of drugs if each was chosen for a plausible reason.

10. Immunosuppressed patients receive multiple courses of prophylactic and therapeutic antimicrobial therapy, and thus are at high risk for acquiring drug-resistant pathogens. Immunosuppressed patients are likely to be colonized by MRSA, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae, or azole-resistant *Candida* spp. Such prior inpatient and outpatient antibiotic exposure needs to be considered when choosing empiric antimicrobial regimens.

11. Antibiotic therapy should be narrowed when the causative organism is known. For targeted therapy (when the causative organism is known) monotherapy is usually adequate.

   Once the causative organism(s) and their antimicrobial susceptibilities are known, empiric regimens can be narrowed to focus on the identified organism. In some situations a positive blood culture result likely represents only part of the infectious process—for example, when there is *E. coli* bacteremia associated with a perforated bowel and bowel abscess. In such cases broad-spectrum drugs, including one active against the isolated organism, is appropriate. However, there are situations such as primary *Staphylococcus* bacteremia or meningococcemia or bacteremic pneumococcal pneumonia when it is likely that there is only one causative organism. For a patient with a life-threatening infection in such a case, should the clinician choose monotherapy or use multiple drugs with activity against the causative pathogen? There has been considerable discussion as to whether combination therapy produces superior outcomes for targeted therapy, including in current versions of the "Management of Adults With Hospital-Acquired and Ventilator-Associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society" (http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organ_System/Lower/Upper_Respiratory/Hospital-Acquired_Pneumonia_(HAP)/) and the Surviving Sepsis Campaign Guideline on Management of Sepsis (http://www.survivingsepsis.org/Guidelines/Pages/default.aspx).

   In most cases when the targeted organism is susceptible to an antibacterial or antifungal or antiviral drug with known clinical efficacy, there is no reason to use more than one drug. There are some exceptions, such as pneumococcal pneumonia or sepsis, in which case a macrolide appears to add efficacy to a β-lactam drug; streptococcal bacterial endocarditis, for which a β-lactam plus an aminoglycoside may be optimal; cryptococcal meningitis, for which amphotericin B plus flucytosine is optimal; or tuberculosis, which requires four-drug therapy initially. In most other situations, including staphylococcal bacteremia, monotherapy is appropriate and prudent. Other situations in which combination therapy is likely to be indicated are cases in which the causative organism is nonsusceptible or resistant to all active drugs, or when the only drugs with activity have questionable clinical efficacy (e.g., colistin or tigecycline). In such situations, combination therapy is reasonable given the lack of better alternatives.

12. Foreign bodies and infectious foci should be assessed promptly for removal or drainage.

   Removal of infected foreign bodies and drainage of sequestered foci are tenets of critical care medicine. Such interventions are especially important for improving outcome in patients who have compromised inflammatory or immunologic defenses. This is most often an issue for intravascular catheters. Some immunosuppressed patients have permanent indwelling lines that are difficult to remove. Some have limited access that makes finding new, feasible sites for access time-consuming and potentially hazardous. In unstable patients or patients with persistent infection, such foreign bodies need to be considered for removal, although considerable clinical judgment rather than formulaic guidelines are needed to determine the optimal timing of such removal or site change.

13. Pharmacokinetics and pharmacodynamics require special attention.

   ICU patients characteristically require attentive monitoring to ensure the adequacy and safety of drug therapy. Immunocompromised patients often have multiple prior and concurrent insults to their renal and hepatic function. They often receive multiple drugs that can produce drug-drug interactions. Thus their pharmacokinetics can be especially difficult to predict.

Ideally peak and trough concentrations should be monitored for all antimicrobial agents to ensure optimal pharmacodynamics. However, few ICUs have access to antibiotic levels other than vancomycin, aminoglycosides, and voriconazole, especially in real time, such that adjustments could be made to account for current physiologic changes.

Many current immunosuppressive agents such as cyclosporine, tacrolimus, and sirolimus can have clinically important interactions with certain antibiotics, and thus close attention needs to be maintained to ensure that antimicrobial therapy is optimized and immunosuppression is properly managed.

14. Noninfectious syndromes specific to the immunosuppressive disorder can masquerade as infections.

Clinicians dealing with specific populations must be familiar with the noninfectious syndromes that occur, such as graft-versus-host disease, immune reconstitution syndrome, bronchiolitis obliterans, chemotherapy-induced cardiomyopathy, and veno-occlusive disease of the liver. Failure to recognize these entities exposes them to the toxicities and expense of unnecessary antimicrobial therapy and prevents institution of the appropriate therapy for the noninfectious syndrome.

Management of Specific Patient Populations

Cancer Patients With Neutropenia

Prevention of Infection and Preemptive Therapy

A distinction should be made between prevention of infection and preemptive therapy to reduce the impact of infections on patient survival.

- Prevention of infection includes interventions that prevent the host from acquiring a particular pathogen. Environmental control, including contact, respiratory, and airborne isolation, is well known and effective as a strategy to prevent infections. Other examples of effective preventive strategies include oral and skin hygiene, immunizations, oral antimicrobials, and colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF]).
- Preemptive therapy is defined as the initiation of an intervention when a pathogen is detected but before clinically apparent disease occurs. For example, after stem cell transplantation, CMV viremia is usually monitored on a scheduled basis. If the serum PCR becomes positive above a certain threshold, natural history studies demonstrate that pneumonitis, colitis, or systemic disease is likely to occur, and thus therapy is started preemptively before any clinical manifestations of disease occur. This strategy is especially advantageous when the optimally active antimicrobial is toxic or expensive (i.e., this strategy allows withholding the drug until replication of the organism becomes evident).

Infection prevention for neutropenic patients starts with the same general approaches used for all ICU patients: hand hygiene, oral hygiene, and antiseptic body washes for the patient. Established isolation precautions to prevent transmission of pathogens from other patients to the immunosuppressed person are also especially important.[17] Most programs also provide patients a "neutropenic diet" consisting exclusively of cooked foods to avoid pathogens associated with raw fruits and vegetables.[18] Avoidance of plants and flowers is also likely useful. For high-risk patients, such as allogeneic stem cell transplant recipients in the early posttransplant period, protective isolation is highly encouraged with high-efficiency particulate air filters, positive air differential between patient room and surroundings, at least 12 air exchanges per hour, and continuous pressure monitoring.[10,11]

For high-risk patients most programs use oral prophylactic regimens that target gram-negative bacilli including *P. aeruginosa.*[10,11] Levofloxacin is commonly used because it has activity against many gram-negative bacilli and has activity against oral flora such as viridans streptococci that are recognized to break through other prophylactic regimens. The benefits of such prophylaxis are debated given that there are adverse effects, including altering the host's microbial flora, predisposing to *Clostridium difficile* infection, and the drug-specific toxicities unique to individual drugs such as QT prolongations associated with quinolones and the enhanced susceptibility to *C. difficile* enterocolitis. Antibacterial prophylactic drugs are usually started in high-risk patients when cytotoxic therapy is initiated and stopped when the ANC has been above 500 cells/μL for 1 to 2 days. The use of prophylactic drugs has led to a shift in pathogens causing disease in neutropenic patients from gram-negative bacilli to gram-positive organisms.[19–25]

Reactivation of herpes simplex virus (HSV-1 and HSV-2) and varicella-zoster virus (VZV) occurs especially in patients with acute leukemia and those undergoing human stem cell transplants. HSV and VZV infections can be prevented with antiviral prophylaxis. Patients receiving hematopoietic stem cell transplants and certain other immunosuppressed persons who are seropositive for HSV or VZV should receive antiviral prophylaxis with famciclovir or valacyclovir.[26,27]

Antifungal prophylaxis against invasive fungal organisms with fluconazole, voriconazole, or posaconazole is often used for high-risk patients. The targets include fungemia caused by *Candida* spp. and invasive disease, especially pulmonary infections, caused by molds such as *Aspergillus* or *Rhizopus* spp.[28–33]

Prophylaxis against *Pneumocystis* pneumonia (PCP) is appropriate in selected patients who have T-cell immuodeficiencies in addition to neutropenia. Neutropenia alone is not a risk factor for PCP. Trimethoprim-sulfamethoxazole is always the drug of choice in terms of efficacy. However, given this drug's potential to cause bone marrow suppression, some programs prefer atovaquone or aerosol pentamidine.

For antibacterial, antifungal, and antiviral prophylaxis, the antimicrobial pressure on selecting resistant organisms is leading to a shift in the causes of disease to newly recognized pathogens or previously recognized by now drug-resistant pathogens that "break through" prophylaxis.[20,22,23,34,35] This reinforces the concept that when patients develop new syndromes while using antimicrobial prophylaxis, empiric regimens must take into consideration pathogens that are likely to evade the prophylactic regimen.

Although neutropenia itself is not a risk factor for PCP, the concurrent compromise of cell-mediated mechanisms by the underlying disease or chemotherapy often warrants the use of *Pneumocystis* prophylaxis. Trimethoprim-sulfamethoxazole is the prophylaxis of choice if the patient can tolerate sulfa drugs and if bone marrow suppression is not a contraindication. In such circumstances aerosolized pentamidine or oral atovaquone can be used. Unlike bacteria, viruses, and other fungi, there is no evidence to date that *Pneumocystis* develops clinically important resistance to prophylactic drugs.

Colony-stimulating factors (CSFs, also referred to as myeloid growth factors or hematopoietic growth factors), including granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF), are recommended by some guidelines for afebrile neutropenic patients in whom the anticipated risk of fever and neutropenia is 20% or higher.[17,36–38]

When patients are in the ICU and develop acute syndromes, the choice of antimicrobial therapies clearly must take into consideration the prophylactic drugs that patients have been receiving. Thus for patients who have been receiving levofloxacin, trimethoprim-sulfamethoxazole, acyclovir, and voriconazole for prophylaxis, the selection of an empiric antimicrobial regimen should focus on drugs active against pathogens that would likely break through such prophylaxis.

Diagnostic Approach to Febrile Syndromes in Patients With Neutropenia

All neutropenic patients who develop a new fever should at a minimum have blood samples drawn for two blood cultures, with one obtained peripherally and one obtained through the lumen of the indwelling catheter that has either been in place the longest or is most suspicious for being infected. Other sites should be cultured as clinically indicated. The more time points that are sampled, and the higher the blood volume collected for culture, the more likely the blood culture result is to be positive. Drawing sample for two separate blood cultures at the onset of a new fever is a reasonable approach. Additional samples should be drawn for blood cultures if the fever persists, new clinical manifestations occur, or if the patient's condition worsens, although there is no specific algorithm other than "clinical judgment" that can be supplied to direct exactly how often such blood cultures should be obtained.

In the era of readily available imaging and laboratory testing, physical examination is often neglected as a method to assess the severity of the patient's illness and determine the cause of the infectious disorder. Physical examination is useful to identify sites that merit more focused investigation. With impaired inflammatory response, findings on examination may be subtle and require special attention to subtle changes in symptoms or signs.

Diagnostic microbiology is shifting rapidly from a system based on in vitro cultures, biochemical identification, and in vivo susceptibility testing to molecular approaches that can identify organisms and their susceptibility directly in human specimens or from isolates on a laboratory plate or tissue culture.[39–41] For immunosuppressed patients, such molecular techniques can permit recognition of causative organisms that might have been missed by conventional techniques, but may also pose difficult challenges for interpretation. Immunosuppressed patients may have detectable levels of normally latent viruses such as CMV, adenovirus, BK virus, and EBV. Finding such pathogens by PCR in the serum, for instance, does not necessarily indicate that the circulating virus is the cause of the febrile process or needs to be treated. Molecular diagnostics may also identify small quantities of pathogens that would be dismissed as irrelevant in immunocompetent patients, such as *P. jirovecii* or an *Aspergillus* species in a BAL. However, in a neutropenic patient such organisms might be the cause of life-threatening pathology and thus are rarely ignored—that is, their presence results in the initiation of therapy.

Quantitative PCR may provide some clues as to the relevance of the pathogen, but interpretation of such quantification is very complex and nonstandardized and depends both on the quantity of pathogen present and the quality and size/volume of the specimen collected. In addition, some pathogens in neutropenic patients persist for many weeks or months after the acute event has resolved; finding norovirus in the stool or RSV in BAL may represent colonization or shedding from an illness months ago rather than the cause of a new or emerging process. Thus the sensitivity of molecular techniques adds considerable opportunity for detection of true causative organisms but also complexity for determining whether the identified organism is causing disease, is transmissible, or merits treatment.[17,42–44]

Biomarker monitoring is standard for most programs treating immunosuppressed, neutropenic patients. Weekly serologic molecular (e.g., PCR) testing for CMV—and in some programs EBV, BK virus, adenovirus, and *Toxoplasma*, and periodic monitoring for hepatitis B virus (HBV) or hepatitis C virus (HCV) in certain patients—can provide useful information about the likelihood of impending or developing infectious syndromes.[45,46] Similarly, monitoring for fungal infections either weekly, or when clinically indicated, via β-D-glucan and/or galactomannan can provide useful information about fungal infections, although the sensitivity and specificity of such tests need to be well understood.

To supplement biomarker monitoring, patients who are already febrile with poorly defined sources may benefit from serial computed tomography or magnetic spectroscopy for chest, abdomen, pelvis, or central nervous system (CNS) imaging to identify pathology not apparent on routine imaging, ultrasound screening, or physical examination, thus providing the diagnostic team information on what further tests to pursue. In patients with radiographic abnormalities of the lungs (focal or diffuse), early BAL or biopsy may permit early institution of therapy and thus improve long-term prognosis.

Treatment of Infections in Patients With Neutropenia

Cytotoxic chemotherapy puts patients at risk for infection by suppressing myelopoiesis and by compromising the integrity of the gastrointestinal mucosa. Thus much of the invasive bacterial and *Candida* disease that occurs is a result of translocation or penetration of gastrointestinal flora across gastrointestinal mucosal surfaces, surfaces that may be eroded by cytotoxic therapy or graft versus host disease.

In the 1960s and 1970s, aerobic gram-negative bacilli such as *E. coli, K. pneumoniae,* and *P. aeruginosa* predominated as pathogens in neutropenic patients. In the 1990s the spectrum of causative pathogens in neutropenic patients shifted to gram-positive cocci including viridans and β-hemolytic streptococci, staphylococci (including oxacillin-resistant *S. aureus* [MRSA] and methicillin-sensitive *S. aureus*), and enterococci (including VRE).[20,22,23,34,35] *Candida* species became more frequent as pathogens, especially as patients have been receiving broad-spectrum antibacterial agents and have long-term venous access devices in place. The causative *Candida* species are also shifting from *Candida albicans* to other species owing to the effectiveness of azole prophylaxis. More recently, as prophylactic antimicrobial regimens have become broader and as immunosuppressive regimens have become more potent, invasive molds, reactivated viruses, and multidrug resistant bacteria have become more prominent, thereby complicating the empiric regimens that need to be instituted to ensure optimal patient outcomes when acute infectious syndromes develop.

Empiric therapy should be initiated because of fever (temperature of 38.3°C once or 38.1°C twice) alone in an asymptomatic patient, or the development of a clinical syndrome compatible with infection regardless of temperature. As indicated earlier, even subtle changes in clinical status should trigger diagnostic and therapeutic responses in these patients who are highly vulnerable to rapid progression of infectious processes. As with sepsis in general, fever plus neutropenia or a new syndrome comparable with infection in a neutropenic patient should trigger prompt broad-spectrum clinical antimicrobial therapy.

The management of febrile, neutropenic fever is summarized in guidelines that are widely used to direct care in North America.[10,11]

Algorithms for managing such patients are shown in Figs. 50.2 through 50.4.

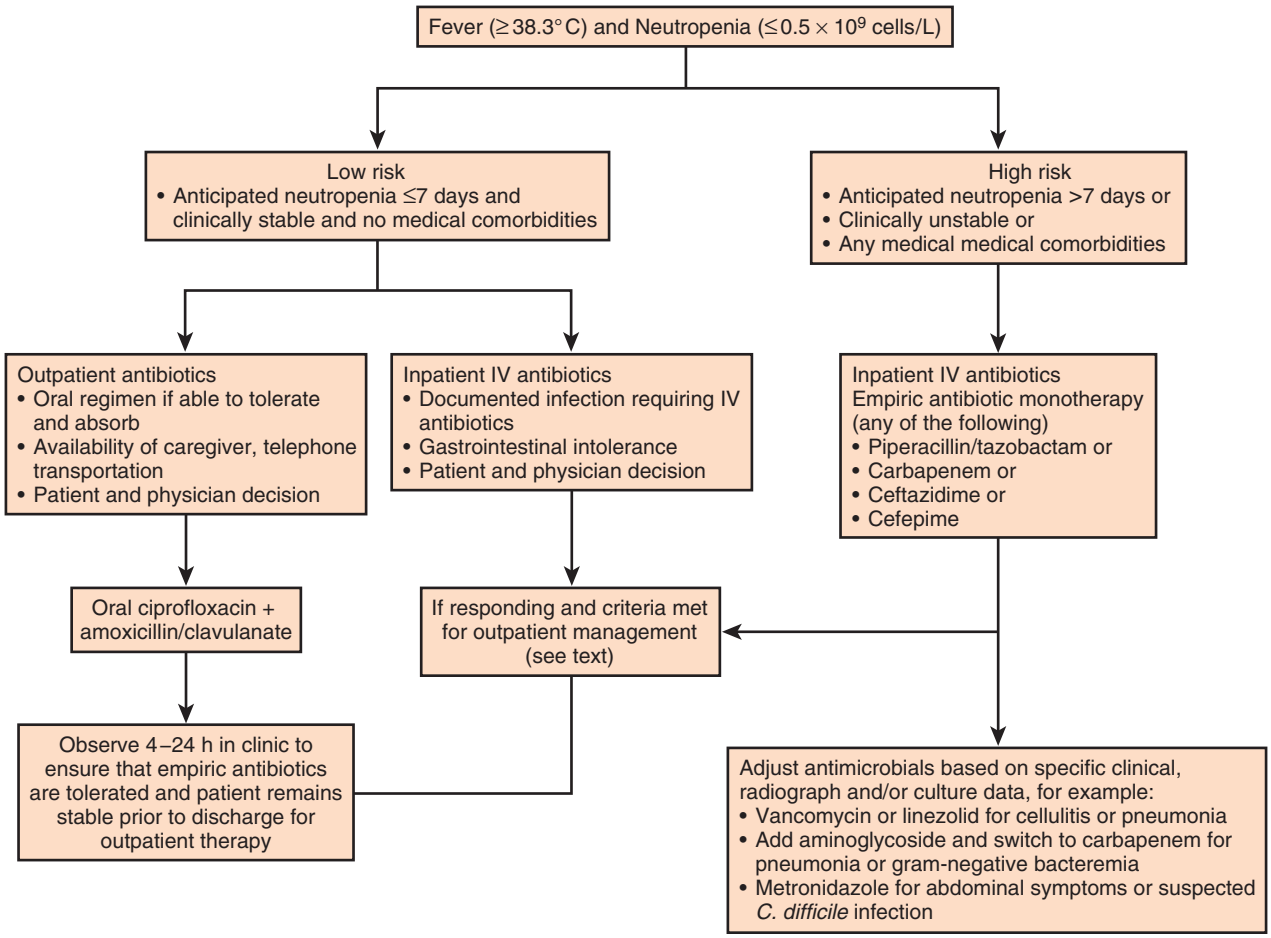
The initial empiric regimens needs to be broad, as with any patient admitted to the ICU with a likely infectious syndrome. There are many reasonable options that can be selected based on host factors, local epidemiology, drug toxicities, and cost.

Some programs continue to treat neutropenic patients with septic presentations with monotherapy for bacterial processes using drugs such as a carbapenem, piperacillin-tazobactam, or cefepime. Ceftazidime is also used, but this cephalosporin has poor activity against many streptococci and thus is falling out of favor with some programs. Given the fact that such patients often have considerable exposure to prior antimicrobials, indwelling lines, gastrointestinal mucosal ulcerations, and are neutropenic, at many institutions the empiric regimen typically is composed of several drugs, including a drug active against MRSA, a drug active against anaerobes, and a drug active against gram-negative bacilli. Because gram-negative bacilli have so much antibiotic resistance in this era, more than one drug class may have to be used in some epidemiologic settings to provide activity against the pathogens commonly seen in a particular hospital's patient population.[22,34,35,47–60]

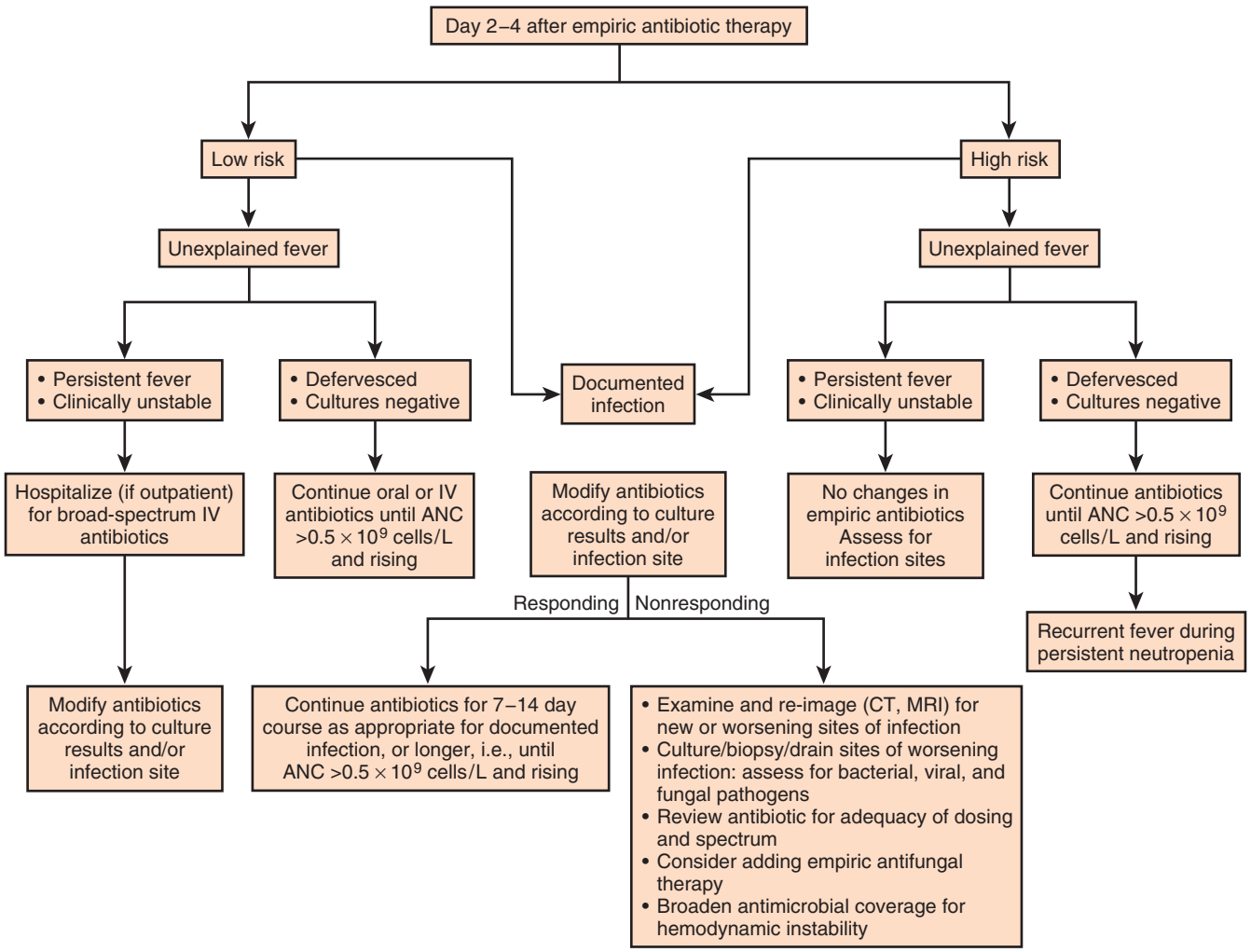
Coverage of MRSA with vancomycin or daptomycin empirically is controversial because of concern about overuse of these drugs leading to contributions to resistance, changing flora, and antibiotic toxicities. But in the ICU it can be difficult to avoid using multidrug regimens empirically, especially for patients who have been receiving fluoroquinolone prophylaxis and patients with indwelling vascular access devices. Linezolid is often avoided because of its potential to cause thrombocytopenia and neutropenia, especially after several days in patients with compromised marrow function.

Although combinations that are bactericidal and/or synergistic are often advocated, it is not easy to predict which regimens will in fact be synergistic or bactericidal for a given pathogen, nor is there good evidence that for this indication such considerations are clinically relevant.

Antifungal therapy is often reasonable to add to the empiric regimen. *Candida* is a common cause of bloodstream infections and can cause septic shock (molds rarely cause this syndrome and yeasts other than *Candida* spp. are uncommon in this population), and thus the inclusion of an echinocandin is prudent given the lack of toxicity of this class of antifungal drugs and the lack of drug interactions associated with these drugs.[55,57–60] Coverage for mold infections should also be considered for febrile events. Molds are rare as causes of septic shock, but they are common causes of life-threatening focal infections such as those in the lungs or CNS. Voriconazole or posaconazole is often used for mold plus yeast activity. Fluconazole is active against most *Candida* spp. but has



• **Fig. 50.2** Initial management of fever and neutropenia. *C. difficile, Clostridium difficile; IV,* intravenous. (From Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:e56–e93, used by permission of Oxford University Press.)



• **Fig. 50.3** Reassessment after 2 to 4 days of empiric antibiotic therapy. *ANC,* Absolute neutrophil count; *CT,* computed tomography; *IV,* intravenous; *MRI,* magnetic resonance imaging. (From Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:e56–e93, used by permission of Oxford University Press.)

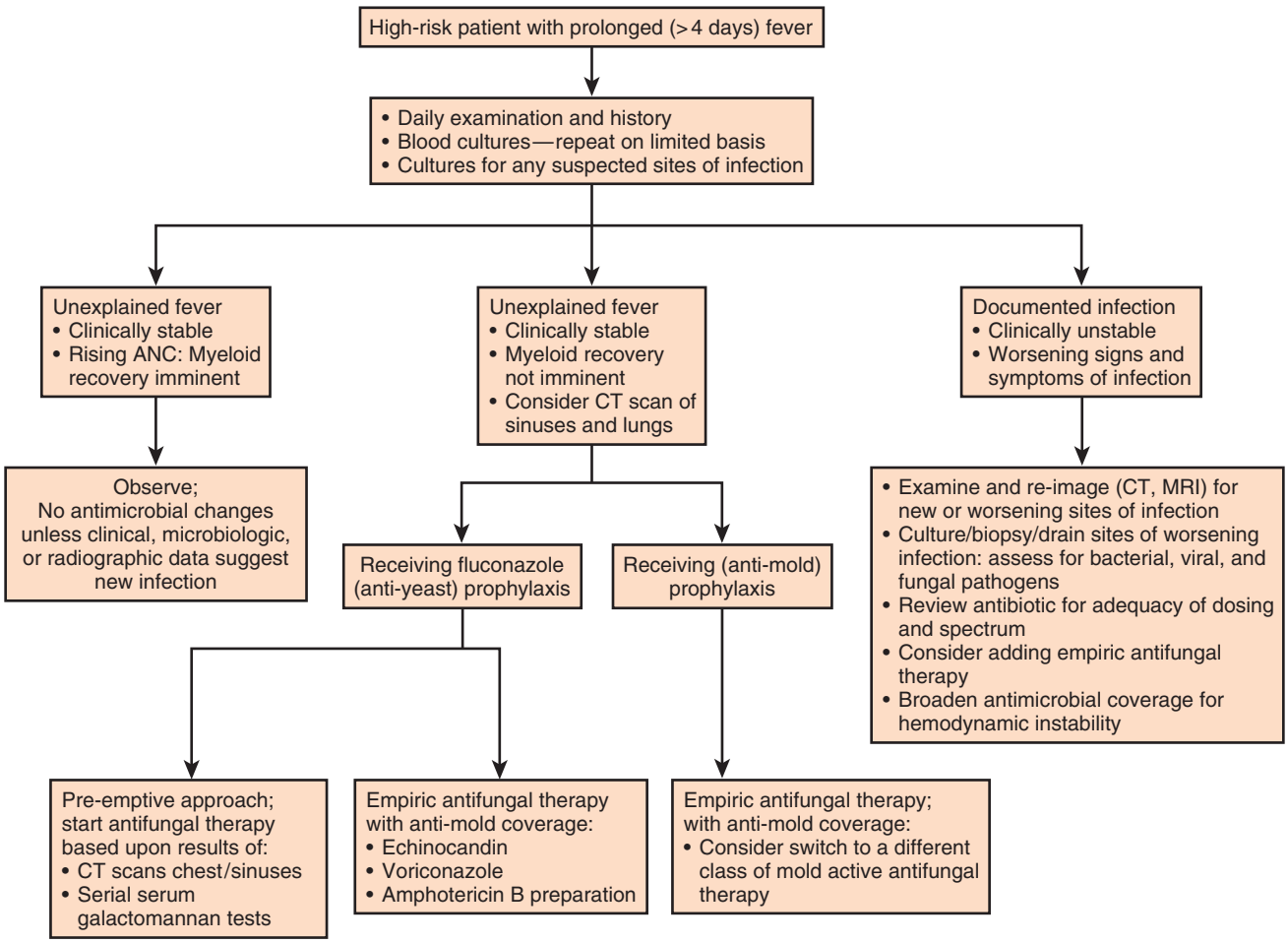
no activity against molds, and it has less activity against non-*albicans Candida* spp. than the more recently approved azoles such as voriconazole and posaconazole and isavuconzole.

The initial empiric regimen can be modified when the site of the infection is identified and when causative organisms are found in the bloodstream or other appropriate culture and when the patient becomes more stable clinically. Vancomycin (or linezolid or daptomycin) is usually stopped if no MRSA or VRE is found 48 to 72 hours after initial cultures from blood and other relevant sites are obtained and the suspicion for such vancomycin-resistant pathogens is low.

If patients respond to the empiric or modified regimens by becoming afebrile and no pathogen or likely site of infection is identified, antibiotics can be stopped after 10 to 14 days if neutropenia fails to resolve, or 5 to 7 days if neutropenia resolves.

If patients do not respond to the empiric regimen, continued investigation for sources should continue, with modifications of the empiric regimen as dictated by the clinical situation. Samples for blood cultures should be drawn periodically if patients remain febrile, with the frequency determined by the duration of fever, evolution of clinical manifestations, and severity of the syndrome.[9,48–50,52–61]

A common challenge in febrile, neutropenic patients is management of indwelling intravascular lines.[61,62] In general, these lines may be left in place initially if examination of the site reveals no indication of infection and the patient is hemodynamically stable after initial fluid resuscitation. Samples for blood cultures should be drawn through the catheter as well as peripherally. Although some experts advocate drawing samples for culture through each port of each catheter, obtaining this many samples is often not feasible because of time, cost, and the volume of blood. If a patient is hemodynamically unstable and does not respond promptly to fluid administration, it is prudent to remove the line in case an infected catheter is the source of the sepsis. Failure to remove the foreign body in this situation probably increases the likelihood of an unfavorable outcome (i.e., embolic phenomena, persistent infection, or recurrent infection). Should results of blood cultures become positive and should the suspicion be high that the catheter is the source, antibacterial therapy without catheter removal may be successful in some settings (e.g., if the pathogen is a bacterium



• **Fig. 50.4** High-risk patient with fever after 4 days of empiric antibiotics. *ANC,* Absolute neutrophil count; *CT,* computed tomography; *MRI,* magnetic resonance imaging. (From Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:e56–e93, used by permission of Oxford University Press.)

that is relatively sensitive to antibacterial therapy), thus avoiding the need to remove the catheter.[61] Situations suggesting that catheter removal is necessary include hemodynamic instability despite aggressive fluid resuscitation, tunnel infection, or infections resulting from yeast or relatively antibiotic-resistant bacteria such as *P. aeruginosa*.

Colony-stimulating factors are useful for accelerating bone marrow recovery. However, once febrile complications have developed, such growth factors have not been shown to change outcome but are plausible to give.

Granulocyte transfusions are also not routinely indicated. There have been no studies in neutropenic patients that have convincingly shown that granulocyte transfusions improve outcome. Moreover, obtaining sufficient numbers of granulocytes to maintain circulating levels greater than 500 cells/μL requires considerable logistical support that most centers do not have.[63–69]

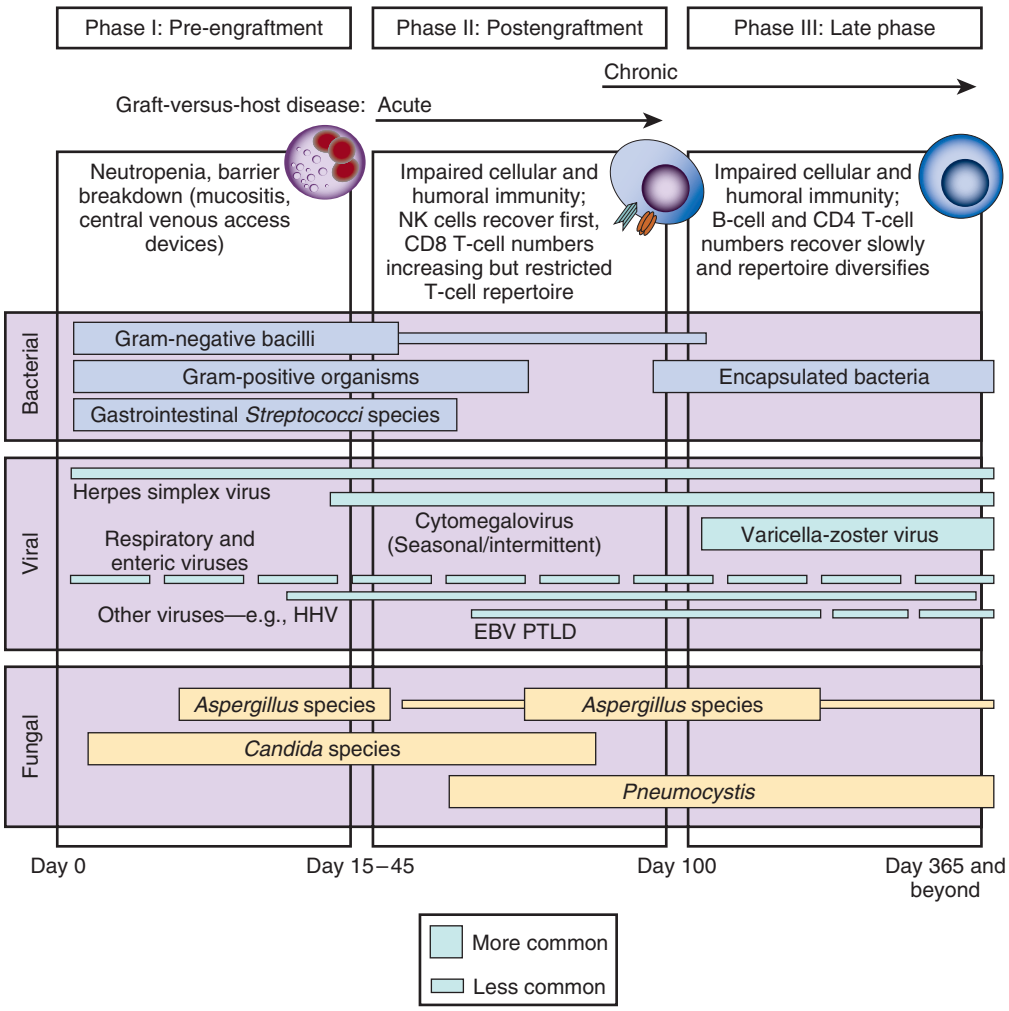
Solid Organ Transplant Recipients

Patients with solid organ transplants present with infectious complications specific to the organ transplanted and the immunosuppressive regimen used. Although solid organ transplant recipients may sometimes become neutropenic, their predominant immunosuppression is due to compromise of their cell-mediated and humoral immune systems by drugs such as the calcineurin inhibitors and corticosteroids. Thus their spectrum of likely causative organism in terms of opportunistic infections is different from the organisms that commonly cause disease in neutropenic patients.[70,71] Figs. 50.5 and 50.6 summarize the typical course of immunologic changes and infectious complications after a solid organ transplant.

In addition to opportunistic infections, each transplanted organ presents risks for infection related to (1) the surgical procedure, (2) anatomic and mechanical barriers that take time to return to normal, and (3) infections present in the donor organ at the time of transplantation.[72–74] Serial imaging of these transplanted organs is especially important to identify anatomic and infectious problems early when they can more readily be corrected or treated.

As with cancer patients who have received cytotoxic chemotherapy or immunotherapy, organ transplant recipients have inflammatory responses that are impaired by the regimens used to prevent graft rejection. Thus serious and life-threatening infections can present subtly with little signs of inflammation and modest or absent fever.

Reactivation of infections that were latent in the recipient or the donor is a common cause of infection in all solid organ



• **Fig. 50.5** Phases of opportunistic infections among allogeneic HCT recipients. *EBV,* Epstein-Barr virus; *HCT,* hematopoietic cell transplantation; *HHV,* human herpesvirus; *NK,* natural killer; *PTLD,* posttransplant lymphoproliferative disease. (From Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15:1143–1238.)

transplant programs. Thus depending on the immunosuppressive regimen and program focus, serial monitoring of often performed for CMV and some combination of, EBV, HSV, VZV, adenovirus, BK virus, *Toxoplasma*, HCV, and HBV.[71,73]

In addition to reactivated opportunistic infection, community-acquired infection, and infections related to the surgical procedure, donor-derived infections are an important consideration.[72,73] The donated organ may have been infected, despite predonation screening, with a bacterial or fungal process, a latent virus, or an unexpected community-acquired organisms such as *Babesia,* HIV, HBV, HCV, *Plasmodium, Trypanosoma chagas*, *Mycobacterium tuberculosis*, or *Legionella.* Organs can also be contaminated with skin flora or waterborne organisms during the procurement and transplantation process.

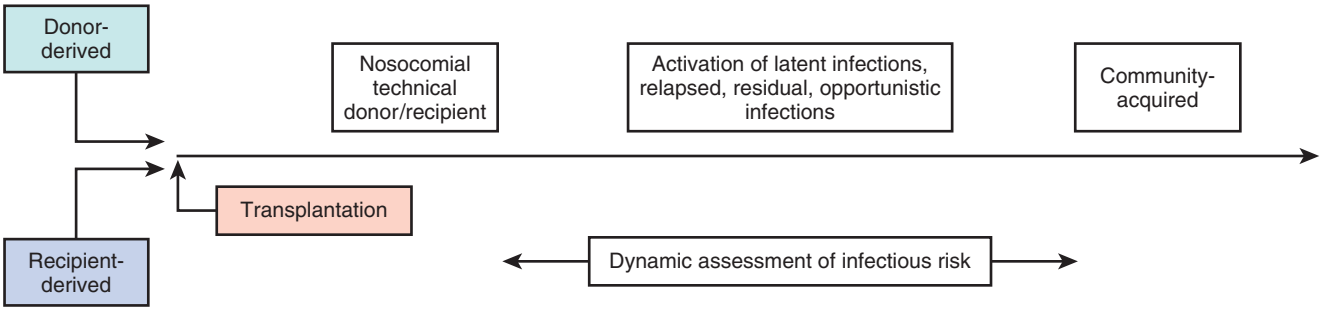
Organ biopsies are often very useful to distinguish graft rejection from infection and to identify the cause of infection if a microbial process is indeed present. Considerable experience and expertise are required to make prudent decisions about when to obtain a biopsy, how often to obtain a biopsy, and what technique should be used to secure a tissue sample adequate for the likely processes being sought.

Monitoring of drug levels for immunosuppressive agents is important to ensure appropriate activity of these drugs and to minimize their respective toxicities. Given the multiple drugs that organ transplant recipients receive, such levels can be difficult to predict. Trying to match the level of immunosuppression to graft viability and infection management is a balancing act that requires experience and judgment rather than a fixed algorithm.

An important concept for approaching infections after solid organ transplant is to focus on the time since transplantation, as well as the level of immunosuppression. Any timeline is a generalization that must be modified according to the organ involved and the specific immunosuppressive regimen used. However, Fig. 50.5 provides a conceptual overview of how such timelines can be useful.[71–73,75–80]

Patients With HIV/AIDS

Opportunistic infections continue to occur in three groups of HIV-infected patients: (1) those who are unaware of their HIV status until they develop an opportunistic infection or tumor such as *Pneumocystis* pneumonia, *Toxoplasma* encephalitis, or Kaposi



Common infections in solid organ transplantation recipients

Antimicrobial-resistant species: • MRSA • VRE • *Candida* species (non-*albicans*) Aspiration Line infection Wound infection Anastamotic leaks/ischemia *Clostridium difficile* colitis Donor-derived (uncommon): HSV, LCMV, rabies, West Nile Recipient-derived (colonization): *Aspergillus, Pseudomonas*	With PCP and antiviral (CMV, HBV) prophylaxis: • BK polyomavirus nephropathy • *Clostridium difficile* colitis • Hepatitis C virus • Adenovirus, influenza • *Cryptococcus neoformans* • *Mycobacterium tuberculosis* Anastamotic complications Without prophylaxis add: Pneumocystis Herpes viruses (HSZ, VZV, CMV, EBV) Hepatitis B virus *Listeria*, *Nocardia*, *Toxoplasma*, *Stronglyoides*, *Leishmania*, *Trypanosoma cruzi*	Community-acquired pneumonia, urinary tract infection: *Aspergillus*, atypical molds, *Mucor* species, *Nocardia*, *Rhodococcus* species Late viral: • CMV (colitis/retinitis) • Hepatitis (HBV, HCV) • HSV encephalitis • Community-acquired (SARS, West Nile) • JC polyomarvirus (PML), skin cancer, lymphoma (PTLD)

• **Fig. 50.6** Usual sequence of infection after solid organ transplantation. *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *HBV,* hepatitis B virus; *HSV,* herpes simplex virus; *LCMV,* lymphocytic choriomeningitis virus; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *NK,* natural killer; *PCP, Pneumocystis* pneumonia; *PML,* progressive multifocal leukodystrophy; *PTLD,* posttransplant lymphoproliferative disease; *SARS,* severe acute respiratory syndrome; *VRE,* vancomycin-resistant enterococci; *VZV,* varicella-zoster virus. (From Fishman JA. Infection in the solid organ transplant recipient. In: Basow DS, ed. UpToDate. Waltham, MA: UpToDate, 2017.)

sarcoma; (2) those who are unable to receive appropriate therapy because social or financial impediments; and (3) those who develop opportunistic infections despite antiretroviral therapy (ART) and opportunistic infection prophylaxis.[81–95]

Spectrum of Clinical Manifestations

Patients with HIV infection develop clinical disease as a result of five basic processes: (1) opportunistic infections and tumors enabled by HIV-induced immunosuppression; (2) the direct effect of HIV on specific organs (e.g., cardiomyopathy, enteropathy, dementia); (3) immunologically mediated processes (e.g., glomerulonephritis, thrombocytopenia); (4) accelerated cardiovascular or renal or cerebrovascular disease as the result of HIV-related inflammation; and (5) processes unrelated to HIV/AIDS.

Management of Antiretroviral Drugs

For any HIV-infected patient in the ICU, clinicians must be cognizant of the need for careful management of antiretroviral drugs.[92] If patients present with a life-threatening opportunistic infection but are not receiving antiretroviral drugs at the time of ICU admission, it would seem plausible to start the drugs and enhance immune response to augment the effect of the specific antimicrobial regimen. However, this is almost never desirable and should be considered only in conjunction with an experienced HIV/AIDS provider.

Administering antiretroviral drugs and having predictable pharmacokinetics in the ICU is difficult because almost all antiretroviral agents are available only in oral form, and thus absorption is unpredictable. Some antiretroviral agents have considerable drug interactions, making pharmacokinetics of the antiretroviral and the interacting drug similarly unpredictable. If antiretroviral drug levels are higher than targeted, drug toxicities are more likely to occur. More ominously, if targeted levels are too low, HIV can develop drug resistance within days, losing that class of drug as a possible part of the anti-HIV armamentarium in that patient for the patient's lifetime.

The desirability of starting ART in the setting of acute opportunistic infections has been studied. The benefit of starting antiretroviral agents depends on the opportunistic infection being studied and the $CD4^+$ T-lymphocyte count at the time that therapy is being considered. There is no survival advantage in starting drugs within the first 2 weeks of therapy for most opportunistic pathogens (e.g., PCP, *Toxoplasma* encephalitis, CMV retinitis, *Mycobacterium avium* complex [MAC] bacteremia). However, for pathogens such as JC virus or *Cryptosporidium* for which there is no specific therapy, there may be no alternative except to start ART and hope that the drugs are absorbed and that the opportunistic infection responds. Moreover, when ART is started at the onset of therapy for an opportunistic infection, the suppression of HIV viremia may lead to rapidly enhanced immune function.

Immune reactivation of inflammatory syndromes can occur, manifesting as mild, moderate, or severe immune response to the replicating or dead organisms, causing organ dysfunction that can be life-threatening. Such rapidly enhanced immune and inflammatory responses can lead to severe physiologic deterioration, especially for fungal and mycobacterial processes such as cryptococcal meningitis, *Mycobacterium tuberculosis* meningitis or pericarditis or disseminated disease, or PCP. Thus starting ART for a patient in the ICU with a serious or life-threatening process requires considerable clinical experience and judgment, especially because there are no validated guidelines to help the clinician make appropriate therapeutic decisions.

If patients enter the ICU already receiving ART, an expert in HIV management should be consulted about the benefits of continuing the drugs rather than interrupting them. There is ample evidence that even brief interruption of antiretroviral drugs can have deleterious effects in terms of long-term loss of CD4 cells and in terms of the occurrence of opportunistic infections.[96,97] Stopping antiretroviral drugs may be the least harmful option. However, given the different half-lives of various antiretroviral agents, such discontinuation should be done in consultation with an HIV-experienced clinician.

Clinicians should refer to the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents and the Guidelines for Antiretroviral Therapy in Adults and Adolescents for more detailed discussion on when to initiate ART in the setting of a specific opportunistic infection (https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0).

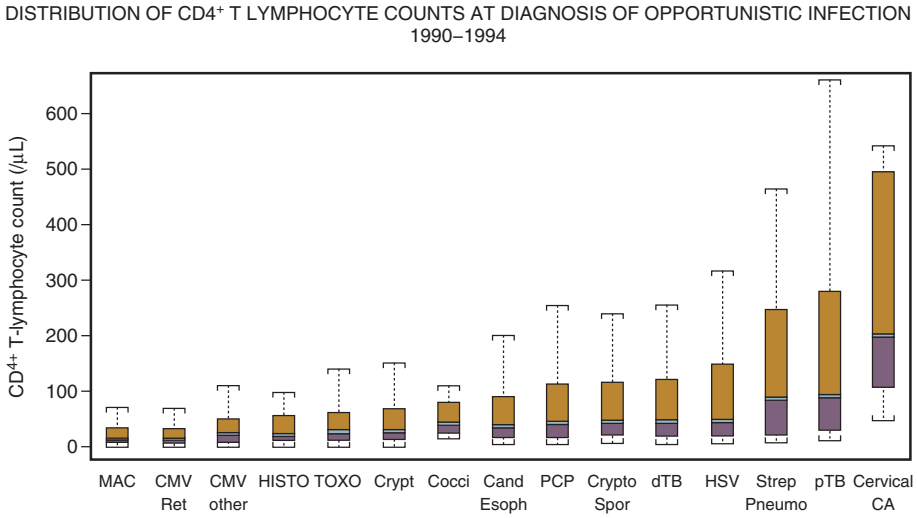
Diagnosis of Opportunistic Infections

The $CD4^+$ T-lymphocyte cell number continues to be a useful marker for predicting the occurrence of opportunistic infections in patients with HIV infection.[98] Fig. 50.7 demonstrates the typical relationship of $CD4^+$ T-lymphocyte counts to the occurrence of opportunistic infections. Knowledge of this relationship permits the focusing of diagnostic, therapeutic, and prophylactic management. This relationship is unique for HIV/AIDS. For other situations such as transplant recipients or patients receiving antiinflammatory or immunomodulating monoclonal antibodies, $CD4^+$ T-cell counts have some utility but are much less sensitive and specific for predicting the occurrence of disease.

For instance, if a patient with HIV infection and a $CD4^+$ T-lymphocyte count of 700 cells/μL presents with diffuse pulmonary infiltrates, the diagnostic evaluation and empiric antimicrobial regimen should focus on common, nonopportunistic pathogens such as *Mycoplasma, Legionella,* and *Chlamydia* organisms, as well as common community-acquired viruses such as influenza plus opportunistic infections that occur at high $CD4^+$ T-lymphocyte counts, such as *M. tuberculosis* or *Streptococcus pneumoniae*. In contrast, if the same patient had a $CD4^+$ T-lymphocyte count less than 50 cells/μL, the evaluation and empiric regimen would focus on pneumocystosis, pneumococcal pneumonia, and tuberculosis, although the previously mentioned processes that occur at high $CD4^+$ T-lymphocyte counts can also occur at lower $CD4^+$ T-lymphocyte counts.

Keeping in mind that $CD4^+$ T-lymphocyte counts are useful predictors of susceptibility to infection is important, but they are not perfect. Occasionally, patients will develop opportunistic infections at "uncharacteristically" high $CD4^+$ T-lymphocyte counts. For instance, 5% to 10% of cases of pneumocystosis occur at $CD4^+$ T-lymphocyte counts greater than 200 cells/μL.[99] Clinical parameters can provide additional clues; for example, oral *candidiasis*, a previous opportunistic infection, a prior episode of pneumonia, or high viral load are independent risk factors for the occurrence of *P. jiroveci* pneumonia, and logically for other infections as well.

Like other immunosuppressed individuals, patients with HIV infection and low $CD4^+$ T-lymphocyte counts require a prompt attempt to define the specific cause of their clinical syndrome. A patient's condition can deteriorate quickly and the range of causative organisms is broad.



• **Fig. 50.7** $CD4^+$ cell count range for common manifestations of acquired immunodeficiency syndrome. *Cand Esoph, Candida* esophagitis; *cervical CA,* cervical cancer; *CMV Other,* other cytomegalovirus diseases; *CMV Ret,* cytomegalovirus retinitis; *Cocci,* coccidioidomycosis; *Crypt,* cryptococcosis; *Crypto Spor,* cryptosporidiosis; *dTB,* disseminated tuberculosis; *HISTO*, histoplasmosis; *HSV,* herpes simplex virus; *MAC, Mycobacterium avium* complex; *PCP, Pneumocystis jirovecii* pneumonia; *pTB,* pulmonary tuberculosis; *Strep Pneumo, Streptococcus* pneumonia; *TOXO,* toxoplasmosis.

Clinical Syndromes

Pneumonia

P. jirovecii is the classic opportunistic infection that causes pneumonia in persons with HIV/AIDS. However, effective management of pulmonary dysfunction in patients with HIV/AIDS requires an organized approach to infectious and noninfectious processes.

Like any patient population, patients presenting with hypoxemia, ventilatory failure, or pulmonary infiltrates could have a wide array of infectious and noninfectious processes. Patients with HIV/AIDS have accelerated cardiovascular disease, increased procoagulants, and increased incidence of chronic obstructive pulmonary disease and pulmonary hypertension. Thus there are multiple noninfectious considerations that occur with increased frequency in HIV-infected persons in the differential diagnosis.

Persons with HIV/AIDS, even those with low $CD4^+$ T-cell counts, are not immune from community-acquired pathogens that are frequently seen in immunologically normal patients. Patients with HIV infection can develop severe pulmonary dysfunction because of common community-acquired pathogens such as *Legionella, Mycoplasma*, and *Chlamydia;* adenovirus; influenza; or respiratory syncytial virus, as well as other opportunistic viruses and fungi. Thus the diagnostic evaluation needs to be comprehensive, emphasizing direct smears of sputum or BAL.

It is important to recognize that the clinical presentations produced by many causative agents can be similar to PCP. For instance, histoplasmosis, tuberculosis, and nonspecific interstitial pneumonitis can present identically to PCP.[99–102] Thus although empiric diagnosis and empiric therapy may be reasonable as initial approaches to some patients with HIV infection and mild pneumonitis, such an approach is usually not appropriate for HIV-infected patients in an ICU.

Evaluation of induced sputum is the first step in the diagnostic approach to PCP if patients can tolerate nebulization of hypertonic saline solution and vigorous coughing to produce a sputum sample. Sensitivity of PCP diagnosis by induced sputum examination can be as high as 80% to 95% at many hospitals (at some institutions the yield is considerably lower).[103] Specificity should be 100% in an experienced laboratory, especially when immunofluorescent antibody staining is used. Other pathogens, including mycobacteria, fungi, and routine bacteria, can be identified in sputum as well. For intubated patients, respiratory secretions obtained by deep intratracheal suctioning are also likely to be useful, although they have not been as carefully studied as induced sputum. Should the diagnosis not be established by evaluation of sputum or intratracheal secretions, bronchoscopy should be performed. BAL should diagnose almost 100% of cases of PCP, even if patients have already received 7 to 10 days of empiric therapy at the time of the diagnostic procedure.[99] A diagnosis of PCP is established by visualizing one or more clusters of organisms. Some laboratories are now using PCR to diagnose PCP, but this test is not standardized and is likely to be highly sensitive but not highly specific for identifying *Pneumocystis* as the cause of the pulmonary dysfunction.[104–107]

Thus a negative PCR result of a BAL sample is a highly reliable test to rule of PCP as a diagnosis. A positive PCR result leaves some uncertainty as to whether *Pneumocystis* is the cause of the pulmonary dysfunction, or an airway colonizer that is unrelated to the current pathologic process.

Diagnostic criteria for other opportunistic infections are reviewed in Chapters 12 and 42. CMV merits special mention. CMV frequently is reactivated in patients with HIV infection and low $CD4^+$ T cells and can be found in the blood and secretions of such patients who have no end organ disease owing to CMV. CMV pneumonia almost never occurs in patients with HIV infection, as opposed to patients with solid organ or stem cell transplants. CMV should be considered the cause of pulmonary dysfunction only if other causative processes have been ruled out and there is convincing histologic or cytologic evidence. Culture of sputum or BAL for CMV does not provide useful information; in particular, patients with $CD4^+$ T-lymphocyte counts below 100 cells/μL will predictably have CMV present in their secretion independent of whether or not pulmonary disease is present.[108] A diagnosis of CMV pneumonia in this patient population is suggested by cytologic testing (especially if many cells with CMV inclusion bodies are seen) and confirmed by the presence of multiple inclusion bodies in lung tissue obtained by transbronchial or open lung biopsy.

Similarly, MAC and HSV can often be found in respiratory secretions of patients with HIV/AIDS with low $CD4^+$ T-cell counts by culture or by nucleic acid amplification tests, but these organisms almost never cause pneumonia in patients with HIV infection. In other patient populations they can clearly cause pneumonia, but the dearth of CMV, MAC, and HSV pneumonia in this patient population emphasizes the point that it is important to know from published literature what the clinical likelihood is for different microbial processes.

Fungal pneumonias other than PCP are generally diagnosed by direct microscopy or culture of respiratory secretions (sputum lavage or BAL). *Candida* organisms almost never cause pneumonia in patients with HIV infection. The frequency of *Cryptococcus, Histoplasma, Blastomyces,* and *Coccidioides* as causes of pneumonia depends on the geographic exposure of the patient. Among these mycoses, antigen detection techniques can be useful for finding *Cryptococcus* and *Histoplasma* organisms in blood or, for *Histoplasma,* in urine. In the Midwestern United States, pulmonary histoplasmosis can cause diffuse pneumonia as commonly as PCP in HIV-infected persons with low $CD4^+$ T-cell counts and can present with identical clinical and radiologic findings.

Therapy for opportunistic infections is summarized in web-based sites that are regularly updated (https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0).

While awaiting a specific diagnosis, it is reasonable to initiate empiric therapy in patients ill enough to merit admission to an ICU. For patients with a $CD4^+$ T-lymphocyte count greater than 250 to 300 cells/μL and serious acute pulmonary processes, levofloxacin or moxifloxacin plus ceftriaxone or, as an alternative, azithromycin plus ampicillin-sulbactam or vancomycin plus levofloxacin, would be reasonable choices. For patients with $CD4^+$ T-lymphocyte counts below 200 to 250 cells/μL, levofloxacin or moxifloxacin plus either trimethoprim-sulfamethoxazole or intravenous pentamidine would be appropriate regimens.

If PCP is documented, trimethoprim-sulfamethoxazole is always the drug of choice in patients who can tolerate it. Regardless of which specific anti-*Pneumocystis* regimen is used, corticosteroid therapy is indicated for any patient who presents with an oxygen pressure (P_{O_2}) below 70 mm Hg or an alveolar-arterial gradient higher than 30 mm Hg.[109–111] This may be counterintuitive, but there are ample controlled studies to support this approach. Patients with an initial P_{O_2} lower than 70 mm Hg are the subgroup with substantial mortality risk for whom corticosteroids have been shown to provide a survival benefit. Corticosteroids also provide more rapid resolution of pulmonary manifestations in patients who

present with better pulmonary function, but survival in this population is so high that clinical trials have not been able to show survival benefit and thus corticosteroids are not conventionally recommended for patients who present with a room air P_{O_2} greater than 70 mm Hg. Some experts are concerned that corticosteroid use will be associated with reactivation of latent infections such as CMV or MAC or tuberculosis. However, reactivation of life-threatening infections has not been associated with this corticosteroid regimen.

How should a patient with AIDS-associated PCP be managed if there is no improvement, or if there is deterioration, after 5 to 10 days of therapy? The median time to improvement in clinical variables is 4 to 8 days; therefore changes in therapy are probably not warranted before 5 to 10 days. At that point the accuracy of the diagnosis should be reassessed. Consideration should be given to repeat bronchoscopy with BAL or, perhaps, transbronchial or video-assisted transthoracic biopsy to determine if CMV, fungi, mycobacteria, or a nosocomial bacterial process is present.

Noninfectious processes such as congestive heart failure or tumor (e.g., Kaposi sarcoma or lymphoma) must also be considered for HIV-infected patients with focal or diffuse pulmonary processes. If pneumocystosis is the only causative process that can be identified and patients are not responding to anti PCP therapy after 4 to 8 days, corticosteroids should be added to the regimen if they have not been already added. Whether switching from one anti-*Pneumocystis* agent to another or adding a second agent is helpful has not been determined by clinical trials. Some human pneumocystosis isolates carry resistance mutations to sulfonamides, but such testing is available only in a few research centers, and the clinical significance of these mutations is unknown. Most experts add parenteral pentamidine to trimethoprim-sulfamethoxazole. Parenteral clindamycin-primaquine could be used as salvage regimens as well. Patients whose conditions have not improved after 14 to 21 days of therapy with specific chemotherapy plus corticosteroids have an exceedingly poor prognosis.

Central Nervous System Dysfunction

Meningitis

In HIV-infected patients with $CD4^+$ counts greater than 200 cells/μL, the causes of meningitis do not differ markedly from those in the normal population; *S. pneumonia, Neisseria meningitides,* and group B streptococci are the most common causes. For patients with $CD4^+$ counts lower than 100 cells/μL, *Cryptococcus neoformans* and *S. pneumoniae* are especially common.[112–114]

A diagnosis of cryptococcal meningitis is typically established by lumbar puncture. Essentially 100% of patients with HIV-related cryptococcal meningitis should have a positive cerebrospinal fluid (CSF) cryptococcal antigen and CSF culture. Most patients will have an elevated CSF protein, low glucose, and elevated mononuclear cell count. Almost all will also have a positive serum cryptococcal antigen.

The therapy of choice for cryptococcal meningitis in the United States is liposomal amphotericin B for at least 2 weeks, plus oral flucytosine. Fluconazole should not be used for initial therapy, although it can be used after the initial 2 weeks if patients have a good clinical response.[115,116]

Some patients with cryptococcal meningitis have symptomatic elevations of CSF pressure. Such patients should have therapeutic lumbar punctures to remove enough CSF to reduce the pressure to 20 to 25 cm H_2O.[117–119]

Multiple lumbar punctures may be needed. If after multiple lumbar punctures the patient still has symptomatic elevation of CSF pressure greater than 20 to 25 cm H_2O, the insertion of a ventricular shunt should be considered, although there are no specific guidelines regarding when to place such a shunt. Corticosteroids should not generally be used to treat elevated intracranial pressure in this situation.[112,120–122]

Focal Central Nervous System Lesions

Patients with HIV infection and $CD4^+$ T-cell counts less than 100 cells/μL may present with focal motor lesions, altered mental status, or seizures. Although the differential diagnosis is extensive, the major considerations are toxoplasmosis and lymphoma.[123,124]

CNS toxoplasmosis may present as one or multiple lesions that represent reactivation of latent disease. Lesions are characteristically enhancing in a ringlike pattern and typically occur in the basal ganglia, but many different radiologic presentations have been documented.

All patients with CNS toxoplasmosis are IgG seropositive for toxoplasmosis using sensitive assays. However, some laboratories use less sensitive assays and thus some patients may appear to be seronegative. If lumbar puncture can be performed, a CSF PCR for toxoplasmosis is positive in about 50% of cases, although there is no standardization of these *Toxoplasma* PCRs, making results variable from laboratory to laboratory.[125,126]

The standard practice for HIV-infected patients with $CD4^+$ T-lymphocyte counts less than 200 cells/μL is to undergo an empiric trial of oral sulfadiazine plus pyrimethamine plus leucovorin. Most patients who have toxoplasmosis will show clinical and radiologic improvement within 2 weeks. If such improvement has not been documented, and the diagnosis is in doubt, a needle biopsy of the intracranial lesion should be considered.[127–129]

CNS lymphoma can present identically to CNS lymphoma. A negative serum IgG for toxoplasmosis and a negative CSF toxoplasma PCR should suggest lymphoma.[130] Most patients with CNS lymphoma will have a positive CSF PCR for EBV, although this test is neither 100% sensitive nor 100% specific for lymphoma. Patients who are CSF EBV PCR negative or in whom the diagnosis is uncertain may require a brain biopsy to document the lymphoma.

Therapy for lymphoma should be determined in consultation with experienced oncologists.

Focal White Matter Lesions

In patients with HIV, JC virus encephalitis (also known as progressive multifocal encephalopathy) causes focal white matter lesions that are associated with progressive motor, sensory, and neurocognitive dysfunction.[131,132] A small fraction of patients can present with rapidly progressive cognitive decline. The computed tomography scan or MRI images of JC virus encephalitis are characteristic of this disease. Diagnosis is usually confirmed by CSF PCR for JC virus.[133]

There is no specific therapy. Patients' conditions may stabilize or improve if ART results in immune reconstitution.[112,131]

Diarrhea

Patients with HIV infection and $CD4^+$ T-cell counts below 100 cells/μL can develop severe diarrhea caused by a wide range of opportunistic pathogens, including CMV, cryptosporidiosis, or enteric bacteria such as *Salmonella*, *Shigella*, or *Campylobacter*. Diarrhea in HIV-infected patients can be so severe that patients can have life-threatening malabsorption, electrolyte abnormalities, and bowel perforations. Patients need a thorough stool evaluation for common pathogens such as *C. difficile*, which is the most

common cause of diarrhea in this patient population, even though it is not an opportunistic pathogen. If results of stool cultures are negative, testing samples for ova and parasites might be indicated if there is a history compatible with exposure.

For patients with negative evaluation of multiple stool samples, a sigmoidoscopy or colonoscopy with biopsy is indicated to assess the presence of CMV. CMV colitis occurs exclusively in patients with $CD4^+$ T-lymphocyte counts lower than 100 cells/μL. CMV colitis is best diagnosed by biopsy; there is no reliable correlation with serum CMV PCR or with stool culture or PCR for CMV. The therapy of choice for CMV colitis is intravenous ganciclovir. Intravenous foscarnet is also effective but is more toxic. Oral valganciclovir is not indicated for patients with severe diarrhea but can be used as maintenance therapy once the CMV colitis is controlled. The most effective remedy for CMV colitis is immune reconstitution with ART. As soon as absorption seems likely, ART should be initiated.

Hypotension

Patients with HIV infection develop hypotension resulting from the same types of disorders as with non–HIV-infected individuals—sepsis from a primary infection or a wound or device (especially an intravascular access device), fluid depletion from vomiting or diarrhea, and hemorrhage from a gastrointestinal lesion are examples of common causes. The evaluation of hypotension in a patient with HIV infection must take into account factors particular to this patient population. HIV-infected patients are susceptible to opportunistic infections; they undergo many procedures that can be associated with infectious complications; and they receive an array of drugs, some of which have cardiovascular effects. Thus evaluating hypotension in this patient population requires a comprehensive and thorough approach. Adrenal function always deserves special attention because several viral processes, fungal and mycobacterial diseases, HIV, and drugs can suppress the adrenal axis and either cause hypotension or exacerbate it.

Prevention of Opportunistic Infection

Intensivists usually focus on the management of acute processes, but if attention is not provided to opportunistic infection prevention, patients hospitalized for one process may develop a second life-threatening process given the high incidence of opportunistic infections. Current recommendations are maintained by guidelines maintained by governmental agencies and professional societies (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0).

Patients with HIV infection typically receive several antimicrobial agents to reduce the likelihood they will acquire opportunistic infections. *Primary prophylaxis* is the term used to indicate strategies that reduce the likelihood of an initial episode of a disease process. *Secondary prophylaxis* is the term that was used to indicate strategies that prevent reinfections and recurrences; *chronic maintenance* is the term used for strategies to prevent relapses. More recently, such prophylaxis is referred to as *chronic suppression* if the goal is to prevent a relapse, and secondary prophylaxis if the goal is to prevent reinfection.

All patients with HIV infection and $CD4^+$ T-lymphocyte counts below 200 cells/μL typically receive anti-*Pneumocystis* prophylaxis. Trimethoprim-sulfamethoxazole is the regimen of choice. Patients who take this drug have very few breakthroughs of PCP and receive considerable protection against toxoplasmosis and certain routine bacterial infections. Alternative regimens include daily dapsone or daily aerosol pentamidine. Prophylaxis against MAC is recommended for patients with $CD4^+$ T-lymphocyte counts below 100 cells/μL; clarithromycin and azithromycin are currently the drugs of choice.[112] This recommendation may change soon in the United States because, in contrast to the 1980s and 1990s. *M. avium* is not seen in the United States frequently as the cause of acute disease in patients with HIV/AIDS.

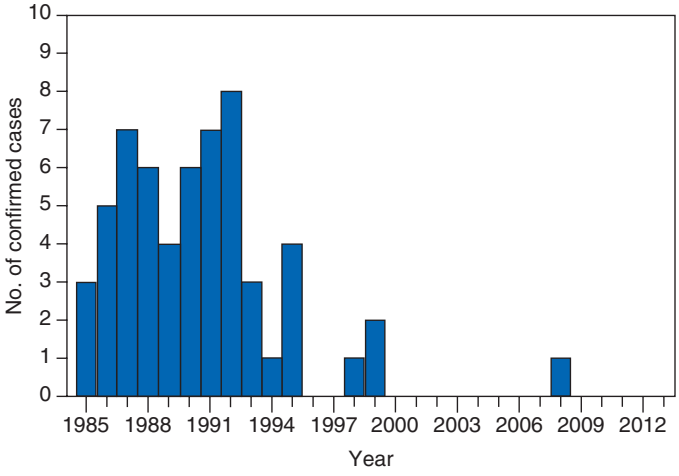
Fluconazole and acyclovir prophylaxis to reduce the frequency of fungal and viral processes, respectively, are not recommended in the United States. Isoniazid prophylaxis is important for any patient with a tuberculin skin test that shows more than 5 mm of induration or a history of substantial recent exposure.

HIV Transmission in the Intensive Care Unit

Transmission of HIV is an issue that requires attention in the ICU.[134–136] No evidence exists that HIV-infected health care professionals can infect patients, regardless of what procedure they perform, with the exception of two unusual and unexplained events. Intensivists should realize that although there are no federal policies defining how HIV-infected practitioners should be credentialed and monitored, many hospitals have relevant policies and procedures. Some are modeled after guidelines from the Society for Healthcare Epidemiology.[135,137]

Patients with HIV pose a risk to health care professionals, although there have been no documented cases of transmission since 2009 in the United States and only one since 2000 (Fig. 50.8).[138]

Whatever risk there is can be substantially reduced by staff education, by strict monitoring for compliance with universal precautions, and by having proper equipment. Guaranteeing that such strategies are in place is the responsibility of ICU leadership, who are committed to ensuring the safety of the workforce not only from HIV infection but also for other pathogens that can be transmitted by needle sticks such as HCV and HBV. Almost all HIV transmission has occurred in an occupational setting as a result of injuries involving sharp instruments (e.g., needles, scalpels). The risk of such injuries is based on older literature before the era



• **Fig. 50.8** Number of confirmed cases (N = 58) of occupationally acquired human immunodeficiency virus infection among health care workers reported to the Centers for Disease Control and Prevention in the United States, 1985–2013. (From Joyce MP, Kuhar D, Brooks JT. Occupationally acquired HIV Infection Among Health Care Workers—United States, 1985–2013. *MMWR Morb Mortal Wkly Rep.* 2015;63:1245–1246.

of antiretroviral prophylaxis, about 1 case of HIV transmission per 250 injuries, but the likelihood of transmission in an individual accident depends on the amount of the source patient's viremia at the time of the accident (late-stage patients generally have more circulating virus than do early-stage patients) and the nature of the accident. Most authorities recommend immediate prophylaxis if a significant injury occurs involving an HIV-infected patient. It is clear that initiating therapy within a period of hours rather than days is best. Many authorities now advocate an antiretroviral regimen for any situation when the patient and health care provider determine that therapy is appropriate and continuation of that therapy for 4 to 6 weeks.[139–142]

Key Points

- Knowledge of an immunosuppressed patient's specific defects in immunologic and inflammatory response helps predict which opportunistic pathogens are most likely to occur.
- ICUs are increasingly successful in enabling immunosuppressed patients to survive acute crises, especially if the defect in immunologic or inflammatory function is reversible.
- For neutropenic patients, gram-positive cocci have become more frequent than gram-negative bacilli as causes of bacteremia.
- Resistance to antimicrobial agents is becoming a major problem including not only bacteria (e.g., carbapenemase-producing Enterobacteriaceae, MRSA, VRE, and penicillin-resistant pneumococci) but also fungi (e.g., fluconazole-resistant *Candida* organisms) and viruses (e.g., acyclovir-resistant herpes simplex and ganciclovir-resistant CMV).
- In neutropenic patients, broad-spectrum empiric therapy should be considered when treating any febrile process; the choice of drugs is influenced by host factors including the specific immunologic defect. Local epidemiology and the patient's prior colonization and antibiotic exposures are also important factors.
- Organ transplant recipients develop a different spectrum of infections than patients with cancer-related neutropenia.
- The infections in organ transplant recipient are related to their immunosuppressive regimen and the organ that is transplanted. Their occurrence follows a predictable time course.
- Infections in organ transplant recipients may be derived from the donor or the recipient as well as from environmental and person-to-person exposures.
- The $CD4^+$ T-lymphocyte count and the HIV viral load are sensitive and specific predictors of the likelihood that an HIV-infected person will develop specific opportunistic infections.
- Adjunctive corticosteroid therapy is indicated for respiratory failure related to PCP.

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Review Questions

1. For patients with prolonged neutropenia owing to stem cell transplant preparative chemotherapy, who are at risk for both yeast and mold infections, which of the following is the preferred prophylaxis for fungal infection?
   a. Fluconazole
   b. Posaconazole
   c. Caspofungin
   d. Micafungin
   e. Liposomal amphotericin B
   Answer: b. In stem cell transplant recipients with prolonged neutropenia immediately before transplantation (e.g., aplastic anemia) and for those who are anticipated to have slow engraftment (>28 days) or whose engraftment fail, prophylaxis with a drug with both anti-mold and anti-*Candida* activity is preferred in contrast to a narrower anti-*Candida* agent such as fluconazole. Thus posaconazole or voriconazole is the preferred agent in this question.
2. Which of the following antimicrobial agents is most likely to be bone marrow suppressive?
   a. Daptomycin
   b. Linezolid
   c. Piperacillin-tazobactam
   d. Metronidazole
   e. Colistin
   Answer: b. Linezolid causes thrombocytopenia, which in patients with normal pretreatment typically occurs after 10 to 14 days. Leukopenia and anemia then follow. Cytopenias may develop earlier in patients with compromised bone marrows (e.g., those recovering from antineoplastic chemotherapy or a stem cell transplant). Linezolid is thus avoided in most populations with compromised marrow function when possible.
3. Which of the following is the most likely cause of diffuse interstitial infiltrates in a patient 2 weeks after lung transplant?
   a. BK virus
   b. Adenovirus
   c. Cytomegalovirus (CMV)
   d. JC virus
   e. Toxoplasma
   Answer: c. CMV is a well-recognized cause of diffuse interstitial pulmonary infiltrates in patients who have received solid organ or hematopoietic stem cell transplants. Adenovirus can also cause similar infiltrates but does so much less commonly than CMV. Adenovirus and BK virus more typically cause hemorrhagic cystitis. JC virus is the cause of JC encephalitis, previously referred to as progressive multifocal leukoencephalopathy. Toxoplasmosis can present as pulmonary infiltrates that mimic *Pneumocystis* pneumonia but is not common, especially in North America where the seroprevalence of toxoplasma is much lower than in Western Europe or the developing world.
4. For a patient with human immunodeficiency virus (HIV) (CD4 count 700 cells/μL, viral load 500,000 copies/μL) who is not yet undergoing antiretroviral treatment, what is the most likely cause of diffuse interstitial infiltrates, fever, hypoxemia, and cough of 3 days' duration?
   a. *Pneumocystis jirovecii*
   b. CMV
   c. *Mycobacterium avium* complex (MAC)
   d. *Cryptosporidium*
   e. Influenza
   Answer: e. For a patient such as this one with a CD4 count of 700 cells/μL, the likelihood of an opportunistic infection is low, and thus influenza is the correct answer here. *Pneumocystis* almost never occurs at such high CD4 counts. MAC and *Cryptosporidium* cause disease in patients with CD4 counts below 100 cells/μL, but neither causes pulmonary disease in HIV-infected patients at any CD4 count with very rare exceptions.
5. Which of the following should be done to evaluate a health care worker who has just sustained a significant needle stick injury from a patient who absconded from the emergency department but who is known to be HIV-infected and not receiving therapy, but little else is known?
   a. *Toxoplasma* antibody test
   b. Hepatitis C virus antibody test
   c. CMV antibody test
   d. Human papillomavirus (HPV) antibody test
   e. Adenovirus antibody test
   Answer: b. Needle sticks are notorious for transmitting hepatitis B virus (HBV), HCV, and HIV. The likelihood of transmission depends on factors related to the source (viral load) and the recipient (for HBV and HCV, prior antibody titers). CMV could be transmitted by needle stick, but such transmissions are extremely rare. *Toxoplasma,* HPV, and adenovirus would not be expected to be transmitted by a needle stick.

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Specific Infections With Critical Care Implications

HENRY S. FRAIMOW AND ANNETTE C. REBOLI

CHAPTER OUTLINE

Overwhelming Infections of the Central Nervous System
- Acute Bacterial Meningitis
- Encephalitis
- Brain Abscess
- Spinal Epidural Abscess

Fulminant Endovascular Infections
- Acute Infective Endocarditis
- Device-Related Endovascular Infections

Primary Bacteremias
- Meningococcemia and Meningococcal Sepsis
- Primary Pneumococcal Bacteremia

Toxin-Mediated Infections
- Staphylococcal Toxic Shock Syndrome
- Streptococcal Toxic Shock Syndrome
- Tetanus
- Botulism
- Diphtheria

Serious Skin and Soft Tissue Infections
- Necrotizing Fasciitis
- Clostridial Myonecrosis (Gas Gangrene)
- *Vibrio* Infections
- Community-Acquired MRSA

Serious Gastrointestinal and Intra-abdominal Infections
- Bacteremia Associated With Enteric Pathogens
- Peritonitis
- Intra-abdominal Abscess
- Biliary Tract Infections
- Pancreatic Infections
- *Clostridium difficile* Colitis

Life-Threatening Infections of the Head and Neck
- Ludwig's Angina, Lateral Pharyngeal Space Infections, and Peritonsillar Abscess
- Lemierre Syndrome
- Epiglottitis
- Mediastinitis

Serious Vector-Borne Infections
- Rocky Mountain Spotted Fever
- Ehrlichiosis and Anaplasmosis
- Babesiosis
- Malaria

Severe Viral Infections
- Viral Hemorrhagic Fevers
- Dengue
- Hantavirus Pulmonary Syndrome
- Influenza

Potential Agents of Bioterrorism
- Anthrax
- Smallpox
- Plague
- Tularemia

Serious infections and their complications are major indications for admission to critical care units worldwide. A wide variety of localized and systemic infections can result in critical illness, and review of all of these syndromes is beyond the scope of this chapter. The diseases discussed here include many of the more common infectious syndromes likely to be encountered by critical care specialists, as well as some less common infections of particular epidemiologic importance or those conditions in which critical care management is an essential component of management, including emerging infectious diseases with potential for spread beyond specific traditional geographic regions. The topics of community-acquired pneumonia, urinary tract infections, and other nosocomial infections are addressed specifically in other chapters.

Overwhelming Infections of the Central Nervous System

Most patients with serious central nervous system (CNS) infections require either admission to an intensive care unit (ICU) or the

participation of a critical care specialist in their management. Patients with CNS infections may already be critically ill at the time of presentation but even if they are less ill initially they also have the potential for rapid progression with development of fulminant complications. They also require prompt initiation of diagnostic and therapeutic interventions to optimize outcomes. Acute CNS infectious syndromes include bacterial meningitis, encephalitis, brain abscess, and spinal epidural abscess, although other primary and secondary infectious syndromes can present catastrophically, such as nonbacterial infectious meningitis, transverse myelitis, suppurative intracranial thrombophlebitis, and mycotic aneurysms. There are also other neurologic sequelae that may follow acute infections, such as Guillain-Barré syndrome. The presentations of various infectious syndromes may overlap, and they may also mimic the presentations of noninfectious CNS catastrophes such as stroke, hemorrhage, and autoimmune CNS vasculitis and encephalitis.

Acute Bacterial Meningitis

Epidemiology, Pathogenesis, Risk Factors, and Clinical Presentation

The annual incidence of community-acquired bacterial meningitis in developed countries has continued to decline over the past several decades.[1–3] Rates in the United States in 2006–2007 were less than 2 cases per 100,000 for all adult cohorts, and a population-based study from the Netherlands in 2013–2014 found rates of less than 1 case per 100,000.[2,3] In recent studies from the United States and the Netherlands, the predominant organisms in microbiologically confirmed cases of bacterial meningitis in adults were *Streptococcus pneumoniae* (>70%), *Neisseria meningitidis* (10%–15%), group B streptococcus (7%), and *Listeria monocytogenes* (4%).[1–3] No pathogen is identified in 10% to as many as 30% of cases of clinically diagnosed bacterial meningitis.[4,5] Both the overall decline in the incidence of community-acquired bacterial meningitis and recent changes in microbiologic etiology reflect the impact of current vaccination strategies.[6] *Haemophilus influenzae* meningitis has been nearly eliminated in both children and adults, and recent introduction of conjugated pediatric pneumococcal vaccines has resulted in decreased rates of invasive pneumococcal disease in both children and adults.[1,6] Conjugate meningococcal vaccines, including quadrivalent vaccines and serogroup B–specific vaccines, have also become available in the United States for adolescents and other high-risk populations with the potential to further decrease rates of invasive meningococcal disease.[7] Another important trend in bacterial meningitis is the increasing prevalence of health care–associated meningitis and ventriculitis.[1,8] The microbiology of nosocomial meningitis differs from that of community-acquired cases, with higher rates of infection caused by staphylococci and aerobic gram-negative organisms, including antimicrobial-resistant strains.[8]

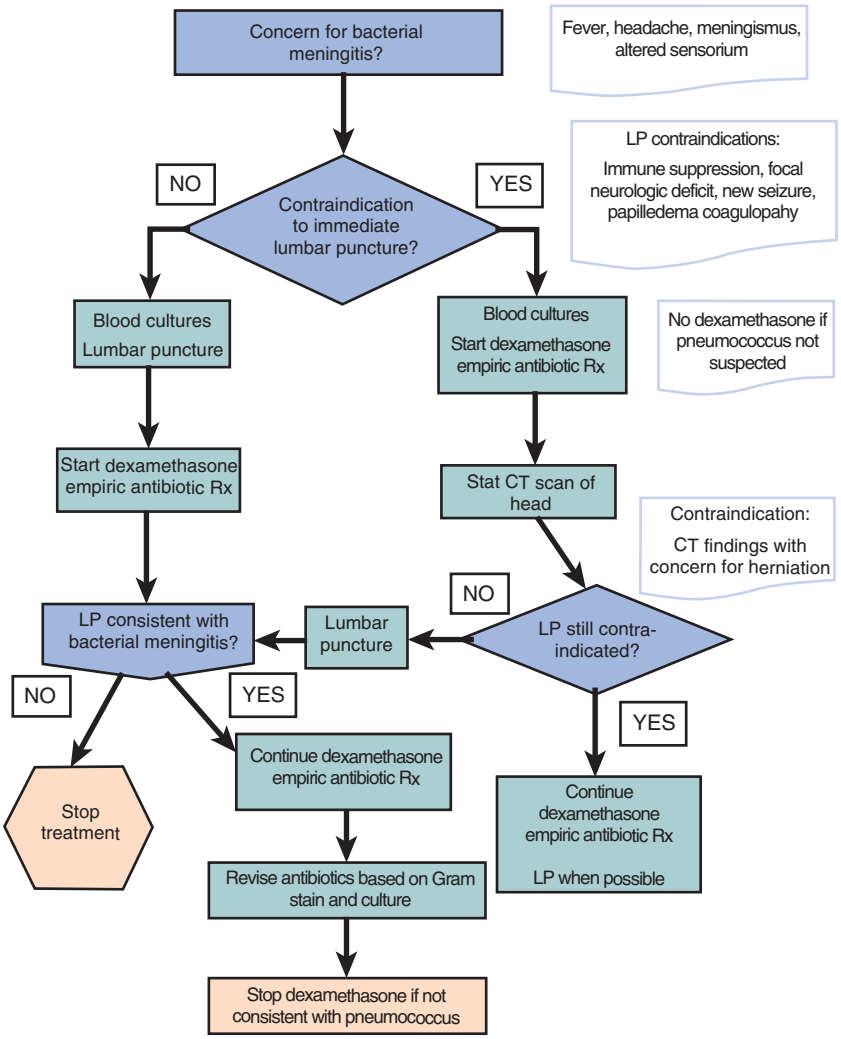
The predominant mode of acquisition of bacterial meningitis results from nasopharyngeal bacterial colonization with subsequent hematogenous spread and invasion of cerebrospinal fluid.[1,5] Less frequently, infection occurs via hematogenous dissemination from distant sites; from other localized intracranial focal infections such as sinusitis, mastoiditis, or otitis; or is secondary to trauma or neurosurgery. Once bacterial organisms have invaded cerebrospinal fluid (CSF), there are a wide variety of immunologic deficits that result in impaired clearance of encapsulated organisms. These include organism-specific deficits such as terminal complement deficiencies predisposing to meningococcal disease,[7] and more general deficits, such as immunoglobulin deficiencies, splenectomy, alcoholism, cirrhosis, diabetes mellitus, and human immunodeficiency virus (HIV).[1] Patients with defects leading to impaired cell-mediated immunity including advanced age and general debility, as well as hematologic malignancies, chemotherapy, and use of tumor necrosis factor (TNF)-β inhibitors, are predisposed to *Listeria* infection.[9]

The presenting symptoms of bacterial meningitis include fever, headache, stiff neck, and altered sensorium. In a large series of 1268 cases from the Netherlands, each of these symptoms individually was found in more than 70% of patients, although only 41% had all of the classic triad of headache, fever, and stiff neck.[3] Other important presenting symptoms in this cohort included nausea in 62%, focal neurologic deficits in one-third of patients, and Glasgow Coma Scale scores of less than 8 in 13% of cases.[3] Rash, especially a petechial or purpural rash, was seen in only 8% of these patients, less than rates of up to 25% reported in earlier series, most with rash had meningococcal meningitis.[3] Presenting symptoms alone without CSF findings and microbiologic data cannot adequately distinguish between bacterial meningitis and viral or other aseptic meningitis. However, certain features are more suggestive of bacterial rather than viral origin, including winter versus summer onset, rapid progression of disease, presentation in shock, and presence of another focal site of bacterial infection, such as sinusitis, otitis, or pneumonia. In addition to viruses, many other infections, including cryptococcal meningitis, tuberculous meningitis, rickettsial diseases, Lyme disease, and syphilis, are in the differential diagnoses of acute bacterial meningitis.

Diagnostic Strategies and Early Management of Suspected Bacterial Meningitis

The early management of suspected bacterial meningitis requires careful coordination and appropriate sequencing of the procedures necessary for appropriate diagnosis (lumbar puncture and imaging studies) and the interventions necessary for optimal treatment (antibiotics and dexamethasone). Rapid initiation of therapy leads to improved outcomes but may decrease specific microbiologic yield on CSF analysis.[1,5] Lumbar puncture, the key diagnostic study, can usually be performed safely without any imaging studies, but computed tomography (CT) scan may be required to minimize the risk of this procedure, leading to potential delays in institution of antimicrobial therapy.[5,10] One widely implemented standard algorithm for the initial management of bacterial meningitis is shown in Fig. 51.1.[5]

The primary tenet of this algorithm is that the initiation of treatment assumes highest priority, and that any delay in performing a lumbar puncture either because of the need for imaging before the procedure or because of other patient-specific contraindications should not delay antibiotic therapy. Brain herniation from elevated intracranial pressure (ICP) is a feared but rare complication of lumbar puncture when performed for diagnosis of suspected meningitis, but a recent study of a cohort of 301 patients with suspected bacterial meningitis demonstrated the relative safety of lumbar puncture without CT scanning in patients without specific clinical contraindications.[10] Proposed criteria for performing imaging before lumbar puncture include new-onset seizures, prior CNS disease, immunocompromised state, papilledema, focal neurologic deficits, or moderate to severe impairment of consciousness.[5] Although only approximately 45% of patients with bacterial meningitis have criteria for neuroimaging before lumbar puncture, it has become standard practice in many hospitals for all patients with suspected meningitis to undergo imaging first to look for evidence of brain shift.[1,5] Less stringent criteria for the need



• **Fig. 51.1** Algorithm for early management of suspected bacterial meningitis including when to suspect the diagnosis, when imaging prior to lumbar puncture is appropriate, and when to initiate and discontinue empiric antibiotics and adjuvant dexamethasone. *CT,* Computed tomography; *LP,* lumbar puncture; *Rx,* treatment. (Based on Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267–1284; and additional information from Hasbun R, Abrahams J, Jekel J, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med*. 2001;345:1727–1733; Glimåker M, Johansson B, Grindborg Ö, et al. Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture. *Clin Infect Dis.* 2015;60:1162–1169; and Brouwer MC, McIntyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev.* 2015;12(9):CD004405.)

for CT scan before lumbar puncture have decreased time to antibiotic administration and improved outcome in recent series.[11] Both noncontrast CT and magnetic resonance imaging (MRI) can be used for this purpose. Considerations for the optimal imaging modality may be different when studies are done to manage complications of meningitis or to better characterize space-occupying lesions. Other contraindications to performing lumbar puncture include coagulopathies and the presence of local disease such as stasis ulcers, burns, or cellulitis overlying the lumbar puncture site.

The diagnosis of bacterial meningitis is heavily reliant on CSF studies, including opening pressure, cell count, protein, glucose, Gram stain, and culture. Typically patients with bacterial meningitis have elevated opening pressures of 200 to 500 mm H_2O, including 40% with opening pressure greater than 400 mm in one recent cohort.[1,5] White blood cell (WBC) counts may range from 100 to 10,000 cells/mm^3, with most counts in the range of 1000 to 5000 cells/mm^3; very low CSF WBCs are associated with a worse prognosis. Usually a polymorphonuclear (PMN) cell predominance of 80% or greater exists, although up to 10% will have a lymphocytic predominance, particularly early on. CSF-to-serum glucose ratios are less than 0.4, and CSF protein levels are nearly always increased.[5,12] In studies comparing cohorts of patients with bacterial and viral meningitis, CSF glucose ratios of less than 0.31, total WBC of greater than 2000 cells/mm^3, and total PMN of greater than 1180 cells/mm^3 have been predictive of bacterial rather than viral etiology.[13] Gram stains are positive in 60% to 90% of cases of bacterial meningitis, and results on Gram stain are reported to be 97% specific as to etiology.[5] Yield of Gram stain is higher on specimens concentrated by Cytospin centrifuge (Thermo Fisher Scientific, Waltham, MA). Highest diagnostic yield from Gram staining is for *S. pneumoniae* meningitis; Gram stains in *Listeria* meningitis may reveal organisms in only one-third of cases because of the lower inoculum of bacteria in the CSF. In patients without prior antibiotic exposure, cultures are positive in up to 90% of cases. Initiation of antibiotic therapy before lumbar puncture will not significantly alter cell count, protein, glucose, and even Gram stain results but will decrease CSF culture yield by up to 20%.[5] Blood cultures should be performed in all patients with suspected bacterial meningitis and should be done before initiation of antibiotics, even if the lumbar puncture is delayed.

Additional CSF and blood tests have been used to confirm a diagnosis of bacterial meningitis or help distinguish bacterial from viral disease. An elevated CSF lactate of greater than 4.2 mmol/dL is reported to be a sensitive marker for bacterial meningitis, but specificity has been questioned.[12] Elevated serum C-reactive

protein levels are not specific for bacterial meningitis, but a low C-reactive protein level has good negative predictive value for bacterial meningitis in patients with abnormal CSF and negative CSF Gram stains.[5] Serum procalcitonin may also prove useful for diagnosis.[12]

Non–culture-based pathogen-specific tests are increasingly being used to diagnose bacterial and viral meningitis. Latex agglutination tests for bacterial antigens are widely available, but they have not been shown to contribute significantly to the management of most patients with suspected meningitis and false-positive test results are reported.[5] Nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) of CSF for bacterial DNA may be useful to confirm an etiologic diagnosis. Multiplex NAATs for concurrent testing for several bacterial and viral pathogens have recently become commercially available. NAAT studies have the potential advantages of rapid diagnosis and enhanced sensitivity, especially in the setting of previously administered antimicrobial therapy that can decrease yield of culture based methods.[12] The FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics, Salt Lake City, UT), recently available in the United States, is one example of a multiplex NAAT that can detect 14 different bacterial, viral, and fungal pathogens in a single CSF sample.[14] Additional CSF studies that may be useful for diagnosis of other specific meningeal infections include CSF cryptococcal antigen tests and Venereal Disease Research Laboratories (VDRL) slide test.

Initial antibiotic therapy for suspected bacterial meningitis is commonly initiated before culture and even Gram stain results are available. Initial empiric therapy must include agents active against the most likely pathogens based on the patient's age and underlying illnesses and modified for other specific risk factors, such as nosocomial acquisition (Table 51.1). Treatment regimens must reflect local rates of antimicrobial resistance, particularly rates of high-level resistance to penicillin and third-generation cephalosporins in *S. pneumoniae*. Standard regimens include vancomycin administered at doses targeted to achieve adequate CSF levels (serum troughs of 15 to 20 μg/mL) and a third-generation cephalosporin, either ceftriaxone or cefotaxime. In areas with increased rates of pneumococcal resistance to third-generation cephalosporins, rifampin may be added. When there is risk for *Listeria* infection based on age older than 50 years or on other specific risk factors such as alcoholism or altered immunity,

TABLE 51.1 Empiric Treatment of Suspected Bacterial Meningitis in Adults[a,1,2,5,8]

Host Factors to Consider	Age >50 years? Risk for *Listeria monocytogenes* and aerobic gram-negative rods		
	Immune suppression? Includes host defects (e.g., HIV, alcoholism, lymphoma) and treatment-related (e.g., posttransplant, corticosteroids)		
	Health care–associated? Includes trauma, postneurosurgical, shunt- or ventriculostomy-related		
	Life-threatening penicillin/β-lactam allergy? Aztreonam or fluoroquinolone alternatives for gram-negative rods; trimethoprim-sulfamethoxazole an alternative for *L. monocytogenes*		
Host	**Likely Pathogens**	**Empiric Therapy**	**Additional Considerations**
Age 15–50 years Without Immune Suppression	*Streptococcus pneumoniae, Neisseria meningitidis*, group B β-hemolytic streptococci	Vancomycin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Age ≥50 years Without Immune Suppression	*S. pneumoniae, N. meningitidis,* group B β-hemolytic streptococci, *L. monocytogenes,* aerobic gram-negative rods	Vancomycin + ampicillin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Immune Suppression	*S. pneumoniae, N. meningitidis,* group B β-hemolytic streptococci, *L. monocytogenes*, *Staphylococcus aureus*, aerobic gram-negative rods including *Pseudomonas aeruginosa*	Vancomycin + ampicillin + cefepime or meropenum[c]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Health Care–Associated: Trauma, Postneurosurgical, or Shunt-Associated[c]	*S. aureus*, coagulase-negative staphylococci, aerobic gram-negative rods including *P. aeruginosa*	Vancomycin + ceftazidime or cefepime or meropenem[c]	Dexamethasone not indicated Consider rifampin for staphylococci Consider intrathecal therapy for shunt-/ventriculostomy-associated infection
Health Care–Associated: Basilar Skull Fracture	*S. pneumoniae*, *Haemophilus influenzae*, group A β-hemolytic streptococci	Vancomycin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*

[a]Age older than 15 years.
[b]Third-generation cephalosporin: ceftriaxone 2 g q12h or cefotaxime 2 g q4–6h.
[c]Dosing of other agents (modified for renal insufficiency): vancomycin targeted to vancomycin trough levels of 15–20 μg/mL; ampicillin 2 g q4h; ceftazidime 2 g q8h; cefepime 2 g q8h; meropenem 2 g q8h.
HIV, Human immunodeficiency virus.

high-dose ampicillin is added to the regimen. For patients with health care–associated bacterial meningitis, cefotaxime or ceftriaxone should be replaced by a β-lactam such as cefepime, ceftazidime, or meropenem that has activity against *Pseudomonas aeruginosa*, with choice based on local susceptibility data.[8] Antibiotic therapy should then be modified based on culture and susceptibility results. Standard recommended treatment durations are 7 days for meningococcal disease and *H. influenzae*, 10 to 14 days for S. *pneumoniae*, and 21 or more days for *Listeria*.[1,5]

The benefit of adjuvant corticosteroids in decreasing mortality and neurologic sequelae in patients with bacterial meningitis continues to be debated.[15,16] In one large, randomized, placebo-controlled trial of 301 adults with suspected bacterial meningitis and cloudy CSF, adjuvant dexamethasone decreased mortality from 15% to 7% and decreased unfavorable outcomes from 25% to 15%.[15] Benefits of corticosteroids were most evident in those with pneumococcal infection and those with a moderately impaired level of consciousness. Additional prospective cohort studies and meta-analyses of available data confirm the benefits of corticosteroids for decreasing hearing loss and decreasing neurologic sequelae, although the evidence for mortality benefit in patients with confirmed or suspected pneumococcal meningitis is weaker. No benefit was demonstrated for meningococcal disease or for other organisms, nor was any benefit clearly demonstrated in prospective studies of adults with bacterial meningitis in developing countries.[12,16] The recommended steroid regimen is 10 mg of dexamethasone every 6 hours for 4 days and initiated before or concurrent with the first dose of antibiotics.[1,5] The benefit for steroids administered after antibiotic initiation is not defined.

Patients with suspected or confirmed meningococcal meningitis should be placed in isolation to prevent nosocomial transmission via respiratory droplets during the first 24 hours of therapy. Meningococcal prophylaxis is indicated for household and other close contacts of meningococcal cases including first responders. Conversely, patients with Gram stains and clinical presentations consistent with nonmeningococcal disease should also be quickly identified to eliminate unnecessary administration of meningococcal prophylaxis.

Complications of Bacterial Meningitis, Need for ICU Monitoring, and Outcome

Patients with bacterial meningitis often require ICU care either to manage complications evident on presentation or for monitoring for any complications that may subsequently develop during their course.[1] Some criteria for admission to an ICU (Table 51.2) include sepsis and septic shock, respiratory compromise or pulmonary infiltrates, high risk of brain herniation, moderately impaired and deteriorating level of consciousness, new or evolving neurologic deficits, and the presence of seizures.[1,17,18] Patients with generally good outcomes can be defined early in their course on the basis of age, Glasgow Coma Scale score, APACHE II (Acute Physiologic Assessment and Chronic Health Evaluation II) score, absence of focal neurologic abnormalities, and favorable laboratory features, but these stratification schemes still fail to identify some patients

TABLE 51.2 Major Complications of Bacterial Meningitis Requiring ICU Level of Care for Monitoring and Management[1,3,4,5,18]

Type of Complication	Etiologies, Prevalence	Management Strategies
Neurologic Complications		
Increasing intracranial pressure	Brain edema, 6%–10%	Strategies: osmotic diuresis, intracranial pressure monitoring, head of bed elevation, prophylactic lumbar drain Glycerol and hypothermia not beneficial and may result in higher mortality
Hydrocephalus	Communicating hydrocephalus, 3%–8% Obstructive hydrocephalus uncommon	Repeated lumbar puncture, lumbar drain, ventriculostomy
Focal neurologic deficits	Arterial infarct or vasculitis, 10%–15% Venous infarction, 3%–5% Hearing loss, 14%–30% Cranial nerve deficits, especially eighth nerve, 15%–30% Hemorrhage, <1% Brain abscess, subdural empyema <1%	Radiographic studies to look for focal intracranial complications Administer dexamethasone for suspected pneumococcal meningitis to decreases risk of hearing loss
Seizures	Multiple etiologies, 14%–33%	Continuous EEG monitoring, antiepileptic agents Prophylactic antiepileptic agents not routinely recommended
Agitation	Common	Careful sedation
Other Complications		
Hyponatremia	Up to 25%–30%	? Hypertonic saline solution Presence of hyponatremia did not affect outcome
Sepsis and cardiorespiratory failure	38%	Hemodynamic support, mechanical ventilation
Pneumonia	17%, most often with *Streptococcus pneumoniae*	Ventilatory support

EEG, Electroencephalographic.

with more complicated courses, and conversely, some patients with poor Glasgow Coma Scale scores may still have good outcomes.[2,3,17] Some authors recommend ICU admission for all cases of bacterial meningitis, as patients may benefit from early intensive monitoring for the presence of new neurologic signs or subtle seizures and for effective control of agitation.[1,17]

The major complications that occur during the course of bacterial meningitis have been reported in both older and more recent post–steroid era case series. Complications most notably include deteriorating level of consciousness, which may be due to development of meningoencephalitis (15%–30% of cases); seizures (14%–33%); brain edema (6%–10%); or hydrocephalus (3%–8%).[1,2,17] Increased ICP is associated with worse prognosis, but no single approach to treatment has been confirmed to be effective in all cases.[1,2,17] Elevation of the head of the bed, mannitol, hyperventilation, repeated lumbar punctures, prophylactic lumbar drainage, prophylactic ventriculostomy, and normal fluid and electrolyte homeostasis have all been proposed for management of increasing ICP. Patients with severely increased pressure with impending herniation may require ventriculostomy with continuous CSF pressure monitoring. Often multiple interventions may be necessary for targeted strategies where ICP is maintained at less than 20 mm Hg. Glycerol and induced hypothermia were also recently studied as potential interventions for management of ICP and for cerebral protective effects in bacterial meningitis, but trials were stopped because of worse outcomes in the intervention arms.[18] All patients with bacterial meningitis should be monitored for seizures, including nonfocal seizures that may only manifest as worsening level of consciousness, but routine use of prophylactic antiepileptic medication is not recommended.[5] Focal neurologic deficits early in the course of meningitis are most often caused by cerebrovascular complications or arteritis secondary to inflammation or less commonly to venous infarcts. The most common late neurologic complication is hearing loss, described in up to 20% of patients overall and in up to 34% of those with pneumococcal meningitis.[1,2] The incidence of hearing loss appears to be decreased in patients treated with dexamethasone.[1,12,15] Subdural empyema, brain abscess, and hemorrhage are all rare but potentially catastrophic complications of bacterial meningitis.

Repeat lumbar punctures are no longer routinely recommended in patients with bacterial meningitis who are improving.[5] Repeat lumbar puncture is indicated in those with worsening or suboptimal clinical response at 48 hours or in patients who develop recurrent fevers. Repeat CSF analysis may also be indicated for infections caused by more drug-resistant organisms such as cephalosporin-resistant *S. pneumoniae*, especially if treated with dexamethasone, as steroids may potentially decrease antibiotic penetration into CSF and delay sterilization. Repeat imaging by MRI or enhanced CT scan should be performed in patients with clinical deterioration or persistent decreased level of consciousness to assess for intracranial complications as described earlier. Overall mortality rates for bacterial meningitis without the use of steroids are reported to be approximately 20%, and an additional 14% have moderate or major neurologic sequelae.[1,17] The prognosis for meningococcal meningitis is better than for pneumococcal infection. Late neuropsychiatric cognitive effects are seen in up to 10% of cases of bacterial meningitis.

Encephalitis

The other major CNS infectious syndrome besides bacterial meningitis presenting with fever, headache, altered sensorium, and meningeal signs is acute encephalitis, which is most commonly of viral etiology. Although there is significant overlap between clinical presentations of patients with bacterial meningitis and viral encephalitis, the presentation of viral encephalitis is dominated by evidence of parenchymal brain dysfunction, including moderate to severely impaired sensorium, delirium, psychosis, focal neurologic findings, and seizures.[19,20] The presence of meningismus is more variable, but most patients have some evidence of meningeal enhancement on imaging and inflammatory cells in CSF.

A wide variety of viruses can cause encephalitis, but management strategies focus on the most common etiologies, especially those most likely to respond to specific interventions such as encephalitis caused by herpes simplex virus (HSV).[20–32] Other herpes group viruses with worldwide distribution capable of causing encephalitis include varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus, especially in immunocompromised patients.[19,20,22] Influenza virus, mumps, measles, and enteroviruses are also important etiologies of acute viral encephalitis worldwide. Acute HIV infection may present as fulminant meningoencephalitis.[19,20] Acute presentations of progressive multifocal leukoencephalopathy caused by JC virus are also increasingly reported in patients with HIV infection and other immunocompromised patients.[23] In addition to viruses with worldwide distribution, there are many vector-borne encephalitis-causing viruses having more regional and seasonal distributions.[22] Important pathogens include Eastern, Western, and Venezuelan equine encephalitis; Japanese B encephalitis; St. Louis encephalitis; La Crosse encephalitis; and Nipah encephalitis. New cases of meningoencephalitis may be one of the first indications of spread of an emerging infectious disease into a new geographic area.[24] Recently West Nile encephalitis emerged as a major pathogen in the Western Hemisphere, first appearing in New York City in 1999 but with cases now distributed throughout the country.[25] Another recently emerging virus associated with encephalitis is Zika virus, a mosquito-borne *Flavivirus* that appeared in Brazil in 2015 and rapidly spread through the Western Hemisphere. Guillain-Barré syndrome is the most common serious neurologic manifestation and is seen in approximately 1 in 4000 infections in children and adults, but rare cases of encephalitis and encephalomyelitis have also been reported.[26]

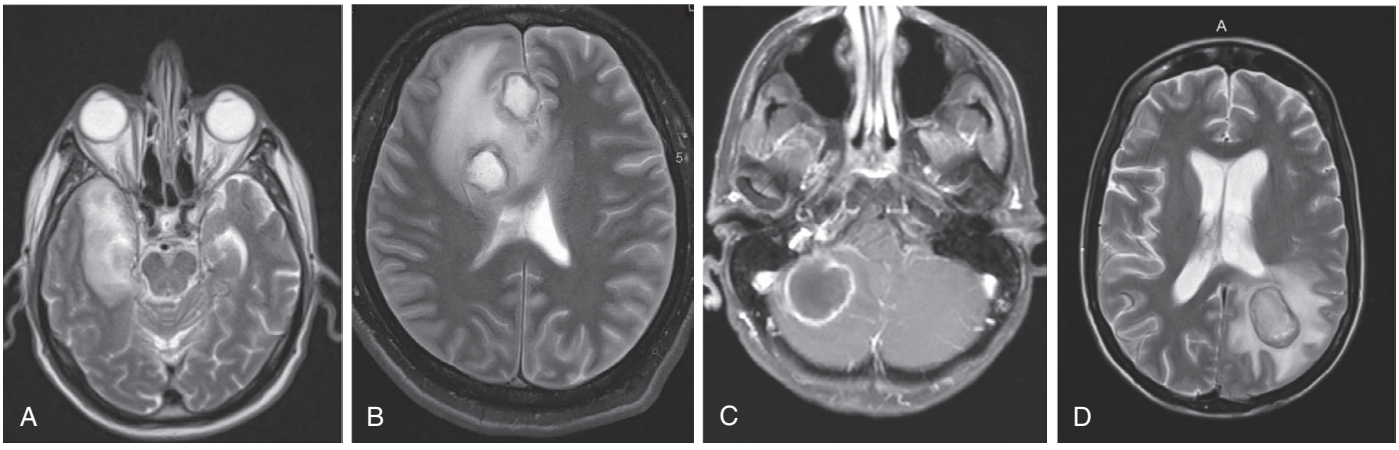
Rabies, although extremely rare in developed countries, also needs to be considered in the differential diagnosis of fulminant encephalitis, both for its epidemiologic implications and for the potential of survival now for patients with this previously universally fatal infection who have received aggressive ICU management.[27] In addition to viral infections, many atypical bacteria, fungi, and protozoal organisms can present as acute meningoencephalitis. Particularly important to consider early in the differential diagnosis are infections that may respond to specific antimicrobial treatment, including rickettsial diseases such as Rocky Mountain spotted fever, and meningoencephalitis from spirochetal infections including leptospirosis, neurosyphilis, and Lyme disease.[22,28,29] Important clues to these diseases include epidemiologic history and associated clinical features such as rash or icterus. Recently developed consensus case definitions and standardized approaches to diagnosis for infectious encephalitis should facilitate understanding of this heterogeneous syndrome, in which diagnoses are determined less than 50% of the time even after aggressive evaluation for infectious etiologies.[30]

Herpes simplex encephalitis is the most common sporadic cause of serious viral meningoencephalitis, causing 3% to 10% of cases of infectious encephalitis in adults with an estimated frequency of about 1000 to 2000 cases per year in the United States.[20,21,31]

Most cases beyond the neonatal period are caused by HSV type 1, usually as reactivation disease and not primary infection; HSV type 2 commonly causes aseptic meningitis but much less commonly presents as fulminant encephalitis.[21,31] Herpes encephalitis is an acute necrotizing process, typically causing hemorrhagic necrosis with particular predilection for the frontotemporal lobes and cingulated gyrus. Mortality rates are up to 70% in untreated cases, with 95% of survivors having serious neurologic sequelae.[21,22] Cases of herpes encephalitis beyond the neonatal period occur throughout life, but the highest case rates occur in those younger than 20 years or age or in adults older than age 50 (half of cases). Presentation may include a prodromal viral syndrome in 50% of cases, followed by a generally rapid onset of headache, confusion, and altered level of consciousness. Meningismus, focal neurologic findings, and seizures are also common.[20–32] Concurrent herpetic rashes are not generally seen in patients with HSV encephalitis. In one series of patients with encephalitis, focal CNS disease was much more likely than diffuse CNS disease to be caused by HSV.[32] The approach to cases of suspected herpes encephalitis, as well as other viral or unknown encephalitis, includes early initiation of antiviral therapy and concurrent rapid clinical evaluation that includes imaging, CSF studies, and electroencephalogram (EEG) to establish a diagnosis.[20–32] CT scans can remain normal up to 4 to 5 days into the course; thus MRI is considered the imaging modality of choice. MRI results are positive in more than 90% of cases, often showing changes of edema and necrosis in the medial temporal lobes, insular cortex, and cingulate gyrus as soon as 2 to 3 days into the illness (Fig. 51.2). EEGs are abnormal in nearly all cases, but early findings are nonspecific with characteristic periodic lateralizing epileptiform discharges often not seen until later in the course.[21] CSF findings include low- to moderate-grade lymphocytic pleocytosis in 85% and elevated protein in 80%; elevated red blood cell counts and mildly decreased glucose levels are common but not universal, and cell counts may be completely normal in 8% of cases.[21,31] In recent management guidelines, PCR of CSF for HSV DNA has replaced brain biopsy as the diagnostic method of choice for HSV encephalitis.[20–32] In two trials comparing PCR with brain biopsy, the sensitivity of PCR was 98% and specificity was 94% for diagnosing HSV encephalitis; the negative predictive value of PCR on CSF obtained more than 72 hours into the course of illness was close to 100% for excluding HSV.[22,33,34] PCR has also expanded understanding of the range of clinical presentations of HSV encephalitis including recognition of less severe cases.[34] Viral culture has low sensitivity for diagnosis in older children and adults, and CSF and serum antibody studies have little role in the diagnosis.[21,22] Treatment should be initiated on the basis of clinical suspicion pending PCR results using intravenous (IV) acyclovir at high doses of 10 mg/kg every 8 hours and continued for 14 to 21 days. Treatment is generally discontinued when negative PCR results are available or an alternative diagnosis is established. In patients with a low probability of HSV encephalitis who have normal imaging results, CSF pleocytosis of less than 5 cells, and normal mental status, a single negative PCR assay is adequate to exclude the diagnosis more than 99% of the time; in patients with higher clinical evidence for HSV encephalitis, repeating PCR testing of CSF before stopping antiviral therapy may be appropriate.[21] There are insufficient data to recommend oral valaciclovir as an alternative to parenteral therapy at this time.

West Nile Virus Encephalitis

Since first emerging in the Western Hemisphere in 1999, West Nile virus (WNV) has become a major infectious cause of invasive neurologic disease throughout the United States, with nearly 1500 cases from 43 states reported in 2015.[25] WNV is a mosquito-borne arbovirus affecting birds, mammals, and humans. Of human cases, 80% are asymptomatic and most of the remainder have West Nile fever, but 1% develop neuroinvasive disease manifesting as meningitis, encephalitis, and/or a polio-like flaccid paralysis syndrome.[35,36] The risk of encephalitis increases with age or with immunosuppression, particularly organ transplantation, and manifestations can range from mild disorientation to coma and death.[25,35] Parkinson-like tremors are also commonly reported. The flaccid



• **Fig. 51.2** Magnetic resonance imaging (MRI) of intracranial infections. A, MRI imaging showing herpes encephalitis appearing as a "mass-like" lesion in the right temporal lobe in a patient with subacute presentation of seizures and altered mental status. B, MRI imaging of two periventricular brain abscesses in the right frontal lobe with surrounding edema and mass effect and impinging on the ventricle. Ventricular rupture is a catastrophic complication of brain abscesses. C, MRI imaging showing characteristic ring enhancement after administration of gadolinium of a right cerebellar brain abscess that grew *Streptococcus intermedius* and microaerophilic streptococci. D, MRI imaging of an inflammatory mass lesion in the occipital lobe in an HIV-positive patient presenting with headache and seizures; cultures grew *Mycobacterium tuberculosis*.

paralysis syndrome, caused by viral infection of anterior horn cells, may have an abrupt onset and patients may require prolonged ventilatory support. The fatality rate is 9% for WNV neuroinvasive syndromes, and survivors may have prolonged or permanent deficits.[35,36] CSF findings of WNV are similar to those of other viral infections with lymphocytic pleocytosis predominating. Neuroimaging results may be normal, but some scans may demonstrate abnormal signal in the basal ganglia, thalamus, and other deep brain structures or abnormal signal in anterior horn cells of the spinal cord.[35,36] Diagnosis is confirmed by the finding of WNV-specific immunoglobulin (Ig) M antibodies in CSF and serum or by nucleic acid–based PCR of CSF, serum, or other fluids.[35] Treatment is primarily supportive; multiple interventions such as ribavirin, interferon alfa, and immunoglobulin have been studied, but there is limited evidence for benefits.

Brain Abscess

Brain abscesses are focal infections of brain parenchyma, occurring (1) from direct spread from local, contiguous infection (ear, sinuses, mastoid, bacterial meningitis); (2) from hematogenous spread of infecting organisms from distant sites; or (3) by direct inoculation from trauma or surgery.[37,38] The incidence in developed countries is reported as 0.4 to 0.9 cases per 100,000 per year, with a higher incidence in immunosuppressed populations.[37] Modern imaging modalities have improved the initial management and follow-up care of patients with brain abscess, but morbidity and mortality of this syndrome remains high. Presenting symptoms may be indistinguishable from those of other CNS infections. Headache is the most frequently reported symptom; fever is common but prevalence is less than seen in bacterial meningitis.[38,39] Focal neurologic findings reflect the location of the abscess. Seizures, reported in 25% in one series, and decreased level of consciousness are also common; systemic sepsis is less common.[37–39] Brain abscess symptoms may be much more subtle and nonspecific compared with bacterial meningitis or viral encephalitis, contributing to delay in diagnosis. Microbiology reflects the source of the original infection and most commonly includes streptococci, staphylococci, oral anaerobes, and enteric gram-negative organisms, but multiple other bacterial, fungal, tuberculous, and atypical organisms can also be found and many specimens are polymicrobial.[38–40] Molecular testing for bacterial DNA has been used to identify pathogens from culture-negative specimens.[40] In areas of high HIV prevalence, opportunistic brain infections, especially toxoplasmosis, and CNS lymphoma become more prevalent than bacterial pyogenic abscesses, and knowledge of HIV status is crucial to initial management of mass lesions.[41] CNS tuberculomas are also important considerations in patients in or from TB endemic areas, especially immunosuppressed patients or patients with HIV infection.[42]

The diagnosis of brain abscess is suggested by the clinical presentation and imaging findings by either CT or MRI showing enhancing parenchymal lesions, usually with surrounding inflammatory changes.[37,38] Radiographic appearance may be indistinguishable from a malignant lesion, although MRI with diffusion-weighted imaging in one study demonstrated 96% specificity for distinguishing brain abscess from primary or metastatic cancer. Management of suspected abscess includes either stereotactic aspiration or surgical drainage to both establish a microbiologic diagnosis and for primary treatment of the abscess. Blood and CSF cultures, if lumbar puncture can be safely performed, will provide positive microbiologic results in only up to 25% of patients. Smaller lesions (<1 cm) can be treated with antibiotics alone, but larger lesions will require either aspiration or open drainage.[37,38] Duration of treatment traditionally has been at least 6 to 8 weeks of parenteral therapy but now most often is determined by resolution of the abscess on serial imaging studies. Unlike bacterial brain abscesses, toxoplasmosis lesions in patients with AIDS are usually multiple and may respond to empiric toxoplasmosis therapy without need for further invasive diagnostic procedures.[41]

Spinal Epidural Abscess

Spinal epidural infections most commonly arise by contiguous spread of infection into the spinal canal as a complication of vertebral infections or, less commonly, as a complication of epidural procedures such as epidural injections or epidural catheterization.[43–46] Vertebral infections result from hematogenous infection of vertebral bodies or disk space or by direct introduction of organisms from surgery or trauma. In addition to affecting the vertebral bodies and/or intervertebral disk spaces, vertebral osteomyelitis may expand into surrounding paravertebral soft tissues and spinal canal and even rarely into the medullary spinal cord. Paravertebral and epidural infections can rapidly progress, resulting in severe neurologic symptoms from compression of nerve roots or the spinal cord, or by infarction of the spinal cord from inflammation and vasculitis of vertebral arteries.[43,44] Thus an aggressive diagnostic and therapeutic approach is necessary to prevent catastrophic consequences such as irreversible paraplegia and death.

The incidence of spinal epidural infection from large retrospective reviews is reported as approximately 0.2 to 2 cases per 10,000 hospital admissions, but the frequency of this diagnosis may be increasing, perhaps because of improvements in radiographic diagnosis.[45,46] Incidence in adults increases with age older than 30 years; important predisposing factors include diabetes, injection drug use, alcoholism, immunosuppression, underlying spinal disorders, trauma, invasive procedures, and extraspinal sites of infection that cause significant bacteremia.[43,45,46] Infections can occur at any level of the spinal cord, although most series report predominance of lumbar involvement. Approximately two-thirds of infections are caused by *Staphylococcus aureus*, with a variety of other gram-positive organisms (coagulase-negative staphylococci, viridans streptococci, β-hemolytic streptococci), as well as gram-negative organisms all reported in lesser numbers.[44–46] Granulomatous infections including tuberculosis and brucellosis remain major etiologies of vertebral and epidural infection in many areas of the world. Approximately 10% are culture-negative.[45]

Presenting symptoms are back pain in more than 95% of cases and fever in two-thirds of cases; unfortunately, these symptoms are extremely nonspecific.[44,45] Thirty percent of patients present with evidence of early neurologic deficits such as muscle weakness, incontinence, or sensory deficits, and up to one-third have evidence of paralysis on examination.[44–46] Associated laboratory features include leukocytosis in two-thirds of cases and elevated erythrocyte sedimentation rate in nearly all cases. The most sensitive imaging modality is MRI with gadolinium, with reported sensitivity of greater than 95%, but most infections were also visualized on CT and unenhanced MRI.[44,45] Owing to the lack of specificity of the presenting symptoms, especially back pain, the overall yield of MRI studies when performed to look for spinal epidural abscess is low, and algorithms using specific risk factors such as history of recent *S. aureus* bacteremia, recent spinal procedures or contiguous focus of infection, and elevated inflammatory markers have been proposed to facilitate more rapid diagnosis in the appropriate setting.[46,47] Until recently, standard therapy included emergent

drainage of the abscess and systemic antibiotic therapy. Over the past 2 decades there has been an emerging literature on more conservative medical management using percutaneous aspiration and antibiotics without open surgical drainage.[43–46] These reports have suggested that outcomes are similar or better (i.e., less neurologic sequelae) without open surgery.[44] Several recent reviews and meta-analyses have failed to show a clear difference between medical and surgical outcomes, but there was significant heterogeneity between studies and significant patient selection bias and in other studies failure rates for medical therapy exceeded 40%.[48] Indications for surgery include neurologic progression on treatment or lack of clinical response; thus those managed without surgery require careful monitoring.[44,45] Other proposed indications for surgical management include those with more severe neurologic deficits on initial presentation, older age, diabetes, methicillin-resistant *S. aureus* (MRSA) infections, and cervical infections.[44,45,48]

Fulminant Endovascular Infections

Infectious endocarditis and other endovascular infections are common causes of bacteremia and sepsis, and these patients are frequently admitted to critical care units for management of sepsis and other complications. Often the diagnosis of endovascular infection is unsuspected and initiation of appropriate treatment is delayed. Even relatively stable patients with bacterial endocarditis, especially left-sided endocarditis, require careful monitoring and management of potential major complications, including heart failure or other cardiac events, and for septic emboli, especially intracranial emboli. The role of early surgical intervention in improving outcome has become increasingly appreciated in the management of complicated bacterial endocarditis, especially *S. aureus* endocarditis.

Acute Infective Endocarditis

Several recent large case series and population-based studies have addressed changes in the epidemiology of bacterial endocarditis over the past 30 years.[49,50] In some population-based studies the annual incidence of endocarditis of 5 to 7 cases per 100,000 has not changed significantly over time, but other hospital-based databases suggest that rates of endocarditis have been increasing in the United States.[49,50] The International Collaboration on Endocarditis Prospective Cohort Study of 1779 cases from 39 medical centers in 16 countries has illustrated the recent changes in microbiology and clinical presentation of bacterial endocarditis.[51] In most recent cohorts, *S. aureus* rather than *S. viridans* streptococci were the predominant pathogens with an increasing proportion of cases considered as either nosocomially acquired or health care–associated.[51] *S. aureus* endocarditis is associated with significantly higher mortality, a higher rate of stroke, and other systemic embolization and a higher rate of sustained bacteremia than endocarditis caused by other organisms.[51,52] The increased antibiotic resistance in organisms causing endocarditis, notably the increasing prevalence of MRSA and antibiotic-resistant Enterococci, is reflected in recent guidelines for treatment of endocarditis from the American Heart Association (AHA) and the European Society of Cardiology (ESC).[52,53] Other important recent epidemiologic trends are the decreased importance of congenital valvular and rheumatic disease as predispositions, the increasing age of patients, and the increased role of hemodialysis and indwelling cardiac devices such as pacemakers and implantable defibrillators as risk factors.[49,50,54]

Infectious endocarditis must be considered in the differential diagnosis of a broad range of clinical syndromes. Fever is the single most common presenting symptom, often accompanied by other constitutional symptoms of anorexia, weight loss, and fatigue. Onset may be acute or subacute. Signs and symptoms may be caused by direct cardiac effects of infection, including new or changing heart murmur, worsening congestive heart failure and valvular dysfunction, and onset of heart block from myocardial abscesses.[52,53] The clinical presentation may also be dominated by systemic manifestations of emboli or immune complex disease, including such findings as skin lesions, splenomegaly, glomerulonephritis, cerebrovascular events, and other acute vascular embolic events. Patients with acute, fulminant endocarditis, particularly *S. aureus* endocarditis, may present with concurrent cardiogenic and septic shock.

The Modified Duke Criteria for Diagnosis of Infective Endocarditis are a prospectively evaluated set of criteria that are widely utilized for establishing a clinical diagnosis of infective endocarditis.[55,56] The modified Duke Criteria rely predominantly on blood culture results and echocardiographic findings as the major clinical criteria for diagnosis; additional minor clinical criteria (fever, underlying predisposition, embolic phenomena, immunologic phenomena) can also be used as supporting evidence for determining confirmed or suspected cases.[56] Patients with endocarditis have sustained bacteremia; in the absence of prior antibiotic therapy the yield of at least one positive blood culture after three sets are drawn is greater than 90%, and typically multiple cultures are positive. Two to three separate sets of blood cultures should always be obtained in suspected endocarditis before initiation of therapy. Blood culture–negative infectious endocarditis cases may be caused by prior antimicrobial therapy or fastidious or difficult-to-cultivate organisms.[52,53] Follow-up blood cultures are critical to document sterilization of blood on treatment and should be repeated frequently until negative. Echocardiography should be performed as soon as possible on all patients with suspected endocarditis.[52,53] Transthoracic echocardiography (TTE) is reported to have sensitivity of 60% to 75% compared with as high as 95% for transesophageal echocardiography (TEE) for the diagnosis of native valve infection. In both the AHA and ESC guidelines, TTE is recommended the initial testing mode of choice, but for patients with a high initial risk for endocarditis, moderate to high clinical suspicion of endocarditis despite negative TTE, or difficult TTE study, this should be quickly followed by TEE.[52,53] Other indications for TEE include evaluation for prosthetic valve endocarditis, and for many even with diagnostic TTE to better assess for complications such as perivalvular abscess that may affect management (Table 51.3).[52] In children and uncomplicated adult cases in which TTE is diagnostic, TEE may not be necessary. If initial studies are negative, TEE should be repeated in 5 to 7 days if clinical suspicion remains high.[52,53]

Embolic complications may occur at any time with an overall incidence of 20% to 50% in cases of infective endocarditis; risk decreases but still remains high for at least the first 2 weeks after initiation of antimicrobial therapy, especially with large vegetations.[50,54,57] Risks for embolization include specific organisms, especially *S. aureus*, Candida, HACEK organisms, and *Abiotrophia*, increased vegetation size (>10 mm) and mobility as determined by echocardiography; mitral versus aortic valve involvement; and anterior versus posterior location on the mitral valve.[52,53] More than half of clinically manifesting emboli involve the CNS, most commonly in the middle cerebral artery distribution.[52,58] In addition to emboli, other risks for mortality include congestive heart failure, abnormal mental status, comorbidities, higher APACHE score,

TABLE 51.3 Use of Echocardiogram in the Diagnosis of Infective Endocarditis

Pretest Risk Assessment	Explanation/Examples	Most Appropriate Initial Study[a]	When to Perform TEE	Additional Comments
Lower clinical suspicion	Includes patients without underlying predispositions, no blood culture results suggesting endocarditis, and no other clinical manifestations of endocarditis	TTE	TTE negative: stop if suspicion remains low TTE positive: Perform TEE if high-risk echocardiographic features (large/mobile vegetation, valve insufficiency, possible perivalvular abscess) or to assess for other cardiac complications	Perform TEE if clinical suspicion increases Perform TEE if complications occur during therapy
Higher (moderate to high) clinical suspicion	General: includes patients with predispositions (e.g., prosthetic valve, congenital valve disease, prior endocarditis), suspicious blood culture results, or suspicious clinical features (e.g., new valvular insufficiency, embolic phenomena)	TTE or TEE	If TTE inadequate If TTE negative and clinical suspicion persists If TTE positive, to better assess for cardiac complications	Consider repeat TEE if high clinical suspicion persists Perform TEE if complications occur during therapy Consider repeat TTE or TEE to assess clinical response (e.g., vegetation size)
	Staphylococcus aureus bacteremia	TTE	If TTE inadequate or if negative TTE but persistent clinical suspicion Consider if planning short-course (14-day) therapy for bacteremia If TTE positive, to assess for complications	Repeat TEE by 5–7 days for persistent bacteremia
	Concern for prosthetic valve Endocarditis	TTE or TEE	If TTE positive, to better assess for cardiac and perivalvular complications	Consider repeat TEE by 5–7 days if initial TEE negative and high clinical suspicion persists Repeat TEE to evaluate for complications during therapy
	Evaluation for infected cardiac device (AICD, pacemaker, other)	TTE or TEE	If TTE inadequate If TTE negative	Intraoperative TEE may be more sensitive; negative studies do not exclude infected lead
	Right-sided endocarditis	TTE	If TTE inadequate	TEE better for pulmonic valves

[a]The sensitivity of TTE is approximately 70%, and the sensitivity of TEE is approximately 96% for native valve endocarditis. The sensitivity of TTE is approximately 50%, and the sensitivity of TEE approximately 90% for prosthetic valve endocarditis. The specificity of echocardiography is only 90%.

AICD, Automatic implantable cardioverter-defibrillator device; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation.* 2015;132:1435–1486; and Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J.* 2015;36:3075–3128.

and *S. aureus* infection.[52,59] Congestive heart failure has the highest association with mortality.[52,59] Medical therapy (versus surgical therapy) was also associated with higher 6-month mortality in one recent study.[59]

The decision to perform valvular surgery for patients with active endocarditis remains complex, and indications for surgery must be balanced against the patient's clinical status and predicted operative mortality. Indications for surgery include refractory congestive heart failure; persistent infection despite optimal antimicrobial therapy; fungal or other difficult-to-treat organisms; one or more emboli during the first weeks of antimicrobial therapy; and valvular complications of dehiscence, perforation, fistula, and large perivalvular abscesses (Table 51.4).[52,53] Vegetation size and location are also emerging as independent indications for surgery.[52] The ESC guidelines list refractory heart failure and cardiogenic shock as the strongest indication for emergent valve surgery. The risk of infecting a new prosthetic valve during surgery for active endocarditis is only 2% to 3%; thus active infection is not a contraindication to surgery when indicated for complications associated with high associated mortality.[52,53] Several studies have suggested decreased mortality of cohorts of patients who were managed with early surgical intervention, especially those with left-sided *S. aureus* endocarditis, but to date there has been only one small randomized trial of medical versus surgical therapy.[52,53] The optimal surgical procedure and the role of more conservative procedures such as vegetation resection remain controversial. For tricuspid valve endocarditis with large vegetations, uncontrolled infection, and ongoing septic pulmonary emboli, valve resection and valve repair are alternatives although valve replacement may eventually be required for severe right heart failure.[52,53]

Anticoagulation in patients with active endocarditis can present difficult management dilemmas and the level of evidence informing decisions is low. Initiation of anticoagulation in patients not already receiving it and without other indications is not recommended.[52,53]

TABLE 51.4 Indications and Relative Contraindications for Early Surgical Intervention for Acute Left-Sided Infective Endocarditis

Indication	AHA Guideline[52]	ESC Guideline[54]	Comments
INDICATIONS FOR SURGERY FOR NATIVE VALVE ENDOCARDITIS			
Heart failure	Indicated with valve dysfunction and symptoms or signs of heart failure (class I) Reasonable if severe regurgitation and vegetation size >10 mm (class IIb)	Emergent[a] for refractory pulmonary edema or cardiogenic shock (class I) Urgent[a] for heart failure or echocardiogram with poor hemodynamics (class I)	Most common indication for surgery in endocarditis
Heart block, annular or aortic abscesses	Indicated (class I)	Urgent for locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation) (class I)	Intracardiac infection is not curable with medical therapy
Persistent infection with ongoing bacteremia ± fever	Indicated after >5–7 days (class I)	Urgent for persistent positive blood cultures (class IIa)	For patients receiving appropriate antibiotics, and other sources/ embolic foci are controlled
For prevention of emboli: recurrent emboli or persistent/enlarging vegetations	Reasonable with recurrent emboli and persistent/enlargin vegetations (class IIa) May be considered with vegetations >10 mm especially involving mitral left anterior leaflet and with other relative surgical indications (class IIb)	Urgent for persistent vegetations >10 mm after one or more emboli (class I) Urgent for vegetation >10 mm with stenosis or regurgitation (class IIa) Urgent for very large vegetations >30 mm (class IIa) Urgent for large vegetations >5 mm and no other indication (class IIb)	Criteria include both patients having recurrent emboli on appropriate antibiotic therapy and patients with echocardiogram features suggesting ongoing high risk for further emboli
Fungi or multidrug-resistant bacteria	Should be considered (class I)	Urgent/elective (class I)	Examples: vancomycin-resistant enterococci and multidrug-resistant gram-negative bacilli
ADDITIONAL INDICATIONS SPECIFIC TO PATIENTS WITH PROSTHETIC VALVE ENDOCARDITIS			
Heart failure from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	Indicated (class I)	Emergent for severe acute regurgitation/ fistula, refractory edema (class I) Urgent for abscess/fistula (class I)	
Relapsing PVE	Reasonable (class IIa)	Not specifically addressed	
Staphylococcal or non-HACEK gram-negative	Not specifically addressed	Urgent/elective (class IIa)	
IMPACT OF ACUTE NEUROLOGIC EVENTS ON TIMING OF SURGERY			
Nonhemorrhagic silent embolus or transient ischemic attack	May be considered without delay (class IIb)	No delay if surgery indicated (class I)	Angiography for aneurysm should be considered if unexplained CNS symptoms
Acute stroke without hemorrhage on CT scan/MRI	May be considered without delay (class IIb) For major ischemic stroke, it is reasonable to delay surgery for 4 weeks (class IIa)	No delay if surgery indicated (class IIa)	Surgery is not appropriate for patients with severe neurologic damage or coma For patients with major CNS events, delay seems reasonable
Intracranial hemorrhage	Reasonable to delay surgery for 4 weeks (class IIa)	Surgery should be delayed for >1 month (class IIa)	

[a]Emergent indicates immediate/as soon as possible; urgent indicates during acute hospitalization.

CNS, Central nervous system; *CT,* computed tomography; *HACEK, Haempholus, Actinobaccilus, Cardiobacterium, Eikenella, Kingella*; *MRI*, magnetic resonance imaging; *PVE*, prosthetic valve endocarditis.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation.* 2015;132:1435–1486; and Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J.* 2015;36:3075–3128.

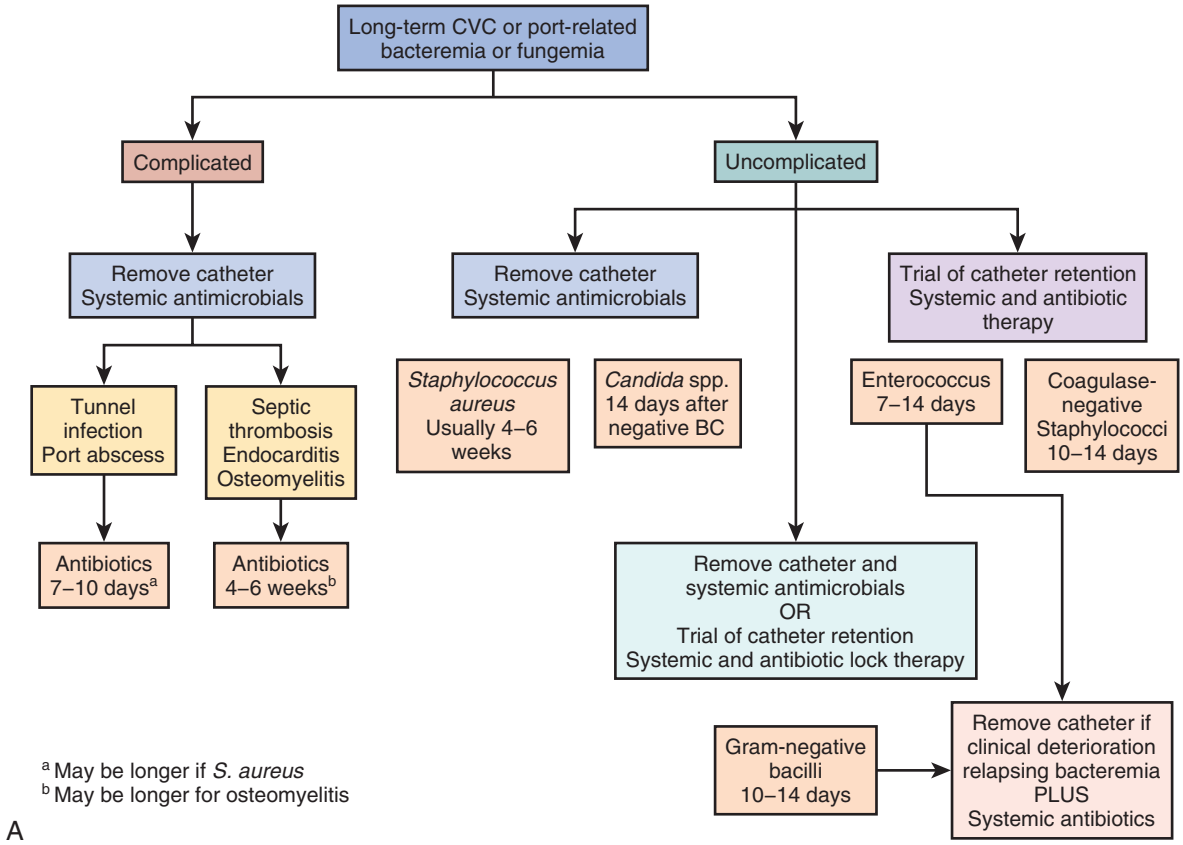
CNS embolic events in left-sided infective endocarditis are common and anticoagulation may increase the risk of hemorrhagic CNS events, and there is no proven benefit for aspirin therapy in humans, despite benefits in animal models.[52] In patients already receiving anticoagulation for mechanical valves or other specific indications, a change of warfarin to bridging therapy with heparin or low–molecular-weight heparins in the initial phase of therapy is a reasonable option, especially when surgical intervention is being considered. If possible, anticoagulation should be discontinued for 2 weeks after acute CNS embolic events.[52,53] Neurologic events, most commonly emboli but also mycotic aneurysms, are the second leading cause of mortality in acute endocarditis after heart failure. Decisions on timing of surgery and management of anticoagulation perioperatively and postoperatively in patients with CNS events are particularly challenging. An acute nonhemorrhagic CNS event is not a contraindication to urgent or emergent surgery, but surgery should be delayed for at least a month after a hemorrhagic event.[52,53]

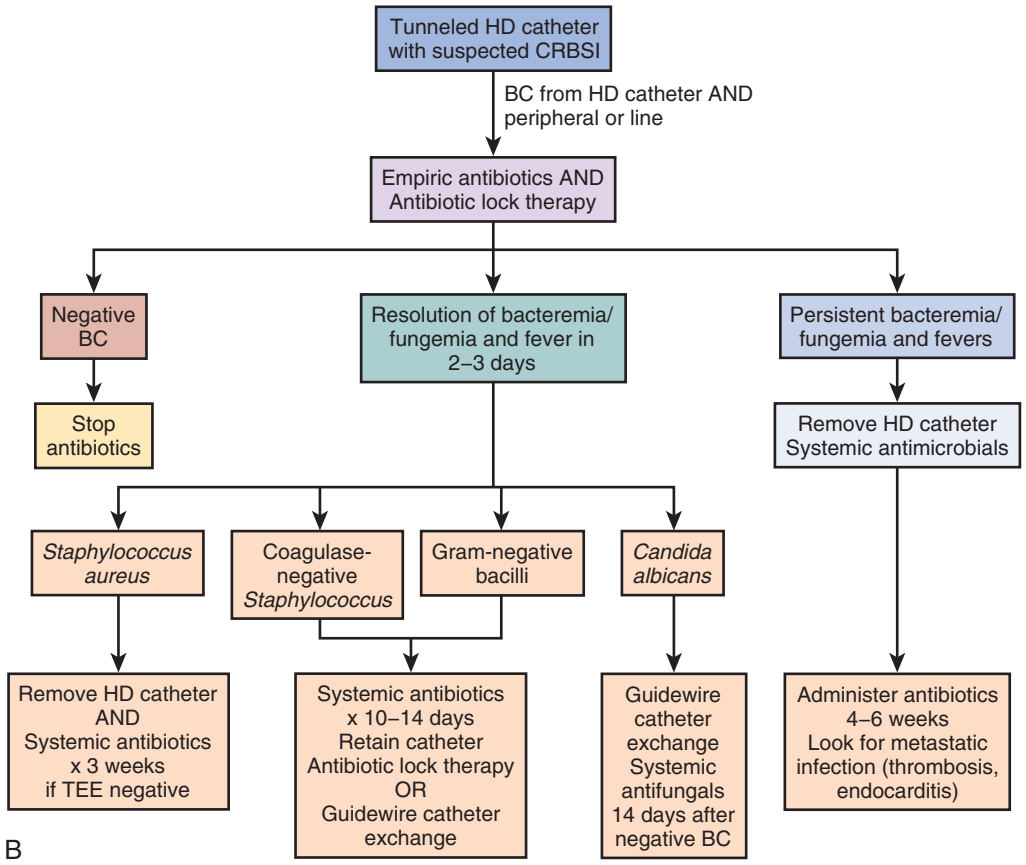
Optimal antibiotic therapy for patients with infective endocarditis is outlined in the AHA and ESC guidelines.[52,53] Individual treatment regimens, including choice of antibiotic, the need for combination antibiotic therapy, and treatment duration are based on the organism, susceptibility data, location of the infected valve, and whether the infection is complicated or uncomplicated. Left-sided *S. aureus* endocarditis is generally treated for 6 weeks with a parenteral β-lactam or vancomycin; addition of gentamicin during initial therapy is no longer recommended owing to a lack of benefit and increased nephrotoxicity.[60] Vancomycin is still recommended for methicillin-resistant staphylococcal infections, although daptomycin may be an alternative. Uncomplicated right-sided endocarditis in injection drug users may have a more benign course. There is evidence for use of 2-week courses of β-lactam therapy or daptomycin therapy for uncomplicated MSSA infections that quickly respond to treatment; short-course regimens are not recommended for MRSA infection or when vancomycin must be used for methicillin-sensitive *S. aureus* (MSSA).[52] Oral therapy with a fluoroquinolone plus rifampin for 4 weeks has also been used in patients with uncomplicated right-sided endocarditis caused by quinolone-susceptible strains.[52] Treatment of highly penicillin-susceptible viridans streptococcal endocarditis and *Streptococcus gallolyticius* (formerly *S. bovis*) endocarditis is 4 weeks of a β-lactam or vancomycin; gentamicin is added for disease caused by relatively penicillin-resistant strains. Selected patients with uncomplicated viridans streptococcal infections have been treated with 2 weeks of combination therapy. β-Lactam therapy for susceptible isolates is always preferred to vancomycin in nonallergic patients. *Enterococcus faecalis* endocarditis is usually treated for 4 to 6 weeks with synergistic combinations of antibiotics, owing to low inherent cidality of cell wall–inhibiting penicillins or vancomycin alone. Recent studies have demonstrated comparable effectiveness with decreased nephrotoxicity using 6 weeks of penicillin plus ceftriaxone compared to penicillin plus an aminoglycoside. Regimens for enterococcal infections, especially antibiotic-resistant *E. faecium*, need to be modified on the basis of specific resistance patterns. Prosthetic valve infections require longer treatment courses and use of combination therapy, and failure rates of medical therapy in treating prosthetic valve disease are high.[52]

Device-Related Endovascular Infections

Endovascular infections other than valvular infections have become increasingly common as causes of bacteremia and sepsis. This is due to the increased use of indwelling devices, including vascular catheters for chemotherapy and other long-term parenteral therapies, use of accesses for hemodialysis, and the expanding indications for implantable cardiac devices for patients with congestive heart failure and arrhythmias. Infection is the most common serious complication of peripherally inserted central venous catheters, tunneled catheters, and totally implanted intravascular devices.[61–63] Patients presenting with sepsis and focal findings related to the catheter, such as tunnel infection, port abscess, or cellulitis; those with associated venous thrombosis; or those with concurrent endocarditis or osteomyelitis require removal of the catheter.[61] Management decisions are more difficult in patients with sepsis or bacteremia without local signs of infection where catheter removal is not a trivial procedure. Determination of the catheter as the source of a bacteremia can sometimes be made with use of paired central and peripheral blood cultures. Positive central with negative peripheral blood cultures or central cultures that are positive significantly earlier than peripheral cultures may implicate the catheter as the source.[61] The majority of infected permanent catheters require removal; selected uncomplicated catheter infections in nonseptic patients whose blood has sterilized with antibiotic treatment can be treated with catheter retention and antibiotic therapy, especially infections caused by coagulase-negative staphylococci and other less virulent organisms.[61] Algorithms for the management of suspected and confirmed line infections in patients with long-term access devices are shown in Fig. 51.3. Antibiotic lock therapy, in which antibiotic solutions are used to fill the catheter lumen to maintain high antibiotic concentrations in the catheter and catheter hub, have yielded higher rates of catheter salvage than parenteral antibiotics alone.[61] Hemodialysis catheter infections pose particular management challenges because of the high prevalence of infection in these patients and the need to preserve dialysis access. Catheter salvage strategies and guidewire exchange strategies are used more frequently in hemodialysis catheter–associated infections and treatment durations may differ.[62]

Recent studies suggest that rates of implanted cardiac devices, including permanent pacemakers and automatic implantable cardioverter-defibrillator devices (AICDs), are increasing. AICDs are increasingly being implanted in older and more debilitated patients, likely contributing to the increasing prevalence of AICD infections.[53,62] Infection rates are much higher for revision procedures than for primary insertions and probably higher for AICDs compared with permanent pacemakers.[62] Device infections include both pocket infections and lead infections and both can occur concurrently; lead infections may be complicated by sepsis and septic shock, suppurative thrombophlebitis, and endocarditis. Lead infections almost always require explantation of the entire device and mortality is higher when removal of infected leads is delayed.[63,64] Diagnosis is typically made by blood cultures and TEE. TEE may show vegetations on the leads or associated endocarditis, but negative TEE does not exclude the diagnosis and incidental lead masses can be seen in up to 10% of TEE done for other reasons when there is no concern for infection. Intraoperative TEE may be helpful in some cases. The most common organisms are coagulase-negative staphylococci and *S. aureus* in 60% to 80% of cases.[62] Most infected leads can be removed percutaneously, especially because experience with laser extraction of AICD leads is increasing, although very large vegetations may be an indication for an open procedure. Devices should not be replaced until bacteremia has completely resolved.





• **Fig. 51.3** Algorithms for management of catheter-related bloodstream infection (CRSBI) in bacteremic patients with long-term central venous catheter *(CVC)* or ports (A) and for suspected CRSBI in patients with tunneled hemodialysis catheters (B) including indications for removal versus attempt at salvage of infected indwelling long-term catheters. *BC,* Blood culture; *HD,* hemodialysis; *TEE*, transesophageal echocardiography. (Data from Mermel LA, Allon M, Bouzon E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1–45.)

Primary Bacteremias

In 10% to 30% of patients presenting from the community with bacteremia and sepsis, the primary source of the bacteremia remains unknown, even after careful clinical and radiographic evaluation.[64,65] This includes patients with infections manifesting as a primary bacteremia, as well as those with probable secondary bacteremia from an occult focus. Bacteremia of unknown etiology is associated with higher mortality.[64] Primary bacteremias are more common with certain microorganisms and with specific host predispositions. These syndromes, if unrecognized, have particularly high morbidity and mortality. Patients with impairment in immunoglobulin production or function and impaired or absent splenic function are predisposed to infections with encapsulated organisms such as S. *pneumoniae, N. meningitidis, H. influenzae*, and group B streptococcus.[66] Patients with advanced liver disease and cirrhosis are predisposed to these as well as a variety of other spontaneous bacteremias.[67] Patients with cell-mediated immune defects may present with other unusual bloodstream infections such as *Listeria* and *Salmonella* sepsis. Severe neutropenia greatly increases the risk of spontaneous bacteremia and sepsis from endogenous gastrointestinal flora, and the management of fever in neutropenic patients incorporates empiric initiation of broad-spectrum antibacterial therapy including activity against *Pseudomononas*.[68] Several important bacteremia syndromes are described in the following sections.

Meningococcemia and Meningococcal Sepsis

Invasive meningococcal disease can present as either bacterial meningitis or as the syndrome of meningococcemia with meningococcal sepsis without meningitis.[7] The proportion of primary meningococcemia cases depends in part on the serotypes present in the community. The annual incidence of meningococcal disease in the United States is approximately 0.3 cases per 100,000, with mortality of 10% to 15% and significant residual morbidity in up to 20%.[7] In addition to young children, adolescents and young adults 11 to 19 years of age are at increased risk for meningococcal disease, but risk persists throughout life and is increased in those with certain immune deficiencies such as terminal complement deficiency and cirrhosis.[7,69] Patients with meningococcemia present with fever, headache, malaise, vomiting, and myalgias.[69,70] Most patients will also present with rapid development of a characteristic nonblanching petechial or purpuric rash, but the rash can be maculopapular or absent. Early symptoms that may be important clues to the diagnosis are leg pains and cold hands and feet.[70] If untreated, disease may progress rapidly within 24 hours to fulminant purpura and hemorrhagic shock. Early recognition and rapid initiation of antibiotic therapy with a penicillin or third-generation cephalosporin can significantly improve outcomes. PCR of blood is useful for diagnosis, especially in patients who received antibiotics before hospitalization.[7,70] Several multivalent conjugated meningococcal vaccines as well as serogroup B–specific vaccines are both now available in the United States for routine vaccination of adolescents and other high-risk populations.[7,71]

Primary Pneumococcal Bacteremia

Pneumococcal bacteremia is most commonly a consequence of pneumococcal pneumonia, but 5% to 10% of episodes occur without an identified underlying focus.[72] Severe episodes may present with fulminant sepsis and purpura fulminans clinically indistinguishable from meningococcal sepsis. Important risk factors for pneumococcal sepsis include asplenia and hyposplenism, HIV infection, sickle cell disease, alcoholism, malignancy, and other immunocompromised states, although this syndrome can occur in otherwise healthy adults and children without predisposing risks.[66,72] *S. pneumoniae* causes 50% to 90% of cases of the fulminant sepsis syndrome that occurs in postsplenectomy or functionally asplenic patients.[67] Rates of invasive pneumococcal disease including bacteremia in adults in the United States have declined after introduction of conjugate pneumococcal vaccines.[73] Other causes of the postsplenectomy sepsis syndrome include *N. meningitidis*; *H. influenzae*; and, less commonly, *Capnocytophaga canimorsus, Escherichia coli, Salmonella*, and the vector-borne parasitic infections malaria and babesiosis. Immunization with pneumococcal, meningococcal, and *H. influenzae* vaccines is recommended for those at risk for postsplenectomy sepsis.[66]

Staphylococcus aureus Bacteremia

S. aureus bacteremia can occur from localized staphylococcal disease such as skin and soft tissue infection or pneumonia, endovascular infection, and endocarditis. It can also be of occult origin. Regardless of the initial source of bacteremia, there is significant risk for development of late complications, including endocarditis, bone and joint disease, or other metastatic foci, in up to one-third of cases.[74] Features associated with complicated *S. aureus* bacteremia include prolonged bacteremia, prolonged fever, and embolic lesions. MRSA bacteremias may have worse outcome than MSSA bacteremias.[75] Longer-course parenteral therapy (at least 4 weeks) is recommended for patients with complicated disease, whereas 2 weeks of treatment may be adequate for selected patients with uncomplicated bacteremia, although late complications and relapse of bacteremia may occur even with more prolonged courses of therapy.[74] TEE has been recommended to exclude endocarditis in patients with otherwise clinically uncomplicated *S. aureus* bacteremia when short-course therapy is being considered.[74,75]

Toxin-Mediated Infections

Staphylococcal Toxic Shock Syndrome

S. aureus produces multiple virulence factors that contribute to its success as a human pathogen. These virulence factors potentiate local adherence, tissue invasion, and avoidance of host defenses, all features that are important in the pathogenesis of localized skin and soft tissue infection, pneumonia, bacteremia, and metastatic infections. Staphylococci also produce a variety of exotoxins that are released into the systemic circulation and act at distant sites.[76] Some of these exotoxins are directly pathogenic to specific cells, such as exfoliative toxin B, which causes staphylococcal scalded skin syndrome. Other exotoxins function as potent superantigens, antigens that bypass the intermediate T-cell antigen processing steps by binding directly to Vβ domains on T-cell receptors. This causes direct activation of multiple T-cell classes resulting in unopposed release of large amounts of cytokines, including interleukin (IL)-2, IL-4, IL-6, interferon gamma, TNF-α, and IL-1β. The resulting "cytokine storm" can lead to shock, multiorgan failure, and death.

The most well-studied staphylococcal superantigens are the pyrogenic antigens toxic shock syndrome toxin (TSST)-1 and TSST-2 and enterotoxins B and C. TSST-1 and enterotoxin B are the primary exotoxins causing the staphylococcal toxic shock syndrome.[76] First described in 1979 as a unique syndrome primarily associated with menstruating women using super-absorbent brands

of tampons, staphylococcal toxic shock syndrome can potentially occur from any infection or colonization caused by an exotoxin-producing strain, including both MSSA and MRSA.[77,78] Disease is associated with conditions leading to exotoxin production in a host who lacks preexisting antibodies to TSST-1. The overall incidence of this syndrome, as well as the proportion of cases associated with menstruating women, has decreased since 1980 and is estimated at 0.5 to 1 case per 100,000 per year in the United States.[78] Toxic shock syndrome is characterized by the acute onset of fever, hypotension, myalgia, scarlatiniform or erythroderma-like rash, nausea, vomiting, diarrhea, and development of multiple-organ failure, including renal failure, elevated liver enzymes, and disseminated intravascular coagulopathy (DIC).[77–79] Typically the rash evolves and results in late desquamation of hands and feet. Specific criteria for the diagnosis of staphylococcal toxic shock syndrome have been recently updated (Box 51.1).[79] Treatment is primarily supportive, but antistaphylococcal agents are administered to treat the underlying staphylococcal colonization or infection; some evidence suggests that immunoglobulin may be beneficial by binding exotoxin and attenuating the cytokine response.

Streptococcal Toxic Shock Syndrome

Group A β-hemolytic streptococci are also capable of producing a toxic shock–like syndrome analogous to staphylococcal toxic shock syndrome.[76,80] Most often this is seen in the setting of severe bacteremic streptococcal soft tissue infection or with streptococcal necrotizing fasciitis. In one large survey of invasive streptococcal infections in Ontario, 13% of cases were complicated by toxic shock syndrome, and the mortality rate of these infections was 81%.[80] The pathogenesis of this syndrome has been attributed to streptococcal pyrotoxins functioning as superantigens. Binding of streptococcal M protein-fibrinogen complexes to polymorphonuclear (PMN) cells causing PMN activation and endothelial damage may also be important. Clinical criteria for the diagnosis of streptococcal toxic shock syndrome in the United States were recently updated (see Box 51.1).[81] In addition to antibiotics that decrease toxin production, such as clindamycin and linezolid, IV immunoglobulin has also been used for treatment of streptococcal toxic shock syndrome and recent studies suggest that both clindamycin and IV immunoglobulin contribute to increased survival.[82] Other streptococcal species have also been reported to produce a toxic shock–like illness including viridans streptococci, groups B, C, and G β-hemolytic streptococci, and *Streptococcus suis*.

Tetanus

Tetanus is a syndrome of increased muscle rigidity and convulsive spasms caused by a toxin produced by the environmental spore-forming anaerobic bacterium *Clostridium tetani*.[7] Since the introduction of routine immunization, tetanus has become increasingly rare, with the incidence of U.S. cases decreasing from 3.9 per million in 1947 to 0.10 cases per million in 2001–2008.[7] Clinical disease is caused by contamination of wounds, most commonly traumatic wounds, with bacterial spores. Spores then germinate and produce toxins including tetanospasmin, a highly potent neurotoxin that inhibits neurotransmitter release, resulting in blockage of inhibitor impulses and unopposed muscle contractions. Cases predominate in the summer or wet season, and the disease is now most common in older adults because of either missed primary immunization or waning effects of childhood immunization.[7] The most common syndrome is that of generalized tetanus

• BOX 51.1 CDC Criteria for Diagnosis of Nonstreptococcal (i.e., Staphylococcal) and Streptococcal Toxic Shock Syndromes

Toxic Shock Syndrome Other Than Streptococcal—2011 CDC Case Definitions

A. Clinical criteria for diagnosis
   1. Fever ≥102.0°F (≥38.9°C)
   2. Rash: diffuse macular erythroderma
   3. Desquamation 1–3 weeks after onset of rash
   4. Hypotension: systolic blood pressure ≤90 mm Hg for adults
   5. Multisystem involvement (3 or more of the following organ systems):
      Gastrointestinal: vomiting or diarrhea at onset of illness
      Muscular: severe myalgia or CPK levels at least twice the upper limit of normal
      Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
      Renal: BUN or creatinine at least twice upper limit of normal or ≥5 leukocytes per high-power field in absence of urinary tract infection
      Hepatic: total bilirubin, AST or ALT at least twice the upper limit of normal
      Hematologic: platelets <100,000/mm^3
      CNS: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

B. Laboratory criteria for diagnosis
   Negative results on the following tests if obtained:
      Blood, throat, or CSF fluid cultures (blood cultures may be positive for *Staphylococcus aureus*)
      Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles
   Probable case:
      Meets the laboratory criteria and 4 of the 5 clinical criteria above are present
   Confirmed case:
      Meets the laboratory criteria and all 5 of the clinical criteria above including desquamation are present, unless the patient dies before desquamation occurs

Streptococcal Toxic Shock Syndrome—2010 CDC Case Definitions

C. Clinical Criteria for Diagnosis
   1. Hypotension (systolic BP ≤90 mm Hg for adults)
   2. Multiorgan involvement characterized by two or more of the following:
      Renal impairment
      Coagulopathy
      Liver involvement
      Acute respiratory distress syndrome
      A generalized erythematous macular rash that may desquamate
      Soft tissue necrosis including necrotizing fasciitis or myositis, or gangrene

D. Laboratory Criteria for Diagnosis
   1. Isolation of Group A *Streptococcus*
   Probable Case:
      A case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A *Streptococcus* from a nonsterile site.
   Confirmed case:
      A case that meets the clinical case definition with isolation of group A *Streptococcus* from a normally sterile site

ALT, *Alanine aminotransferase;* AST, *aspartate aminotransferase;* BP, *blood pressure;* BUN, *blood urea nitrogen;* CDC, *Centers for Disease Control and Prevention;* CFS, *cerebrospinal fluid;* CNS, *central nervous system;* CPK, *creatine phosphokinase.*

From Centers for Disease Control and Prevention. Streptococcal toxic-shock syndrome (STSS) (Streptococcus pyogenes) Case Definition 2010. Available at: https://wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010/. Accessed August 9, 2017; and Centers for Disease Control and Prevention. Toxic-shock syndrome (other than Streptococcal) (TTS). Case Definition 2011. Available at: https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/. Accessed August 9, 2017.

with descending symptoms of trismus (lockjaw), difficulty swallowing, muscle rigidity, and spasms.[7] Symptoms may persist for several weeks, and complete recovery may take months. Complications include laryngospasm, fractures, hypertension, nosocomial infections, and death. Treatment is primarily supportive, although metronidazole or penicillin may be given to treat potentially infected or colonized wounds.[83] Patients require admission to an ICU for control of rigidity and spasms with benzodiazepines or neuromuscular blocking agents and for ventilator support. Human tetanus immunoglobulin may be administered, but this only binds free toxin, so there may be little benefit by the time of clinical presentation. Routine childhood and adult immunization with tetanus toxoid remains the primary strategy for preventing this rare but often fatal condition. Guidelines for use of immunoglobulin and vaccination in management of potentially infected wounds have been published.[7]

Botulism

Clostridium botulinum is an anaerobic spore-forming bacteria that produces botulinum toxin, a family of closely related but immunologically distinct polypeptide toxins that are among the most potent neurologically acting poisons known.[84] Other, less common clostridial species can also produce botulinum toxin. Botulinum toxin binds irreversibly to synaptic complexes, affecting ganglionic synapses, presympathetic synapses, and neuromuscular junctions. Clinical syndromes include those caused by ingestion of preformed toxin such as food botulism and those resulting from acquisition of the organism and production of toxin in vivo such as infant botulism in very young children and wound botulism from contaminated wounds, most commonly seen in injection drug users. Patients present initially with cranial nerve dysfunction and evolve to descending paralysis without sensory or cognitive effects. Diagnosis is made on clinical grounds; testing of food products or human samples in the United States is performed by the Centers for Disease Control and Prevention (CDC). Treatment is primarily supportive, but heptavalent equine antitoxin active against neurotoxin serotypes A, B, C, D, E, F, or G is available through the CDC; human antitoxin is preferred for infant botulism.[84] Antitoxin is effective in binding free toxin only if given in the first 72 hours. Because of its potency, environmental stability, and potential for aerosolization, botulinum toxin is considered a potential agent of bioterrorism.[84]

Diphtheria

Diphtheria is caused by toxigenic strains of the bacterial species *Corynebacterium diphtheriae*. This disease has become extremely rare in the United States secondary to universal vaccination with diphtheria toxoid vaccine, with an average of one confirmed case per year.[7] Patients with respiratory diphtheria present with sore throat; low-grade fever; occasional neck swelling; and the characteristic grayish adherent membrane covering the tonsils, throat, or nose.[7] Complications include myocarditis, polyneuritis, and airway obstruction, with mortality rates of 5% to 10%. Outbreaks of diphtheria continue to occur in many parts of the world.

Serious Skin and Soft Tissue Infections

Severe skin and soft tissue infections are common. They are characterized by rapidly progressive inflammation and necrosis of skin, subcutaneous fat, and fascia. Occasionally, muscle is also involved. Several terms have been used to describe these infections: *necrotizing fasciitis; synergistic necrotizing cellulitis; progressive bacterial synergistic gangrene; anaerobic cellulitis*; and, when muscle is involved with clostridial infection, *clostridial myonecrosis (gas gangrene)*.[85] Differentiating among these entities is difficult and somewhat artificial. A variety of features of some of the most important necrotizing skin and soft tissue infections are shown in Table 51.5.

TABLE 51.5 Differentiating Features of Necrotizing Skin and Soft Tissue Infections

Feature	Progressive Bacterial Synergistic Gangrene	Nonclostridial Anaerobic Cellulitis	Clostridial Myonecrosis (Gas Gangrene)	Necrotizing Fasciitis Type 1	Necrotizing Fasciitis Type 2
Risk factors	Surgery, ileostomy, colostomy, chronic ulceration	Diabetes mellitus	Trauma, surgery	Diabetes mellitus, surgery, perineal infection	Trauma, surgery, none
Microbiology	Microaerophilic streptococci plus *Staphylococcus aureus*	Non–spore-forming anaerobes ± coliforms, streptococci, *S. aureus*	*Clostridium* spp.	Polymicrobial (Enterobacteriaceae plus anaerobes)	Group A streptococci
Course	Slow	Slow or rapid	Very rapid	Rapid	Very rapid
Pain	++++	++/+++	++++	+++/++++	++++
Gas formation	–	++++	++	++	–
Appearance	Central necrotic ulcer, erythematous periphery	Erythematous skin necrosis	Bullae, necrosis	Bullae, skin	Bullae, necrotic skin and tissue
Drainage	Purulent if present	Purulent	Serosanguineous	"Dishwater," seropurulent	Serous if present
Depth of involvement	Skin, soft tissue	Skin, soft tissue	Muscle	Fascia	Fascia
Systemic toxicity	±	+++/++++	++++	+++/++++	++++

–, Absent; ±, occasionally present; +, minimal; ++, mild; +++, moderate; ++++, marked or severe.

Microbiologically, these infections may be caused by a single pathogen such as group A β-hemolytic streptococcus; however, they are more frequently polymicrobial in nature. Risk factors for these infections include diabetes, old age, peripheral vascular disease, malignancy, alcoholism, renal failure, and immunosuppressive therapy. Infection may follow traumatic injuries that become contaminated by soil. The primary traumatic event may be relatively minor. Initial signs and symptoms may be similar to a severe cellulitis. Immune status, exposure history, and travel history should be assessed.[86] Early findings include fever, tachycardia, moderate to severe pain, and swelling and induration of the skin.[86] Late findings include severe pain or even anesthesia, skin necrosis, hemorrhagic bullae, crepitus, drainage, and signs of systemic inflammatory response syndrome or severe sepsis including multiorgan failure.[86] Laboratory tests usually demonstrate leukocytosis and metabolic acidosis. Plain radiographs may reveal gas in the soft tissues. CT or MRI is useful in delineating the extent of disease or the presence of soft tissue gas. Diagnostic evaluation should also include blood cultures, Gram staining of tissue exudates, and aerobic and anaerobic cultures obtained at surgery or from a needle aspiration. Incision and exploration or biopsy can even be done at the bedside to obtain material for Gram stain, culture, and histologic evaluation.

Skin and soft tissue infections are defined as severe if a patient meets any of the following criteria: (1) ICU patient with an acute change in sequential organ failure assessment score greater than or equal to 2 points owing to infection; (2) non-ICU patient meeting two of three sequential organ failure assessment criteria (altered mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate greater than 22 breaths/min). Once a necrotizing soft tissue infection has been identified, prompt therapy is important. Early aggressive surgical debridement is essential for source control. Serial debridement every 24 to 48 hours may be necessary until there is no longer any necrosis and the patient's condition is stable.[86–88] Because most cases of necrotizing skin infection are polymicrobial, empiric antibiotic coverage should be sufficiently broad spectrum to cover gram-positive cocci (specifically MRSA), gram-negative bacilli, and anaerobes.[89] A reasonable empirical regimen might consist of a β-lactam/β-lactamase inhibitor, a carbapenem, or a third- or fourth-generation cephalosporin combined with an agent effective against MRSA, such as vancomycin or a semisynthetic lipoglycopeptide such as dalbavancin or oritavancin.[86–88] Antibiotic therapy can subsequently be adjusted on the basis of results of cultures and sensitivities.[88] In cases of group A β-hemolytic streptococcal infection, penicillin plus clindamycin is the therapy of choice. Clindamycin is effective in stopping toxin production. Linezolid also has similar activity. The use of IV immunoglobulins for treatment of necrotizing skin and soft tissue infections has been based on the binding of endotoxins produced by streptococci and staphylococci, but use remains controversial as discussed in several recent guidelines.[87] Intravenous IG (IVIG) may be a useful adjuvant therapy for streptococcal or staphylococcal toxic shock when associated with skin and soft tissue infections.[80,87]

Necrotizing Fasciitis

Necrotizing fasciitis is an uncommon, severe infection that causes necrosis of the subcutaneous tissue and fascia with sparing of the underlying muscle. Two predominant types, based on microbiology, are described. In type I, at least one anaerobic species is isolated along with one or more facultative anaerobes and members of the Enterobacteriaceae.[90,91] This form of necrotizing fasciitis most commonly affects the extremities but may involve the abdominal wall, postoperative wounds, perianal area, and groin. It occurs after trauma or a variety of surgical procedures, perirectal abscess, decubitus ulcer, or perforation of the intestines. Patients at increased risk include those with diabetes mellitus, alcoholism, and injection drug use. The involved area is initially erythematous and painful, but over several days skin changes include color changes, formation of bullae, and cutaneous gangrene. The involved area becomes anesthetic secondary to thrombosis of small blood vessels and destruction of superficial nerves. Anesthesia may develop before the appearance of skin necrosis and is an important clue to the presence of necrotizing fasciitis rather than simple cellulitis.[86] Subcutaneous gas is often present, and systemic toxicity is common.[91] When the lesion is probed at the bedside or in the operating room, there is no resistance along tissue planes. In type II (also known as hemolytic streptococcal gangrene), group A streptococci are generally isolated alone or in combination with *S. aureus*.[92] These strains usually produce pyrogenic exotoxin A. Periodically, group C or group G streptococci are causative organisms. Infection usually develops at a site of trauma but may occur in the absence of an obvious portal of entry.[91] The involved area is extremely painful, erythematous, and edematous. Infection spreads widely in deep fascial planes with relative sparing of the overlying skin and therefore may not be recognized. This form of necrotizing fasciitis is present in approximately 50% of cases of streptococcal toxic shock syndrome.[92] Over several days, the skin becomes dusky and bullae develop. Bullae then rupture and evolve into an area covered by necrotic eschar, often resembling a third-degree burn. Streptococci can usually be cultured from fluid of the early bullae and frequently from blood. Complications include metastatic abscess formation, and the mortality rate from this infection is high. Treatment requires surgical source control with immediate surgical debridement and empiric broad-spectrum antibiotics.[90]

Fournier gangrene is a form of necrotizing fasciitis that involves the male perineum, usually the scrotum, but can involve the penis, the perineum, or the abdominal wall. It is caused by anaerobic streptococci along with other bacteria such as *E. coli*; *S. aureus*; β-hemolytic streptococci; *Proteus* spp.; a variety of anaerobes; and, on occasion, *Pseudomonas* spp.[93] The first symptoms are commonly scrotal swelling and pain followed by progressive necrosis of scrotal skin and subcutaneous tissues.[93] The patient may appear toxic. Initially the patient may be erroneously diagnosed with an acute abdomen unless the genitalia are examined. Gangrene of the perineum and sometimes the penis may develop. Urgent and aggressive surgery is necessary along with broad-spectrum antibiotics.

Clostridial Myonecrosis (Gas Gangrene)

Gas gangrene is a life-threatening infection of skeletal muscle most frequently caused by *Clostridium* spp.. It should be suspected when the Gram stain of drainage reveals gram-positive bacilli in a patient who is critically ill. Penicillin G is the drug of choice with or without clindamycin. Aggressive surgical exploration and debridement is the mainstay of therapy. The role of hyperbaric oxygen therapy in the treatment of clostridial myonecrosis or in the treatment of necrotizing fasciitis remains controversial. If used, it must be as an adjunct to surgery.[94]

Vibrio Infections

Various *Vibrio* species including *Vibrio vulnificus* have caused mild to severe cellulitis in patients who sustained lacerations or puncture

wounds when in contact with saltwater in the southeastern United States and the Gulf of Mexico. Recent advances in genetic analysis have led to the reclassification of some *Vibrio* spp. into other genera, including *Grimontia* and *Photobacterium*.[95] Septicemia with secondary necrotizing soft tissue infection may occur after ingestion of raw or undercooked shellfish in immunocompromised hosts, especially those with cirrhosis.[95] An increased incidence of *Vibrio* infections has been described as a result of flooding after natural disasters. Identification of *Vibrio* organisms in the clinical laboratory using conventional methods may be difficult. Newer molecular technologies such as multilocus sequence analysis, 16S ribosomal DNA gene sequencing, and matrix-assisted laser desorption/ionization time of flight mass spectrometry, are promising for the identification of these organisms.[95] Doxycycline, third-generation cephalosporins, and fluoroquinolones are effective therapies, along with aggressive surgical debridement of necrotic tissue.

Community-Acquired MRSA

Approximately 2 decades ago, the emergence of MRSA infections in patients without health care–associated risk factors led to the term *community-acquired MRSA* (CA-MRSA). The recent movement of CA-MRSA strains into nosocomial settings now limits the utility of using clinical risk factors alone to designate community- or health care–associated status.[96] Many of these strains carry the staphylococcal cassette chromosome mec type IV element and the gene encoding Panton-Valentine leukocidin, a toxin that promotes tissue destruction.[96] Although most CA-MRSA infections are mild skin and soft tissue infections, severe, life-threatening cases of necrotizing fasciitis, myonecrosis, necrotizing pneumonia, and sepsis have occurred.[96] Historically, CA-MRSA strains were broadly susceptible to several non–β-lactam antibiotics. For patients with invasive infections caused by CA-MRSA, vancomycin, linezolid, daptomycin, and newer semisynthetic lipoglycopeptides such as dalbavancin are appropriate therapeutic options. Newer cephalosporins such as ceftaroline and ceftobiprole are also active.[97] Rates of resistance among CA-MRSA strains to clindamycin, fluoroquinolones, tetracyclines, and trimethoprim/sulfamethoxazole vary with geographic location.[96]

Serious Gastrointestinal and Intra-abdominal Infections

Bacteremia Associated With Enteric Pathogens

In common with pathogens that cause inflammatory diarrhea, the gram-negative organisms that cause enteric fever syndrome are invasive.[98] Of the enteric pathogens, *Salmonella* spp. are most likely to cause bacteremia and serious infection. Enteric fever is usually caused by *Salmonella enterica* serotype typhi and rarely by *Salmonella paratyphi, Salmonella choleraesuis, Yersinia enterocolitica*, *Brucella* spp., or *Campylobacter fetus*.[99] Features of classic typhoidal fever caused by *S. enterica* include sustained fever, bacteremia, headache, and abdominal pain. Physical findings include "rose spots," which are 2- to 4-mm discrete, irregular, blanching pink macules that are often seen on the anterior chest; hepatosplenomegaly; and relative bradycardia. Multiorgan system dysfunction can occur as a consequence of metastatic infection or immune complex deposition.[97] Intestinal bleeding or perforation may occur as a result of hyperplasia of the lymphoid tissue in the terminal ileum. Diarrhea is seen in less than 50% of cases and only early in the illness. Constipation is a frequent later complaint. The following specimens should be sent for culture: stool, blood, or bone marrow. Serologic findings may provide supportive evidence or may be useful in epidemiologic evaluation.

Therapeutic options include third-generation cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole. Antimicrobial resistance has been reported. Treatment for uncomplicated cases is 12 to 14 days; 30 days of therapy may be necessary for metastatic foci. Metastatic foci are relatively common in the setting of bacteremia. Infection may involve the gallbladder, spleen, bone, joints, and the meninges. There is a propensity to infect preexisting intravascular lesions such as atherosclerotic plaques and aneurysms. Sickle cell anemia and the presence of an orthopedic prosthesis are risk factors for osteomyelitis.[97] Meningitis tends to occur in young children.[97]

Peritonitis

Peritonitis is a localized or general inflammation of the peritoneal cavity that is generally caused by bacteria or fungi but may be caused by a variety of noninfectious agents such as gastric contents, talc, or bile salts. Infective peritonitis has been classified as primary, secondary, or tertiary. Peritonitis is primary when it is not related directly to other intra-abdominal processes.[100] This classification includes spontaneous bacterial peritonitis (SBP), which occurs in patients with underlying ascites from cirrhosis or nephrotic syndrome, and tuberculous peritonitis. Secondary peritonitis most often arises from an enteric source or pelvic focus and includes peritonitis following an acute perforation of the gastrointestinal tract, intestinal necrosis, postoperative peritonitis that may be secondary to an anastomotic leak, and posttraumatic peritonitis following blunt or penetrating abdominal trauma. Intestinal ischemia and frank necrotic bowel may be caused by a variety of processes, including malignancies, vascular insufficiency, volvulus, or intussusception.[100] Rupture of an abscess in the pancreas, liver, or spleen or, rarely, rupture of a distended gallbladder can also cause peritonitis. Localized lower abdominal peritonitis can also result from gynecologic infections such as salpingitis and endometritis. Tertiary peritonitis is described as occurring when clinical and systemic signs of peritonitis persist or recur after treatment for secondary peritonitis. A distinct form of device-associated peritonitis is seen in patients undergoing peritoneal dialysis.

Bacterial peritonitis is typically caused by flora of the large intestine including aerobes, with *E. coli* being the most frequent, and anaerobes, of which *Bacteroides fragilis* is the predominant isolate.[101] Common symptoms include localized or generalized abdominal pain, nausea, and vomiting. Treatment with corticosteroids may mask typical signs and symptoms, delaying the diagnosis. Signs may include abdominal rigidity, distention, fever, and an overall toxic appearance. A rigid abdomen may be seen in the early stages of an acute peritonitis, although it may be absent in a peritonitis that progresses more slowly, such as that caused by tuberculosis, or when sterile bile, pancreatic fluid, or urine leaks into the peritoneal cavity. As intraperitoneal fluid accumulates, abdominal distention and an ileus occur. The WBC count is usually elevated. Bacteremia may occur, and the sepsis syndrome may develop as peritonitis evolves. Aspiration of peritoneal fluid is an essential part of the evaluation for peritonitis. Laparoscopy or laparotomy may be necessary. Studies performed on peritoneal fluid should include a cell count with differential blood cell count, amylase, Gram stain and aerobic and anaerobic cultures, acid-fast smear and culture, and fungal smear and culture.

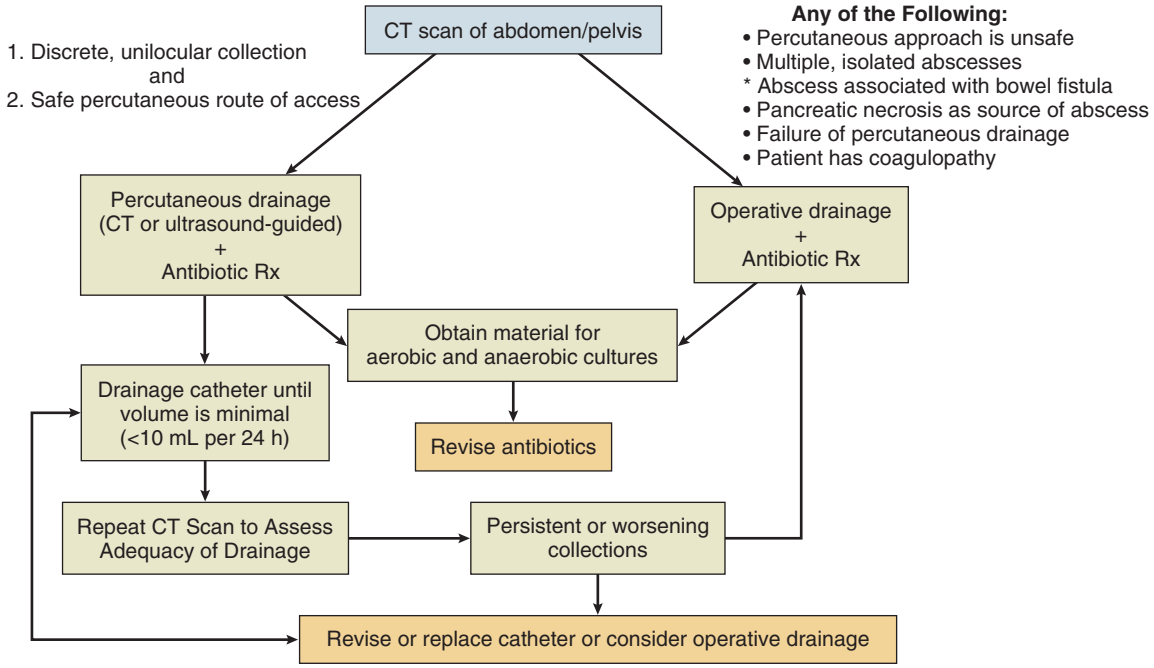
Adequate management of severely ill patients with secondary peritonitis requires source control of infection, antimicrobial therapy, and supportive therapy of organ dysfunction.[102] The primary cause of secondary peritonitis should be sought and eliminated if possible. Liver function tests and a serum amylase level may define a source in the liver, gallbladder, or pancreas. A plain film of the abdomen or a chest radiograph may reveal free air under the diaphragm in the case of a ruptured viscus. A CT scan of the abdomen may reveal an underlying intra-abdominal abscess or other focal process. Antibiotic therapy to cover gram-negative bacillary organisms and anaerobes should be initiated. Risk factors for resistant organisms such as recent hospitalization, comorbidities, previous antibiotic therapy, and colonization should be considered. Options for empiric therapy include combinations such as a third- or fourth-generation cephalosporin or a fluoroquinolone with metronidazole or monotherapy with a β-lactam/β-lactamase inhibitor combination, a carbapenem, or a glycylcycline such as tigecycline.[102–107] Empirical therapy should always include coverage for Enterobacteriaceae and *Bacteroides* spp. The need for empirical coverage of *Enterococcus* spp. is debatable. Empirical enterococcal coverage is warranted in nosocomial secondary peritonitis, in patients with septic shock who have received prior cephalosporin therapy, in immunocompromised patients, in patients with prosthetic heart valves or prosthetic intravascular devices, and in septic patients with recurrent intra-abdominal infections.[102] The optimal duration of therapy is not well defined, although nonbacteremic patients are generally treated for 7 to 10 days.[101] Regimens as short as 2 days of treatment may be adequate in uncomplicated situations with adequate surgical source control and in those with penetrating trauma. Bacteremic patients are generally treated for a total of 14 days using a combination of IV therapy followed by de-escalation to oral therapy.

SBP is caused by the translocation of enteric organisms to regional lymph nodes, which produce bacteremia and ultimately seeding of ascitic fluid.[108] Periodically a urinary tract infection may be the initial source of bacteremia. SBP occurs most commonly in adults with cirrhosis, nephrotic syndrome, or systemic lupus erythematosus.[108,109] Coliforms are the most common pathogens in adults, accounting for 70% of infections, with *E. coli* the most common isolate followed by *Klebsiella* spp. Gram-positive cocci may be seen in up to 20% of cases and anaerobes in less than 5%. Generally SBP is monomicrobial in contrast to the polymicrobial nature of most other forms of peritonitis. Findings of SBP may be subtle, so a high index of suspicion is necessary. Ascites is almost always present.[108] Fever and abdominal pain are seen in the majority of patients. New onset or worsening of hepatic encephalopathy may be seen. Some patients may have abdominal tenderness or rebound tenderness, but these findings are less frequent than in other forms of peritonitis. The most useful diagnostic test is paracentesis.[108–110] Ascitic fluid testing should include cell count with differential, Gram stain, culture, and total protein and albumin to determine the serum–ascites albumin gradient.[110] SBP is defined by an ascitic segmented neutrophil count of at least 250 cells/mm^3 with or without a positive fluid culture and no obvious intra-abdominal source of infection.[109,110] Despite the low sensitivity (≈33%), Gram staining of ascitic fluid should be performed. Patients with other infections of the abdomen, such as tuberculous peritonitis, secondary bacterial peritonitis caused by perforation, or peritonitis caused by noninfectious processes including pancreatitis or malignancy, also may show elevated neutrophil counts. The presence of a single organism generally supports the diagnosis of SBP, although there is a variant of SBP caused by traumatic entry into the bowel during paracentesis that may be polymicrobial, and conversely, gram-negative bacillary organisms may occur as sole pathogens in secondary peritonitis. If mixed gram-positive and gram-negative bacteria are seen, an intestinal perforation is the more likely source.[110] Peritoneal fluid should be cultured aerobically and anaerobically. Blood cultures should also be performed and are positive in up to 75% of patients with SBP.[109] Other than for symptom relief, a repeat paracentesis is necessary only when the patient fails to have a clinical response or when an unusual organism is isolated. Third-generation cephalosporins are the agents of choice for SBP. A fluoroquinolone, such as levofloxacin, is a reasonable alternative. A β-lactam/β-lactamase inhibitor combination such as piperacillin-tazobactam should be considered for patients with health care–associated SBP or for those whose conditions fail to improve. Selective albumin supplementation is an important part of management. It has been shown to prevent renal impairment and is associated with lower mortality. Norfloxacin, ciprofloxacin, and trimethoprim-sulfamethoxazole have been studied for primary and secondary prophylaxis and are effective.[110] Treatment is usually continued for a total of 7 to 10 days, although some studies have shown that a 5-day course of IV therapy may be adequate.[109–112] Mortality is high, ranging from 10% to 46% for this syndrome, and after an initial episode of SBP, the probability of recurrence within 1 year is 70%.[110,111]

Intra-abdominal Abscess

Considering the presence of a potential intra-abdominal abscess in febrile patients without any obvious cause of fever is important, especially if there is a predisposing condition such as diverticulitis, inflammatory bowel disease, or a history of recent abdominal surgery or abdominal trauma. Intra-abdominal abscess formation may complicate either primary or secondary peritonitis. The processes that typically predispose to intra-abdominal abscess formation are the same as those that cause secondary peritonitis and include perforation, complicated acute cholecystitis, suppurative cholangitis, acute appendicitis, diverticulitis, intestinal malignancy, surgical procedures, blunt or penetrating trauma, or intestinal ischemia from a mesenteric vascular occlusion, an intestinal obstruction, or a volvulus. Most commonly, abscesses are postoperative complications of trauma or of gastrointestinal or biliary surgery.[113] Abscesses can be found anywhere within the abdomen including the retroperitoneal space. Generally their location is in proximity with the original site of contamination, but they may develop at distant sites.[114] One example of distal infection is subphrenic abscess, which may be a consequence of a perforated appendix. Symptoms of intra-abdominal abscess may include fever, chills, anorexia, weight loss, and abdominal pain. Unexplained fever may be the only sign of an occult intra-abdominal abscess. An abdominal CT scan is the imaging modality of choice for diagnosis of abdominal abscess. Drainage is essential to establish the diagnosis, obtain microbiology to target antimicrobial therapy, and achieve therapeutic success. This may be accomplished by the insertion of percutaneous catheters, or by laparoscopic or operative drainage.[113,114] Large abscesses cannot be eradicated by antibiotic therapy alone. Criteria for considering percutaneous drainage include the presence of a well-defined fluid collection and a safe percutaneous route of access.[115] Drains should remain in place until drainage volume is minimal, usually less than 10 mL in a 24-hour period.

A repeat CT scan should be performed to demonstrate complete collapse of the abscess cavity.[113] Indications for operative surgical drainage rather than percutaneous drainage include the following situations: (1) when percutaneous drainage cannot be performed



• **Fig. 51.4** Approach to management of intra-abdominal abscesses including indications for consideration of percutaneous versus operative drainage. *CT,* Computed tomography; *Rx,* treatment.

safely; (2) when percutaneous drainage fails; (3) when there are multiple interloop abscesses; (4) when there is a coagulopathy; or (5) when there is infected pancreatic necrosis. Antibiotic therapy is indicated to treat inflammation in the surrounding tissue and to prevent metastatic infection and sepsis from bacteremia. Antibiotic coverage should be directed at abdominal flora, including aerobic and anaerobic organisms, even if anaerobes are not isolated.[103,112,113] The mortality rate with undrained pancreatic, hepatic, or retroperitoneal abscesses is reported to be 45% to 100%.[114] An approach to the management of intra-abdominal abscesses is outlined in Fig. 51.4.

Biliary Tract Infections

Infections of the biliary tract, including the gallbladder and the common bile duct, are usually associated with obstruction to the flow of bile. The biliary tract of healthy individuals is sterile. In acute cholecystitis, infection of the gallbladder is most commonly caused by microorganisms that are generally part of the normal intestinal flora.[116] Most biliary infections are polymicrobial, and anaerobes are more frequently isolated in the elderly and in those with common bile duct manipulation or prior biliary procedures. The source of bacteria is presumed to be the duodenum.[116] Many antibiotics achieve good levels in the bile in the absence of obstruction; however, when obstruction of the hepatic ducts or the common bile duct is present, the levels of such antibiotics are often subtherapeutic. Antibiotic therapy is adjunctive to decompression/drainage, which can be accomplished surgically, percutaneously, or endoscopically via endoscopic retrograde cholangiopancreatography. Antibiotics prevent the development of bacteremia, progression of infection, and development of liver abscesses. Cultures of blood and bile should be obtained. Empiric antibiotic therapy should generally be directed at gram-negative bacteria. In patients who are critically ill, the elderly, and those with prior common bile duct and complex biliary procedures, antianaerobic and antienterococcal therapy should also be instituted.

Acute acalculous cholecystitis is an acute inflammation of the gallbladder that occurs in the absence of gallstones. Individuals at risk include debilitated, hospitalized patients such as those who have had major surgical procedures, prolonged intensive care stays, hyperalimentation, or predisposing conditions that result in bile stasis, cholecystoparesis, or gallbladder ischemia.[116] The symptoms and findings are similar to those of calculous cholecystitis and include fever, right upper quadrant abdominal pain, nausea, vomiting, leukocytosis, and elevated liver function tests with an obstructive pattern. Diagnostic imaging modalities include ultrasonography, CT scanning, and hepatoiminodiacetic acid scanning. If an open or laparoscopic cholecystectomy cannot be accomplished because of the patient's underlying condition, then urgent percutaneous cholecystostomy should be performed. In addition, broad-spectrum antibiotics should be instituted.

Acute cholangitis is a serious infection with high morbidity and mortality rates. The most common cause of acute cholangitis is obstruction and subsequent infection associated with stones in the common bile duct, which have usually migrated from the gallbladder. Other causes of biliary tract infection include malignant obstruction of the bile duct secondary to pancreatic cancer, cholangiocarcinoma, cancer of the papilla of Vater, or portahepatic metastases. Periodically biliary strictures, pancreatitis, and infection with the intestinal nematode *Ascaris lumbricoides* can cause obstruction. Bacteria enter the bile duct from the gastrointestinal tract through the bloodstream or lymphatics.[117] The most common presenting symptoms are fever, abdominal pain, and jaundice, also known as *Charcot's triad*. Septic shock may occur if treatment is delayed. Blood cultures should be obtained, and ultrasound or CT scanning should be performed. Broad-spectrum antibiotics should be initiated, and biliary decompression accomplished either endoscopically with an endoscopic sphincterotomy, via a

percutaneous transhepatic biliary drainage procedure, or by surgical decompression. Endoscopic or percutaneous procedures may be the initial treatment of choice in patients who are seriously ill and at high risk for complications. Once biliary drainage has been accomplished, antibiotic therapy can be shortened to 2 to 3 days in mild cases and 5 to 7 days for moderate or severe cholangitis. Elective surgery, which generally includes cholecystectomy and bile duct exploration, can be deferred to a later date when the patient's condition has stabilized.

Pancreatic Infections

Although acute pancreatitis is usually a sterile inflammatory process, infectious complications may occur. In addition, a variety of viral infections (rubella; coxsackievirus type B; mumps; Epstein-Barr virus; cytomegalovirus; and hepatitis A, B, and C); *Mycoplasma pneumoniae*; and parasites such as *A. lumbricoides* have been implicated as causes of pancreatitis.[118] Some patients may develop sterile or infected pancreatic or peripancreatic necrosis, infected pancreatic pseudocysts, or abscess formation as complications of acute pancreatitis.[118] Sterile necrosis of either the parenchyma or the duct system usually occurs very early in the clinical course of severe pancreatitis. Risk for infection increases as necrosis becomes more extensive. Of patients with acute pancreatitis, only approximately 5% develop pancreatic infections; however, the highest mortality rate from pancreatitis occurs in these patients.[118] The incidence of infection increases over the first few weeks and peaks during the third and fourth weeks. Patients with extensive necrosis, those who are very ill, and those with early infection have the highest mortality rates.[118] CT scan with high-dose contrast is the most useful modality for predicting who is at risk for the development of infection. Between 40% and 70% of those with more than 30% necrosis seen on CT scan will ultimately become infected.[118] If gas bubbles are seen in the region of the pancreas, it should be presumed that infection is present. Clinically, it is extremely difficult to determine whether patients with necrotizing pancreatitis have superimposed infection because sterile pancreatic necrosis may cause leukocytosis and fever even in the absence of infection, and approximately 50% of infected patients may not show early clinical signs of infection. CT-guided fine-needle aspiration of necrotic pancreatic tissue for Gram stain and aerobic and anaerobic culture is a useful procedure to determine the presence of infection.[118] The microbiologic picture resembles that of the intestinal flora. *E. coli* is most frequently isolated, followed by *Klebsiella pneumoniae, Enterococcus* spp., *Pseudomonas* spp., and *S. aureus*.[100] Fifteen percent of organisms isolated are intestinal anaerobes. Fungal infection of necrotic pancreatic tissue is being reported with increased frequency. *Candida albicans* is the predominant fungal pathogen.[119] Treatment of pancreatic infection usually involves débridement of infected tissue or drainage of infected pseudocysts or abscesses combined with antimicrobial therapy based on cultures of the infected site. Surgical management often requires multiple staged procedures. Antibiotics that penetrate into pancreatic tissue include the carbapenems, especially imipenem, fluoroquinolones, piperacillin, advanced generation cephalosporins, and metronidazole.[101]

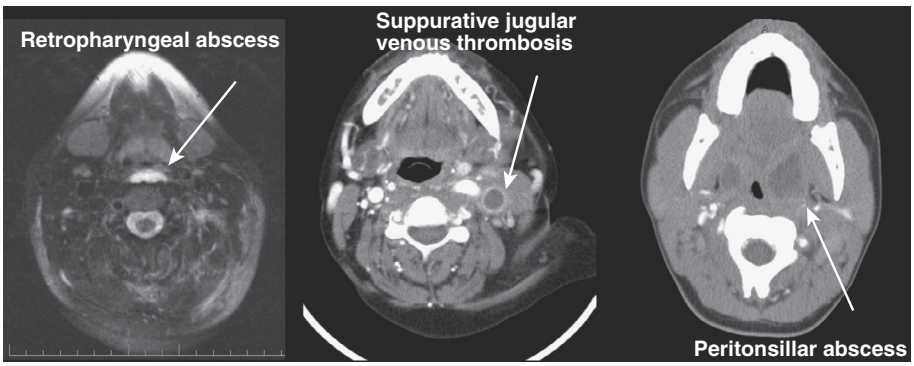
Clostridium difficile Colitis

Clostridium difficile colitis is the most common and costly health care–associated infection in the United States.[120] Manifestations of *C. difficile* infection may range from asymptomatic carriage to a fulminant, relapsing, or life-threatening colitis.[120] Antibiotics or chemotherapeutic agents have been associated with alteration of normal bowel flora and growth of *C. difficile*.[121] Diarrhea may develop while a patient is receiving antibiotics or several weeks after completion of a course of antibiotics. *C. difficile* forms spores that are resistant to heat, common disinfectants, and alcohol-based hand sanitizers, contributing to transmission in health care facilities but also in the community.[121] Only strains that produce toxins are capable of causing diarrhea or colitis.[121] Common symptoms include fever, which may be either low grade or high; crampy abdominal pain; and diarrhea, which is watery, profuse, and foul-smelling. Approximately 50% of patients have leukocytes in smears of the stool. Leukocytosis is common. The diagnosis is established by positive stool testing for *C. difficile* toxin or the presence of pseudomembranes on colonoscopy or pathology in a patient with diarrhea or radiologic evidence of ileus or toxic megacolon.[122] Complications of severe disease include electrolyte derangements, dehydration, toxic megacolon, and colonic perforation. Some patients may have little or no diarrhea but present with toxic megacolon, colonic perforation, peritonitis, or even septic shock without other localizing symptoms. An epidemic strain of *C. difficile,* NAP1/B1/027, produces an additional toxin and causes outbreaks of illness characterized by increased severity, poorer response to antibiotic therapy, and frequent relapse.[122] Treatment of *C. difficile* infection involves discontinuation of the causative antibiotic whenever possible. Oral metronidazole remains the first-line treatment for mild to moderate disease; empiric therapy with oral metronidazole should be started while testing for *C. difficile* toxin is being performed. If patients do not have a favorable response within 5 to 7 days, they should be switched to oral vancomycin. Oral vancomycin should be administered to those with severe infection or unresponsiveness to or intolerance of metronidazole. A combination of oral vancomycin and IV metronidazole should be administered to patients with severe/complicated disease. For patients who are unable to tolerate oral medication, IV metronidazole, vancomycin retention enemas, or vancomycin instillation through a colonic catheter should be administered. Fidaxomicin is more active against NAP1/B1/027 strains than vancomycin. First recurrence may be treated with metronidazole, vancomycin, or fidaxomicin but subsequent recurrences should be treated with fidaxomicin or vancomycin. The use of fecal microbial transplantation in recurrent or severe disease such as toxic megacolon has yielded favorable results with high success rates.[122] Surgery is indicated for complications such as severe toxic megacolon and colonic perforation. A variety of surgical procedures, including diverting ileostomy, cecostomy, colostomy, and subtotal colectomy, have been performed to manage toxic megacolon. Subtotal colectomy is considered the procedure of choice for the management of fulminant toxic megacolon.

Life-Threatening Infections of the Head and Neck

Ludwig's Angina, Lateral Pharyngeal Space Infections, and Peritonsillar Abscess

Infections arising from the flora of the mouth and posterior pharynx can involve the fascial planes of the neck and have the potential to progress rapidly and cause serious life-threatening illness.[123,124] In general, these infections are polymicrobial and the microbiology reflects the normal flora of the mouth. These infections spread



• **Fig. 51.5** Magnetic resonance imaging and computed tomography images showing a variety of life-threatening head and neck infections including retropharyngeal abscess (A), suppurative jugular venous thrombosis (B), and peritonsillar abscess (C). (Images provided by Dr. Joshua Brody, Department of Radiology, the Cooper Health System, Camden, NJ.)

rapidly through contiguous fascial spaces and it is essential that they be diagnosed and treated expeditiously to prevent serious sequelae such as airway obstruction, hematogenous infection, and mediastinitis. Potentially life-threatening infections of the head and neck may involve three cervical spaces. Fascial planes both separate and connect these areas. The spaces and infectious manifestations are as follows, and representative images are shown in Fig. 51.5:

1. The submandibular space may be affected by infection involving the flora of the mouth and tongue. A bilateral cellulitis of the soft tissue, known as *Ludwig's angina*, is the most important common infection in the submandibular space. Manifestations of this infection include swelling and upward displacement of the tongue and submandibular swelling. An odontogenic focus is the origin of infection in up to 90% of cases.[125,126] Other causes include oral malignancies and facial trauma. Complications include airway obstruction and mediastinitis.
2. The lateral pharyngeal space consists of an anterior and a posterior compartment divided by the styloid process. The anterior compartment is composed of musculature, and the posterior compartment has nerves and blood vessels. Infection in the anterior compartment causes soft tissue swelling that results in unilateral trismus caused by irritation of the internal pterygoid muscle, induration and swelling along the angle of the jaw, bulging of the palatine tonsil into the posterior pharynx, and systemic toxicity. Patients may present with unilateral neck or jaw pain along with ear pain and dysphagia. Pain may worsen when the head is turned because of compression of infected tissue. Dental infection, upper respiratory tract infection, pharyngitis, and otitis media with mastoiditis may all cause lateral pharyngeal space infection.[126,127] The carotid sheath is within the posterior compartment and contains the internal carotid artery, the internal jugular vein, the vagus nerve, cranial nerves IX through XII, and lymph nodes. When infection occurs in this space, patients most commonly present with signs of sepsis without localizing signs at the neck. Generally signs and symptoms are related to complications from involvement of the neurovascular structures. The most common complication is suppurative jugular venous thrombosis. Bacteremia and septic emboli may be seen. The carotid artery may also rupture. The carotid sheath is dense and not easily penetrated; thus generally arterial erosion is usually a complication of infections of longer duration (1–3 weeks). Intermittent bleeding from the mouth or nose may precede rupture.[126] Cranial nerve palsies or Horner syndrome may occur.
3. The retropharyngeal space contains an area that extends from the base of the skull to the diaphragm and hence is a portal for neck infections to extend into the chest. Infections of the retropharyngeal space or prevertebral space may spread as a result of extension through this area. Retropharyngeal space abscesses are relatively uncommon and are most often seen in young children. These abscesses usually result from odontogenic infection, penetrating trauma, or peritonsillar abscess.[126] Peritonsillar abscess, also known as "quinsy," is an unusual complication of acute tonsillitis seen predominantly in adolescents and young adults. Patients usually present with fever, pharyngitis, odynophagia, dysphagia, trismus, drooling, and a muffled voice that has been described as "hot potato" in quality. On examination there is usually swelling of the anterior tonsillar pillars and soft palate. The most common symptoms of retropharyngeal space infection in adults are fever, dysphagia, pharyngeal pain, dyspnea, noisy breathing, and stiff neck. A lateral radiograph of the neck may reveal prevertebral soft tissue swelling. Any deep neck infection has the potential to spread to the mediastinum via the retropharyngeal space.

Other potential complications of infection of the oral cavity are aspiration pneumonia and lung abscess. Because most of these infections originate from an odontogenic focus, the microbiology reflects polymicrobial oral flora and generally includes *Bacteroides* spp., aerobic streptococci, microaerophilic streptococci, peptostreptococci, fusobacteria, *Veillonella* spp., and *Actinomyces* spp. On occasion, enteric gram-negative bacilli, *P. aeruginosa,* or *S. aureus* may play a role.[127]

Deep neck infections are medical and surgical emergencies. Complications include hematogenous dissemination with sepsis syndrome, airway obstruction, necrotizing pneumonia or empyema, osteomyelitis of the mandible or maxilla, mediastinitis, or intracranial extension and cavernous sinus thrombosis. A contrast CT scan or MRI of the neck is important to help define the anatomy including the vascular structures and to indicate the potential need for drainage. Consultation should be obtained from an otolaryngologist. When patients have dyspnea, stridor, or an inability to handle secretions, an artificial airway should be established. Airway obstruction is most likely to occur in infections of the submandibular

space. Surgically obtained specimens should be cultured aerobically and anaerobically. For patients with peritonsillar abscess, high-dose IV penicillin is the therapy of choice. Other treatment options include clindamycin or ampicillin-sulbactam. Patients with peritonsillar abscess should undergo incision and drainage to prevent spontaneous rupture, aspiration pneumonia, airway obstruction, or dissection of infection into the lateral retropharyngeal space. Surgical drainage is especially important for infections involving the retropharyngeal and lateral pharyngeal space. Approximately half of cases of Ludwig's angina in the submandibular space can be cured without surgical intervention.[126]

Lemierre Syndrome

Lemierre syndrome (postanginal sepsis) is a fulminant infectious syndrome caused by acute oropharyngeal infection that is complicated by secondary septic thrombophlebitis of the internal jugular vein. It is usually seen in healthy adolescents or young adults. Most cases arise from the pharynx and peritonsillar tissues with spread through the lateral pharyngeal space leading to internal jugular thrombophlebitis and metastatic complications.[125] *Fusobacterium* spp. are most commonly implicated. Other pathogens, including MRSA, have been isolated.[125] Complications include septicemia, pneumonia, empyema, meningitis, brain abscess, and vocal cord paralysis. This infection may complicate a routine case of infectious mononucleosis.[128] The diagnostic workup should include blood cultures, a CT scan of the neck with contrast, and a chest radiograph or CT of the lungs to look for septic pulmonary emboli. Other organs or large joints may be affected with metastatic infection.[125] Therapy usually consists of surgical drainage of the focus and broad-spectrum IV antibiotic therapy with a β-lactam/β-lactamase inhibitor or a carbapenem or moxifloxacin plus clindamycin or metronidazole. Empirical treatment for MRSA should be considered until culture results are available. Fever may persist for up to 2 weeks despite appropriate antibiotics. Because this is an endovascular infection antibiotics should be given for an extended period of up to 6 weeks. When the patient is afebrile and neck pain has resolved, therapy can be de-escalated to an oral regimen. Use of anticoagulation is controversial and is usually warranted in cases with retrograde cavernous sinus thrombosis.[125]

Epiglottitis

Acute infectious epiglottitis is an inflammatory process of the epiglottis, supraglottis (in adults), and surrounding soft tissues.[125,129] Since the near disappearance of invasive *H. influenzae* infections in children following universal immunization, acute epiglottitis has become primarily a disease of adults, with an annual incidence of 1 case per 100,000 and peak incidence from ages 40 to 50 years. Adult patients present with severe pharyngitis; pain on swallowing; fever; and, less commonly, shortness of breath, hoarseness, drooling, and muffled voice. Findings on examination include marked anterior neck tenderness, lymphadenopathy, and respiratory distress.[129,130] The standard of diagnosis for suspected epiglottitis in adults is visualization of the epiglottis with flexible laryngoscopy.[125] Plain radiographs have lower sensitivity and specificity. CT may be used when flexible laryngoscopy is not an option. Treatment includes maintenance of an airway; depending on severity and rapidity of onset of symptoms, this may include emergent tracheostomy, elective intubation, or only close observation in an ICU for the mildest cases.[129] Antibiotics active against β-lactamase–producing *H. influenzae* and β-hemolytic streptococci should be administered. The role of corticosteroids is unclear.[125] Disease may be more aggressive in patients with HIV infection or other immunocompromised individuals.

Mediastinitis

Acute mediastinitis is an infection of mediastinal structures that can develop from direct extension of pharyngeal and neck infections (descending necrotizing mediastinitis), from esophageal trauma or rupture, or as a complication of cardiothoracic surgical procedures.[131,132] Descending necrotizing mediastinitis and mediastinitis from esophageal procedures have both become uncommon, and most cases are seen as complications of cardiothoracic surgery procedures or from trauma.[131] Symptoms of mediastinitis may initially be mild, but as disease progresses, patients develop chest pain; dysphagia; and respiratory distress, as well as fever, tachycardia, crepitus, and localized swelling. Sepsis is common. Patients with postcardiothoracic mediastinitis will generally have evidence of local or deep sternal wound infection. Leukocytosis is typical. Plain films may show mediastinal widening; mediastinal air-fluid levels; and subcutaneous, mediastinal, or pericardial air. CT is more sensitive than plain radiographs for diagnosis; contrast esophagography with water-soluble contrast is the optimal study for esophageal perforation.[131]

Treatment of infection related to descending neck infection or esophageal perforation requires broad-spectrum antibiotics directed at oropharyngeal flora, including streptococci, oral anaerobes, and gram-negative bacilli in addition to surgical intervention.[131,132] Mediastinitis after cardiothoracic surgery is most commonly caused by staphylococci, but a large variety of other gram-positive and gram-negative organisms have been implicated. Treatment requires surgical drainage and débridement along with antibiotic therapy.[131]

Serious Vector-Borne Infections

Rocky Mountain Spotted Fever

Tick-borne rickettsial diseases can cause severe illness and death in otherwise healthy individuals. Although the various rickettsial diseases may have distinct epidemiologic and etiologic differences, they are clinically similar.[133] Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii*, which is a gram-negative, obligate, intracellular bacterium. Infection is transmitted to humans by a variety of ticks but most frequently by the dog tick, *Dermacentor variabilis*. The incidence is greatest in the southeastern and south central United States. The vast majority of cases occur from April to September but can occur at any time of the year.[134] Reported risks for infection include living in wooded areas and exposure to dogs. *R. rickettsii* infects endothelial cells, resulting in vasculitis, which leads to the characteristic rash and involvement of the lungs, brain, and other organs.[133,135–138] After an incubation period of up to 2 weeks, patients frequently present with fever, rash, and headache.[138] Thirty percent to 40% of patients do not recall a tick bite.[133] Other symptoms include chills; myalgias; nausea; vomiting; abdominal pain that may be severe enough to mimic an acute abdomen; diarrhea; headache; photophobia; mental status changes; conjunctival injection; and, periodically, cough or arrhythmias secondary to myocarditis. The rash is classically an erythematous macular rash that appears initially on the ankles/soles and wrists/palms and spreads centripetally to the arms, legs, trunk, neck, and face.[135–137] The lesions evolve to become petechial. The rash typically appears after 2 to 6 days of illness. Although rash is the hallmark

of this illness, up to 20% of patients are "spotless" or have an atypical rash at presentation.[139] The most characteristic laboratory abnormality is thrombocytopenia. The WBC count is usually normal but more than two-thirds of patients have increased band forms. The creatine phosphokinase level may be elevated, as may transaminases and bilirubin.[133] The chest radiograph may reveal infiltrates consistent with pneumonitis or acute respiratory distress syndrome (ARDS). RMSF is frequently a severe illness. Serious complications, in addition to ARDS, include renal failure, DIC, hemophagocytic syndrome, meningoencephalitis, and gangrene.[133]

Rickettsial infections may be difficult to diagnose. The best way to establish the diagnosis of RMSF in patients with a rash is by obtaining a skin biopsy for immunohistochemical or direct immunofluorescent staining. This test has a sensitivity of 70% and specificity of 100%.[138] PCR can also be performed on tissue specimens.[133] However, both immunohistochemical staining and RMFS PCR may not be readily available in many institutions. Serologic testing by indirect immunofluorescence or enzyme-linked immunosorbent assay may also be performed. Empiric treatment with doxycycline should be instituted for suspected RMSF before laboratory confirmation of a diagnosis.[139] Distinguishing RMSF from meningococcemia is especially important. Gastrointestinal symptoms, a pulse-temperature disparity, periorbital edema, edema of the extremities, conjunctival injection, hepatosplenomegaly, and elevated serum transaminase levels are more likely in RMSF. If there is any doubt as to which infection is present, treatment for both should be instituted empirically.

Ehrlichiosis and Anaplasmosis

Illnesses that cause fever and rash are listed in Box 51.2. Other serious rickettsial diseases include ehrlichioses and anaplasmosis, caused by *Ehrlichia chaffeensis* (human monocytic ehrlichiosis), *E. ewingii* (infects granulocytes), and *Anaplasma phagocytophilum* (human granulocytic anaplasmosis), respectively.[134,138–140] They have a similar presentation, but rash is much less commonly seen than in RMSF. These infections are transmitted by ticks and are distributed across the United States and Europe. All are intracellular pathogens that infect leukocytes. Common laboratory abnormalities include leukopenia, relative lymphopenia, presence of atypical lymphocytes, eosinopenia, thrombocytopenia, and elevated transaminase levels.[140] Anemia and renal involvement are rare. PCR of serum is now the rapid diagnostic test of choice. Blood smear microscopy might reveal the presence of morulae in infected leukocytes, which is highly suggestive of anaplasmosis or, less commonly, ehrlichiosis.[140] Serologic results from paired sera can also be diagnostic. Complications include ARDS, bleeding, rhabdomyolysis, and myocarditis. Doxycycline is the treatment of choice.[138,139]

• BOX 51.2 Differential Diagnosis of Fever With Maculopapular or Petechial Rash

Rocky Mountain spotted fever
Meningococcal disease
Enteroviral infection (echovirus and coxsackievirus)
Human herpesvirus 6 infection (roseola)
Human parvovirus B19 infection (fifth disease)
Epstein-Barr virus infection
Disseminated gonococcal infection
Murine typhus
Ehrlichiosis
Group A streptococcal pharyngitis
Mycoplasma pneumoniae Infection
Leptospirosis
Secondary syphilis
Kawasaki disease
Thrombotic thrombocytopenic purpura
Drug reactions
Immune complex–mediated illness
Toxic shock syndrome
Erythema multiforme
Stevens-Johnson syndrome

Babesiosis

Babesiosis is an infection caused by intraerythrocytic protozoan parasites of the genus *Babesia*. Three species have been reported to cause human disease, of which the most common is *Babesia microti*.[140] *Babesia* spp. in the United States are transmitted by the same tick that causes Lyme disease and patients may present with coinfection. Infection can also be transmitted through transfusions and during pregnancy. Symptoms and signs are similar to malaria and include fever, chills, sweats, headache, myalgia, and arthralgia. Hemolytic anemia, thrombocytopenia, and elevated transaminase levels are the most notable laboratory findings. The elderly and those who are immunocompromised, including asplenic patients, are at higher risk for complicated disease. Severe infection may present as congestive heart failure, renal failure, acute respiratory failure, and/or DIC. The diagnosis can be established by demonstration of the classic tetrad of merozoite forms known as the "Maltese cross sign" on Giemsa-stained thin blood films, by PCR, or by serology. Azithromycin and atovaquone are recommended for uncomplicated babesiosis; clindamycin and quinine are recommended for severe disease. Red blood cell exchange transfusion is indicated for severe hemolysis, greater than 10% parasitemia, and/or hepatic, respiratory, or renal failure.[138]

Malaria

Malaria is a protozoan infection transmitted by female anopheline mosquitoes. The severity of malaria infection depends on a variety of factors, including host immunity and age and the species of malaria. Of the four main human pathogens, *Plasmodium falciparum* causes the most serious infection. Chloroquine-resistant *P. falciparum* has spread through many parts of the world. The incubation period of *P. falciparum* is approximately 12 days. It parasitizes all ages of red blood cells and causes the highest degree of parasitemia of any of the species.[141] *P. falciparum* has worldwide distribution and causes a severe illness frequently termed *blackwater fever*. Common symptoms and signs include fever, chills, headache, myalgia, arthralgia, and hepatosplenomegaly. Other symptoms include jaundice, vomiting, diarrhea, and nonproductive cough.[141] Severe malaria is a multisystem illness with a mortality rate of up to 25% in the nonimmune, untreated patient.[141] Defining criteria for severe malaria include (1) severe normocytic anemia, (2) renal failure, (3) pulmonary edema, (4) hypoglycemia, (5) shock, (6) DIC, (7) metabolic acidosis, and (8) cerebral involvement with coma or generalized seizures. Other signs or symptoms frequently present in severe disease include altered mental status, prostration, jaundice, and high-grade fever.[141] Additional laboratory features include thrombocytopenia, elevated transaminase levels, hyperbilirubinemia, evidence of coagulopathy, elevated blood urea nitrogen and

creatinine levels, and macroscopic hemoglobinuria. Levels of parasitemia are often high. Patients may develop pulmonary edema, or pulmonary edema may occur after successful treatment of parasitemia. ARDS or secondary infection with bacterial pneumonia may also occur.

The differential diagnosis is broad and includes bacterial sepsis, meningitis, rickettsial infections, pneumonia, viral hemorrhagic fever, leptospirosis, severe influenza, meningococcemia, typhoid fever, and viral hepatitis. The diagnostic test of choice has been the thick/thin peripheral Giemsa-stained blood smear, which confirms the diagnosis. Rapid diagnostic tests are excellent in patients with symptomatic malaria who have relatively high parasite densities.[142] Patients from an endemic area may occasionally present with another serious illness that may be erroneously attributed to malaria because of incidental parasitemia. Treatment for severe malaria regardless of species consists of IV quinidine-gluconate combined with IV doxycycline or IV clindamycin.[143] When using quinidine, continuous cardiac monitoring should be performed. IV or intramuscular artesunate is available as an investigational new drug through the CDC for those with severe malaria who are unable to obtain IV quinidine or who are intolerant to it, have a contraindication, or in whom therapy has failed. IV therapy should be continued for at least 24 hours and until the parasite density is less than 1% and oral therapy can be tolerated.[143] If artesunate is not available, artemether can be given. Steroids are not recommended for cerebral malaria. In addition, broad-spectrum antibiotics for bacterial sepsis and pneumonia should be given if there is concern for secondary bacterial infection.

Severe Viral Infections

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers are caused by several different families of viruses. Symptoms generally include fever, myalgia, bleeding/hemorrhage, shock, coma, seizures, and possibly renal failure. The diagnosis is established by viral isolation or serologically. Treatment involves supportive care.

The recent West African Ebola epidemic was the largest documented outbreak. There is usually an abrupt onset of symptoms 8 to 10 days after exposure. The symptoms are nonspecific and include fever, chills, myalgias, and malaise. Patients may develop a diffuse erythematous macular papular rash involving the face, neck, trunk, and arms. Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and severe watery diarrhea that was the hallmark of advanced disease in this epidemic.[144] Shortness of breath, chest pain, headache, and confusion may also occur. The conjunctiva are frequently injected. Cerebral edema has been reported and seizures may occur. Bleeding may not always occur but may manifest as ecchymosis, petechiae, and mucosal hemorrhage. The diagnosis is most commonly established by enzyme-linked immunosorbent assay or viral culture. There is no effective antiviral treatment. Administration of convalescent serum from patients who have recovered is approved for use in infected patients.[144] ZMapp is an investigational monoclonal antibody treatment that has also been used.[144] Investigational drugs and vaccines are under development.

Dengue

Dengue is the most frequent arthropod-borne viral infection worldwide.[144] Generally dengue has a geographic endemicity and is seen predominantly in Africa, South America, and Asia. Dengue is transmitted by mosquitoes and has no other reservoir except humans. It is now endemic in at least 112 countries worldwide, including many parts of the Caribbean, Mexico, Puerto Rico, and Central America, and has recently reemerged in the United States in the Florida Keys and along the Mexican border.[145] In many areas the mosquito vector is *Aedes aegypti*. This mosquito species has adapted to man-made conditions, and therefore urban transmission is frequent. The virus has four major serotypes, each with a number of genotypes.[145] Dengue is generally divided into four clinical syndromes: a mild influenza-like illness; classic dengue (characterized by fever, retro-orbital headache, severe bone pain and myalgia, maculopapular rash, and nausea and vomiting); dengue hemorrhagic fever (DHF); and dengue shock syndrome (DSS).[145] DHF or DSS may manifest after a few days of typical dengue symptoms, and classically symptoms start as the temperature normalizes.[145] Those with DHF have bleeding, petechiae, ascites, pleural effusion, and sometimes encephalopathy. Laboratory features include hemoconcentration, leukopenia, elevated transaminase levels, and thrombocytopenia.[145] DHF and DSS are severe forms of dengue.[145] The differential diagnosis includes many of the infectious entities also in the differential diagnosis of malaria. Noninfectious illnesses in the differential diagnosis include hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Diagnosis can be established serologically or by detection of ribonucleic acid by quantitative reverse transcription PCR.[145] Treatment is supportive.[145]

Hantavirus Pulmonary Syndrome

Acute infections caused by species of hantavirus are transmitted to humans from rodents and are characterized by nephritis and hemorrhage or by a syndrome of acute noncardiogenic pulmonary edema.[146] Four hantaviruses are associated with hantavirus pulmonary syndrome. This syndrome was first recognized in the southwestern United States and is caused by Sin Nombre virus. Rodents, especially deer mice, are the host. Transmission to humans occurs by inhalation of aerosols of rodent urine or feces. Initial symptoms of hantavirus pulmonary syndrome resemble those of influenza and consist of fever, myalgia, headache, and gastrointestinal symptoms. Two to 15 days later, acute noncardiogenic pulmonary edema and shock develop.[146] Laboratory findings at this stage include leukocytosis, hemoconcentration, and thrombocytopenia. Chest radiographic findings include increased vascular markings consistent with pulmonary edema, bilateral infiltrates, and pleural effusions.[146] Treatment is supportive and consists of ventilator support and treatment of shock. This syndrome has a high mortality rate of 50% to 70%, but those who survive improve rapidly after 5 to 7 days and often have complete recovery within 2 to 3 weeks.

Influenza

Influenza results from infection with influenza A or B virus. Infection occurs in yearly epidemics, typically during the winter in temperate climates, with occasional worldwide epidemics referred to as *pandemics*, which occur when there is antigenic shift (a major antigenic change resulting in a new subtype of influenza A).[147] These viruses are spread from person to person primarily through coughing and sneezing.[147] Onset of symptoms is abrupt and occurs after an incubation period of a day or two.[147] Symptoms include fever, chills, headache, myalgia, sore throat, and malaise.[147]

Respiratory symptoms, especially a dry cough, are usually present. As systemic signs and symptoms decrease, respiratory complaints become more prominent. Of these, cough is the most frequent and may persist 1 to 2 weeks after fever resolves. Leukocytosis is common early in the illness, and mild leukopenia may be observed later. Most cases are not associated with any significant complications, but when complications do occur, pulmonary complications are the most frequent. Two types of pulmonary complications are recognized: primary influenza viral pneumonia and secondary bacterial pneumonia.[147,148] Primary influenza viral pneumonia occurs mainly in individuals with cardiovascular disease or in pregnant women. Rapid progression of fever, cough, dyspnea, and hypoxemia usually occurs. Chest radiographs reveal bilateral findings consistent with pulmonary edema. Patients may develop ARDS. Culture of the sputum fails to reveal significant bacteria, whereas molecular diagnostic tests and viral cultures will demonstrate influenza virus. Severe influenza viral pneumonia requires intensive monitoring and support. The mortality rate is high.

Secondary bacterial pneumonia is more common than primary viral pneumonia. It occurs most often in the elderly or those with preexisting pulmonary disease. Following a classic influenza syndrome and a period of improvement of a few days, there is recrudescence of fever and cough accompanied by sputum production and consolidation on chest radiograph. Gram stain and culture of sputum most often demonstrate *S. pneumoniae*, *H. influenzae*, or *S. aureus*. Other rare complications of influenza include Reye syndrome, which is an often fatal CNS and hepatic complication; myositis; transverse myelitis; myocarditis; and pericarditis.[147] Influenza virus is readily isolated from nasal or throat specimens, sputum, or tracheal secretions in the first 2 or 3 days of illness. Inhaled and IV zanamivir, oral oseltamivir, and IV peramivir are active against influenza A and B viruses and are effective in treating acute influenza if started early in the illness.[147] Secondary bacterial pneumonia should be treated with antibiotics. Respiratory syncytial virus is emerging as an important cause of serious illness in the elderly and high-risk adults with clinical manifestations, length of hospital stay, use of ICU, and mortality rates similar to influenza.[149]

Potential Agents of Bioterrorism

Potential agents of bioterrorism include rare infections that may occur sporadically in specific epidemiologic settings, such as anthrax, as well as diseases considered eradicated, such as smallpox. Features of these illnesses are their potential to cause illness and death, the potential for large-scale dissemination, their ability to cause public disruption, and the requirement for specific public health interventions in the setting of an outbreak. Illness is generally severe, and infected patients are likely to require admission to critical care units. Recognition of these syndromes by clinicians is crucial to triggering the appropriate medical, public health, and governmental response.

Anthrax

Bacillus anthracis, the causative agent of anthrax, is an aerobic, gram-positive, sporulating bacillus. When human infection occurs, spores germinate in blood and tissue. Human infection can be of four types: (1) cutaneous, (2) inhalational, (3) gastrointestinal, and (4) injectional.[150] The cutaneous form is the most common and characteristically appears as a painless papule that evolves to a vesicular stage and then to a depressed black eschar surrounded by a ring of vesicles. Untreated, it carries a mortality rate of less than 1%.[150]

The inhalational form is the form most likely to be encountered in the critical care setting. After an incubation period of generally 1 to 7 days but potentially up to 60 days, patients present with fever, malaise, dry cough, and an influenza-like illness. Progression to severe respiratory distress and septic shock occurs. The hallmark of this infection is a hemorrhagic mediastinitis.[150] The mortality rate has been as high as 85%. In virtually all cases, chest radiographs are abnormal and show either a widened mediastinum or pleural effusions. CT scan is particularly sensitive in detecting mediastinal changes.[150] Blood culture results are positive in 70% of cases. Clinical suspicion should be raised by the sudden appearance of multiple cases of severe influenza-like illness with a fulminant course and high mortality rates. The diagnosis is generally established by culturing the organism from blood, CSF, pleural fluid, or vesicular fluid; by PCR; or by biopsy. Therapy for systemic infections is initially empiric and consists of the combination of an oral fluoroquinolone, linezolid, and meropenem if meningitis is suspected and a fluoroquinolone plus clindamycin or linezolid if meningitis has been ruled out.[150] Steroids should be initiated for meningitis.[150]

Smallpox

Smallpox is caused by the variola virus. This serious infection is highly contagious and fatal in about 30% of cases. Two major clinical forms exist; the most common is variola major. This is a severe form that produces extensive rash and high fever. After an incubation period of 12 to 14 days, patients develop high fever, malaise, headache, myalgias, and vomiting. The rash appears initially as small intraoral spots and within 24 hours develops on the face, then spreads to the legs, feet, arms, and hands.[150] The rash appears as papules, which are filled with a thick, opaque fluid and have a depressed center. They evolve into pustules, which are raised, round, and firm to the touch. The differential diagnosis includes varicella. Treatment is supportive. The antiviral agent cidofovir may have activity.[150] Smallpox is contagious; therefore airborne precautions should be used.

Plague

The causative agent of plague is *Yersinia pestis*, an aerobic gram-negative bacillus. The three clinical forms are (1) bubonic, (2) pneumonic, and (3) septicemic.[150] Pneumonic plague is transmitted person to person through inhalation of contaminated aerosols and is highly contagious. After an incubation period of 2 to 3 days, patients develop fever, chills, headache, hemoptysis, dyspnea, stridor, cyanosis, respiratory failure, circulatory collapse, and bleeding.[150] Diagnosis is based on clinical suspicion and confirmed by culture. Treatment is with streptomycin, gentamicin, or doxycycline.[150]

Tularemia

Tularemia is caused by *Francisella tularensis*, which is a gram-negative coccobacillus. Types of infection include ulceroglandular, typhoidal, and pneumonic. If there were to be an intentional release of this agent, infection would likely occur via the aerosol route.[150] Symptoms include cough, substernal pain, abdominal pain, prostration, fever, chills, and headache. Diagnosis is established by culture onto special media, by serologic testing, or by PCR. Treatment is with streptomycin or gentamicin.

Key Points

- Of patients with bacterial meningitis, 95% have at least two of the following symptoms: fever, headache, stiff neck, and altered sensorium.
- Morbidity and mortality rates of bacterial meningitis are decreased with prompt administration of antibiotics.
- When dexamethasone is administered as adjunctive therapy for bacterial meningitis, it should be given before or concurrent with initial antibiotic doses.
- The standard for diagnosis of herpes encephalitis is PCR of CSF, and treatment for suspected herpes encephalitis should be continued until PCR results are back.
- *S. aureus* has become the most common cause of bacterial endocarditis, and *S. aureus* endocarditis is associated with a high risk of complications and high mortality rates.
- Major indications for surgery in acute endocarditis include congestive heart failure, persistent bacteremia and sepsis, ongoing emboli with appropriate antibiotic therapy, and local valvular complications such as dehiscence and perivalvular abscess.
- Staphylococcal and streptococcal toxic shock syndromes are mediated by systemic effects of bacterial exotoxins that trigger massive release of cytokines.
- Necrotizing fasciitis, although uncommon, is a severe infection that causes necrosis of subcutaneous tissue and fascia and requires prompt identification and therapy to minimize morbidity and mortality rates.
- CA-MRSA can cause life-threatening illness, including necrotizing skin infections, pneumonia, and sepsis.
- Empiric antibiotic therapy for bacterial peritonitis should be directed at gram-negative bacillary organisms and anaerobes.
- The presence of an intra-abdominal abscess should be entertained in febrile patients without any obvious cause of fever or in the seriously ill patient who is receiving corticosteroid therapy.
- An epidemic strain of *C. difficile* has enhanced toxin production and causes increased severity of illness, poorer response to therapy, and frequent relapse.
- Serious infections of the head and neck are polymicrobial and most frequently have an odontogenic source.
- Serious complications of influenza include primary influenza viral pneumonia, bacterial pneumonia, Reye syndrome, and myocarditis/pericarditis.

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Review Questions

1. Which of the following is correct about the use of adjuvant dexamethasone for treatment of bacterial meningitis?
   - **a.** Adjuvant dexamethasone reduces mortality in *Listeria* meningitis.
   - **b.** Corticosteroids should be administered within 12 hours of starting antibiotic therapy.
   - **c** Dexamethasone has been shown to be of benefit for treatment of health care–associated bacterial meningitis.
   - **d.** Dexamethasone has been shown to decrease hearing loss and other neurologic sequelae in patients with pneumococcal meningitis.

   Answer: d. The strongest evidence for benefit of dexamethasone in bacterial meningitis has been decreased rates of hearing loss and other neurologic sequelae in confirmed pneumococcal meningitis; the mortality benefit in pneumococcal disease has not been as clearly demonstrated. The benefit of steroids has not been shown in adults for meningitis owing to any other organism and is not recommended for treatment of postneurosurgical or ventriculostomy–associated meningitis as these are rarely due to pneumococcus. Steroids should be administered before or concurrent with the first doses of antibiotics; there are no studies demonstrating benefit if given after antibiotic therapy is started.
2. Which of the following is correct about the diagnosis of suspected bacterial meningitis?
   - **a.** Noncontrast head computed tomography (CT) scan should be done before a lumbar puncture because of the risk of herniation.
   - **b.** A cerebral spinal fluid (CSF) white blood cell (WBC) count of less than 100 cells/mm^3 with a lymphocytic predominance excludes a diagnosis of bacterial meningitis.
   - **c.** Gram staining of spun CSF is positive in 60% to 90% of cases of bacterial meningitis
   - **d.** Initiation of antibiotic therapy for suspected meningitis before lumbar puncture does not significantly decrease the yield of CSF cultures.

   Answer: c. The Gram stain of CSF is a very useful diagnostic study in management of bacterial meningitis and is reported to be positive in 60% to 90% of confirmed cases of bacterial meningitis; the yield on Gram stain is highest for pneumococcal disease. Lumbar puncture without prior CT scan has been demonstrated to be safe in many patients with bacterial meningitis without specific features suggesting a higher risk of focal mass lesions with higher risk of herniation such as new-onset seizures or new focal findings. Although CSF WBC counts of greater than 100 cells/mm^3 are typically found in most patients with bacterial meningitis, a CSF WBC count of less than 100 cells/mm^3 does not exclude the diagnosis and a very low CSF WBC count can be seen with overwhelming infections. CSF profiles in meningitis typically show neutrophilic predominance, but early during infection the profiles may demonstrate a lymphocytic predominance. Administration of antibacterial therapy before lumbar puncture has been reported to decrease the likelihood of a positive CSF culture by as much as 20%.
3. Which of the following is correct regarding viral encephalitis?
   - **a.** Herpes simplex virus type 2 causes about 10% of cases of infectious encephalitis in the United States.
   - **b.** Rabies encephalitis is a uniformly fatal infection.
   - **c.** West Nile virus meningoencephalitis can present with flaccid paralysis or with parkinsonian-like tremors.
   - **d.** A specific etiology will eventually be found in over 75% of patients presenting with infectious encephalitis.

   Answer: c. The manifestations of West Nile neuroinvasive disease include aseptic meningitis, meningoencephalitis, and polio-like flaccid paralysis syndromes. Parkinsonian-like tremors can be a prominent feature of West Nile meningoencephalitis. The incidence of neuroinvasive disease increases with age. Even after extensive diagnostic studies, the etiology remains undiagnosed in more than half of patients presenting with presumed infectious encephalitis. Herpes simplex type 1 infection is the cause of up to 10% of diagnosed cases of infectious encephalitis. Herpes simplex type 2 is associated with aseptic meningitis but much less commonly is a cause of encephalitis. Rabies encephalitis was previously considered uniformly fatal but there have been several recent documented cases of survival after aggressive intensive care protocols.
4. Which of the following is an indication for urgent valve replacement in patients with bacterial endocarditis?
   - **a.** Infection caused *Enterococcus faecalis*
   - **b.** Recurrent septic pulmonary emboli while receiving treatment
   - **c.** Refractory congestive heart failure and valvular insufficiency
   - **d.** Septic embolus to the middle cerebral artery with hemorrhage shown on CT scan

   Answer: c. The most common indication for urgent valve replacement in infectious endocarditis is refractory congestive heart failure and valvular insufficiency. Although early surgery may be indicated for fungi and multidrug-resistant bacterial organisms, patients with more typical endocarditis pathogens such as staphylococci, streptococci, and *Enterococcus faecalis* would generally need to either be failing therapy or have other specific indications to consider urgent surgical therapy. Unlike systemic emboli in left-sided endocarditis, even recurrent pulmonary emboli are not a definitive indication for surgery for right-sided disease. Hemorrhagic embolic brain lesions would be a contraindication to immediate surgical intervention; in such cases surgery is usually deferred for at least 4 weeks.
5. Which of the following statements is correct regarding the role of echocardiography in the diagnosis and management of infective endocarditis?
   - **a.** Echocardiographic findings are a key component of the modified Duke Criteria for diagnosis of infective endocarditis.
   - **b.** Transesophageal echocardiography (TEE) is preferred to transthoracic echocardiography (TTE) as the initial study for diagnosis of infective endocarditis
   - **c.** The sensitivity of TEE is equivalent to TTE for diagnosis of prosthetic valve endocarditis.
   - **d.** A negative TEE study in a patient with a high suspicion for the diagnosis of infective endocarditis does not need to be repeated.

   Answer: a. The diagnosis of endocarditis relies very heavily on echocardiographic findings and is one of the two major criteria in the modified Duke Criteria, in addition to blood culture results. Both the American Heart Association and European Cardiology Society guidelines recommend TTE as the initial screening test for diagnosis of infective endocarditis, but the sensitivity of TEE is higher in most circumstances; when suspicion remains moderate to high and TTE is either negative

or not definitive, TEE should be pursued. The sensitivity of TEE is 90% for prosthetic valve infective endocarditis, which is much higher than the 50% to 70% sensitivity reported for TTE. In patients for whom there is persistent high suspicion for infective endocarditis even after a negative TEE study, a repeat TEE study in 5 to 7 days is reasonable.

6. Which of the following is correct regarding staphylococcal and streptococcal toxic shock syndromes?

a. Antibiotic therapy is a key component of the management of staphylococcal toxic shock syndrome due to super-absorbent tampons.

b. Therapy for toxic shock syndrome caused by severe group A streptococcal infections may include antibiotics that decrease bacterial toxin production such as clindamycin.

c. The incidence of staphylococcal toxic shock syndrome has not changed in the United States in the past 3 decades.

d. The rash of staphylococcal toxic shock syndrome is most commonly petechial or purpuric.

Answer: b. Antibiotics such as clindamycin and linezolid shut down production of bacterial exotoxins in streptococci and are recommended for treatment of severe group A streptococcal skin and soft tissue infections and for suspected group A toxin-mediated syndromes. The role of antibiotic therapy for staphylococcal toxic shock syndrome is less clear than for streptococcal toxic shock syndromes as toxin is often produced by colonizing and not infecting organisms such as in tampon-associated toxic shock syndrome. The incidence of tampon-associated toxic shock syndrome, which was most associated with highly absorbent brands of tampons, has declined markedly since the first descriptions of this syndrome in the 1980s. Rash is a prominent component of the clinical manifestations of staphylococcal toxic shock syndromes and is most commonly a scarlatiniform or erythroderma-like rash that progresses to desquamation.

52

Acute Kidney Injury

THOMAS L. SALAZER AND IRAM AQEEL

CHAPTER OUTLINE

Definition
- Epidemiology

Pathogenesis
- Prerenal Acute Kidney Injury
- Postrenal Acute Kidney Injury
- Intrinsic Acute Kidney Injury

Clinical Manifestations
- Retention of Filtration Markers and Formulas as an Assessment of Glomerular Filtration Rate

Diagnostic Approach
- General Aspects
- Urinalysis and Urine Indices
- Radiologic Imaging
- Other Laboratory Testing
- Renal Biopsy

Prevention
- Maintenance of Renal Perfusion
- Avoidance of Nephrotoxicity
- Prevention of Contrast Nephrotoxicity

Management of Established Acute Kidney Injury
- General Aspects
- Management of Volume Status
- Preventing, Monitoring, and Treating Complications
- Medication Dosing Considerations
- Nutritional Considerations
- Renal Replacement Therapy

Prognosis and Outcomes

Definition

Acute kidney injury (AKI) is the sudden loss of kidney function resulting in the inept excretion and accumulation of metabolic waste products such as urea and nitrogenous waste products with associated dysregulation of water and electrolytes. AKI is not a specific disease entity but rather represents a spectrum of renal dysfunction that can occur as a result of hemodynamic factors such as decreased renal perfusion from dehydration, partial or complete urinary tract obstruction, or parenchymal renal injury. The term *acute kidney injury* has largely replaced prior terminology of acute renal failure. This new terminology reflects an attempt to broaden recognition that even smaller decreases in renal function that do not result in overt organ failure may still represent significant clinical changes that are associated with increased morbidity and mortality.

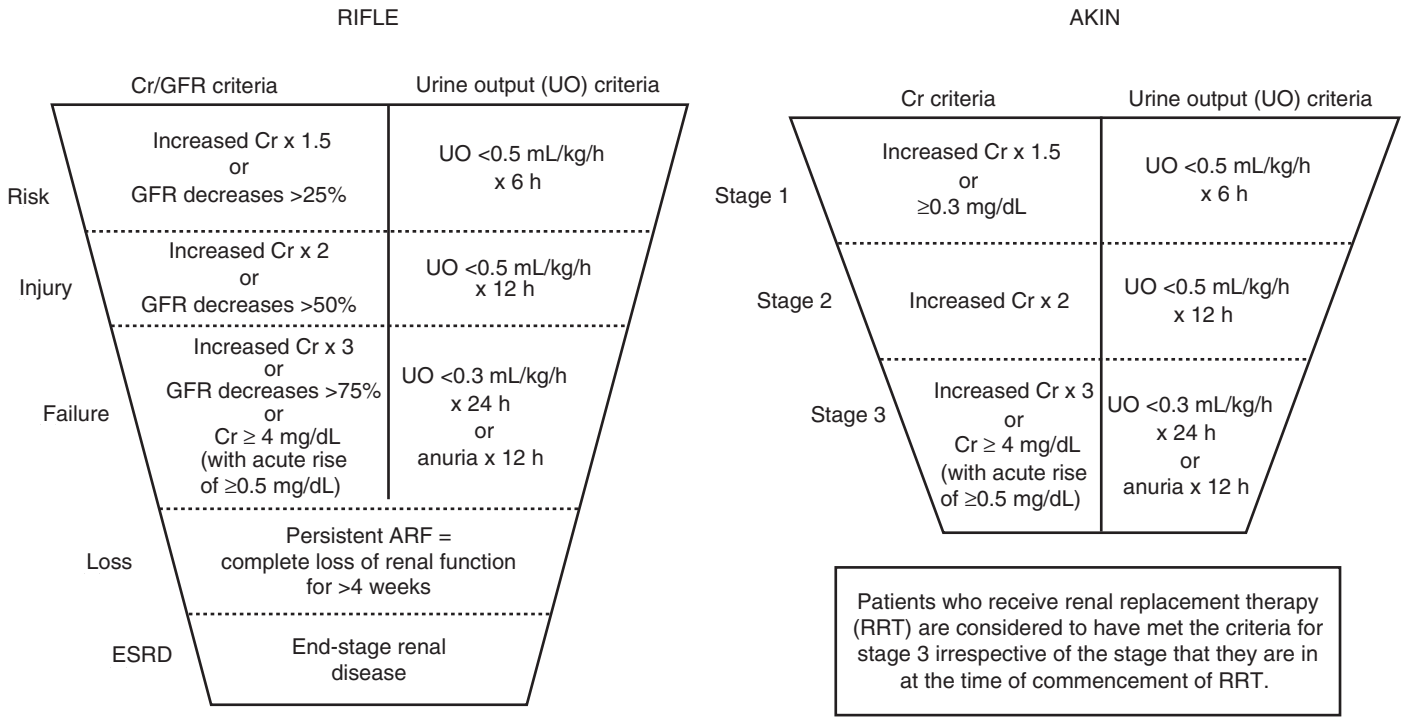
The loss of kidney function has traditionally been defined by the accumulation of metabolic waste products, most notably blood urea nitrogen (BUN) and creatinine. However, creatinine, the classical biomarker for the assessment of glomerular filtration rate (GFR), has several limitations. Creatinine is only a reliable marker of GFR if the patient is in a steady state. Until recently, there has been a lack of consensus on the quantitative definition of AKI. This lack of uniformity has formerly confounded interpretations of clinical studies for diagnosing, classifying, and assessing outcomes of AKI.

Since 2004, three consensus definitions have been developed to improve uniformity in the diagnosis of AKI in critically ill patients. In 2004, the Acute Dialysis Quality Initiative (ADQI) work group developed a consensus definition best known by the acronym RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease).[1]

The classification was based on three diagnostic indices: changes in serum creatinine from baseline, GFR, and urine output. There were three graded levels of kidney dysfunction (risk, injury, and failure) based on the degree of creatinine elevation or the change in GFR or urine output and there were two outcome measures (loss and end-stage renal disease). It was subsequently reported that the RIFLE criteria correlated with prognosis with a stepwise increase in the relative risk of death in patients who met the RIFLE criteria for various stages of AKI.[2] However, several notable limitations with the RIFLE criteria were noted. The change in serum creatinine concentration did not correlate with the percent decrease in GFR cited by the RIFLE criteria classification.[3] Additionally, the relative risk for mortality by RIFLE stage based on the change in serum creatinine did not correlate well with the mortality risk by RIFLE stage based on the decline in urine output criteria.

In 2007, in an effort to further define uniform standards for diagnosing and classifying AKI, the Acute Kidney Injury Network (AKIN) diagnostic criteria were developed. They served as a modified version of the RIFLE criteria. They provided both diagnostic criteria and a staging system for AKI. The diagnostic criteria used were both creatinine and urine output. However, as noted in Fig. 52.1, there were several notable differences between the RIFLE and AKIN criteria.[4]

The AKIN criteria added an absolute rise in creatinine of 0.3 mg/dL or more to the AKIN diagnostic criteria in stage 1. The serum creatinine changes had to occur within 48 hours as opposed to the RIFLE criteria with which changes in creatinine could occur up to 7 days, and the loss and end-stage renal disease (ESRD) were removed from the AKIN criteria as they were considered



• **Fig. 52.1** The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) and AKIN (Acute Kidney Injury Network) criteria. *ARF,* Acute renal failure; *Cr,* creatinine; *ESRD,* end-stage renal disease; *GFR,* glomerular filtration rate. (From Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN—time for reappraisal. *Crit Care.* 2009;13:211.)

outcomes, not stages. Furthermore, because transient oliguria may be an appropriate physiologic response to intravascular volume depletion without any notable change in renal function,[5] the diagnostic changes for urine volume could only be applied after volume status was optimized. Urinary tract obstruction also needed to be excluded in the AKIN criteria if oliguria was used as the only diagnostic criterion. Despite these modifications to the initial RIFLE criteria, the AKIN criteria failed to materially change the classification of AKI or help predict hospital mortality.

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines proposed a modified version of the RIFLE and AKIN criteria.[6] They included a revision to the AKI definition but retained the AKIN staging criteria. In the KDIGO definition for AKI, the time frame for an absolute increase in the serum creatinine of 0.3 mg/dL or higher was maintained at 48 hours, similar to the AKIN definition, while the time frame for a 50% or higher increase in serum creatinine of 7 days was maintained from the RIFLE criteria. The KDIGO criteria did not use changes in GFR for staging; only serum creatinine and urine output were used. The KDIGO criteria also did not stipulate that adequate fluid resuscitation should have been undertaken and urinary tract obstruction be excluded before applying the criteria. Similar to the RIFLE and AKIN criteria, KDIGO criteria suggested that patients be classified to the highest stage of achieved renal dysfunction.

Overall, there is a general consensus among experts that a standardized definition for AKI has epidemiologic benefits as well as clinical benefits for both preventative and therapeutic research.[7] However, as with both the RIFLE and AKIN criteria, the potential clinical usefulness at the bedside with this latest definition and classification of AKI by KDIGO has been questioned.[8–10]

For example, using creatinine as a biomarker for determining AKI has clear limitations; it can result in both false-positive and false-negative diagnosis. Serum creatinine changes may not reflect an actual GFR in the non-steady state. It has been shown that the true GFR after an acute renal ischemic insult will drop rapidly but the serum creatinine peak rise could take many hours to several days before a steady state is reached.[11] Additionally, it has recently been demonstrated that inherent laboratory and biologic variabilities of serum creatinine in the same patient can result in a false-positive rate of AKI diagnosis in up to 30.5% of patients with baseline creatinine values greater than 1.5 mg/dL.[12] Conversely, a biopsy study found that 35% of cases had acute diffuse parenchymal pathology despite not meeting the KDIGO criteria for AKI secondary to a slow rise in serum creatinine.[13] This latter study suggests that using creatinine alone as a marker for parenchymal renal injury could underestimate patients with significant glomerular pathology. Similarly, the use of urine output criteria for a diagnosis of AKI has not been shown to independently predict mortality.[14] There has been an overall concern that despite the increased awareness of AKI using the modified KDIGO definition, this may result in a marked increase in nephrology referrals and as such, it has been recommended that appropriate discretion be used to guide the clinical relevance of an AKI diagnosis.[15]

Despite these potential limitations in using the KDIGO classification of AKI, its use has been endorsed by the National Kidney Foundation and has generally replaced the prior RIFLE and AKIN criteria in diagnosing AKI; its use in clinical practice is now considered the consensus standard. The clinical utility of an early AKI diagnosis is to optimize hemodynamics, promptly treat the underlying cause, and avoid potential nephrotoxins. In the future, more sensitive and specific biomarkers of AKI will likely be

• BOX 52.1 Factors Contributing to the Variability in Incidence of Acute Kidney Injury

Development before hospitalization
Specific definition used for describing acute kidney injury
Location of admission (general medical/surgical ward vs. intensive care unit)
Diagnosis and clinical characteristics (after coronary artery bypass grafting vs. acute ischemic stroke vs. intracranial hemorrhage)

• BOX 52.2 Causes of Intravascular Volume Depletion Associated With Prerenal Azotemia

Decreased in water intake
Gastrointestinal hemorrhage
Diarrhea
Vomiting
Diuretics
Polyuric states (e.g., diabetes insipidus)

developed that would certainly change, alter, or create a new paradigm to current consensus definitions, which hopefully would improve patient outcomes and cost-effectiveness in the delivery of care in patients who develop AKI.

Epidemiology

AKI is a growing concern for health care worldwide and establishing an accurate reported incidence of AKI is important for health care policy, quality initiatives, and the design of clinical trials to enhance clinical decision making. The reported incidence of AKI has been variable and dependent on several factors (Box 52.1).

Despite the limitations of much published data as being retrospective and single-center studies, several large epidemiologic studies have reported an overall increased incidence of AKI over the past several decades in the United States.[16–18] Using data from the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS) representing more than 18 million hospitalizations from 1049 U.S. hospitals, there has been an annual increase of reported AKI of 14% per year from 2001 to 2011, which correlates to a near fivefold increase in AKI during this time frame.[17] In a study conducted by the Centers for Disease Control and Prevention using data from the National Hospital Discharge Survey in the United States, AKI among hospital patients increased from 18 per 100,000 population in 1980 to 365 per 100,000 population in 2005.[15] Data from Kaiser Permanente of northern California reported a rise in incidence for the cohort of AKI not requiring renal replacement therapy (RRT) from 323 to 522 cases per 100,000 person-years between 1996 and 2003.[16]

For hospitalized patients, estimates of the incidence of AKI range from 5% to 7% for the overall hospital population, and 10% to 35% for ICU patients; 4% to 6% of the latter cohort require RRT.[19–21] The variety of ICU settings has also had variable recorded rates of AKI. In a retrospective observational study of more than 600,000 patients admitted to 191 Veterans Health Administration hospitals, the overall frequency of AKI ranged from 9% to 30% with variable rates depending on the primary ICU site of care: 12% for neurosurgical ICU admissions, 20% to 25% for orthopedic and abdominal surgery–related ICU admissions, and 32% in patients undergoing cardiovascular surgery.[22] As expected, the earliest stages of AKI (stages 1 and 2) have a higher reported incidence across these various ICU settings than more advanced stages (stage 3).[23] Varying rates of AKI incidence were similarly reported by Khatri and colleagues in the ICU setting in a single-center sample of more than 500 patients with either acute ischemic stroke or acute intracranial hemorrhage; the incidence of AKI was 14% and 21%, respectively.[24] AKI and dialysis requiring AKI after cardiac surgery has been associated with increased mortality.[25] The reported AKI incidence in this cohort has been reported to be variable at 5% to 10%[26,27]; a recent meta-analysis including more than 242,000 patients after cardiopulmonary bypass surgery reported an AKI incidence of 18.2%.[28] High incidence rates of AKI have been reported after gastric bypass surgery,[29] burns,[30] and trauma[31] and in recipients of living allogeneic bone marrow transplants in whom AKI incidence has been reported between 20% and 73%.[32]

In an attempt to review the worldwide incidence of AKI, a meta-analysis by Susantitaphong and colleagues reviewed 312 studies that included more than 49 million cases of patients primarily in the hospital setting. For the 154 studies that included 3.5 million cases of AKI using the KDIGO definition, 1 in 5 adults and 1 in 3 children worldwide developed an AKI episode during a hospital episode of care.[33] The AKI-EPI study, a cross-sectional study specifically evaluating the worldwide incidence of AKI in the ICU that included 1802 ICU patients, reported an AKI frequency of greater than 50%.[34]

Sepsis and major abdominal surgery are the two most common predisposing risk factors for AKI[35] in critically ill patients; additional contributing factors include baseline chronic renal failure (CRF), cardiogenic shock, liver failure, and medication-associated toxicity. The metabolic syndrome and obesity are also risk factors for AKI.[36] Both preoperative and postoperative proteinuria have been reported as risk factors for patients with AKI undergoing cardiac surgery.[37,38]

Pathogenesis

AKI has traditionally been categorized into either prerenal, postrenal, or intrinsic causes with multiple etiologies in each category. The two most common causes of AKI in the hospital setting are prerenal azotemia and acute tubular necrosis (ATN), accounting for up to 30% to 75% of cases.[39] Although this classification is helpful in forming a differential for AKI, oftentimes multiple causes with differing pathophysiologic features for AKI occur in the same patient.

Prerenal Acute Kidney Injury

Prerenal azotemia results from a decrease in effective blood volume, resulting in a decrease in glomerular perfusion and GFR. There are several mechanistic etiologies, including intravascular volume depletion (hypovolemia), decreased cardiac output, intrarenal hemodynamic changes, obstruction of the renal arteries, and an increased renal venous pressure. Prerenal azotemia from intravascular volume depletion remains the most common etiology for AKI in the hospital setting and typically remains the most easily treatable and reversible (Box 52.2).

Typically, with early treatment of prerenal azotemia, parenchymal renal injury does not occur. However, with delayed treatment, kidney injury with resultant ATN can occur primarily through ischemic effects on the renal tubules in the corticomedullary

junction, which have the least blood flow and the highest oxygen demand.

Autoregulatory processes often occur that attempt to mitigate potential end-organ renal injury from prerenal azotemia. For example, in patients in whom systemic hypoperfusion and a drop in mean arterial pressure develop, both arterial and cardiac baroreceptors are activated, which increases sympathetic neural tone and release of both renin and antidiuretic hormone. These physiologic responses result in arteriolar and venular constriction with a subsequent increase in systemic blood pressure and cardiac output. The release of renin activates the renin-angiotensin-aldosterone system. Renin release helps cleave angiotensinogen to angiotensin I. Angiotensin-converting enzyme cleaves angiotensin I to angiotensin II; the latter stimulates both afferent and efferent arteriolar vasoconstriction. The afferent vasoconstrictor effects are opposed by the vasodilatory prostaglandins. The net effect is to maintain the tone of the afferent arteriole while constricting the efferent arteriole to maintain intraglomerular pressure and glomerular ultrafiltration. When these physiologic regulatory processes are insufficient or overwhelmed, GFR decreases and AKI ensues.

Although the majority of causes of prerenal AKI are secondary to decreased renal perfusion, altered intrarenal hemodynamics from certain vasoactive medications may decrease renal blood flow without decreasing effective circulating intravascular volume. Calcineurin inhibitors, such as cyclosporine and tacrolimus, may cause renal vasoconstriction and subsequent AKI that is often exacerbated in hypovolemic states. Nonsteroidal antiinflammatory drugs (NSAIDs) decrease vasodilatory prostaglandin production through their inhibitory effects of cyclooxygenase. These vasodilatory prostaglandins often help maintain renal blood flow and GFR by afferent arteriolar vasodilatory properties. Use of NSAIDs in patients with baseline prerenal azotemia, congestive heart failure (CHF), or with underlying chronic kidney disease (CKD) are at increased risk for AKI. Medications with specific inhibitory effects on the renin-angiotensin-aldosterone system may also induce an AKI. Typically, intrarenal formation and actions of angiotensin II help to maintain GFR through vasoconstrictive effects on the efferent arteriole. This compensatory autoregulatory mechanism is especially helpful when renal perfusion is decreased. Renin inhibitors, angiotensin-converting enzyme inhibitors (ACEs), and angiotensin receptor blockers (ARBs) may induce an AKI either through their direct inhibition of angiotensin II production or its action. The risk of AKI increases with underlying prerenal azotemia, CKD, renal artery stenosis, or CHF.

Prerenal AKI can also result from an increase in renal venous pressure. This is typically seen in patients with abdominal compartment syndrome (ACS); the latter typically occurs in trauma patients with an incidence ranging from 1% to 14%[40–42] with an overall 4.2% ACS incidence of all medical and ICU patients.[43] Intra-abdominal pressure (IAP) is the steady-state pressure within the abdominal cavity. For most critically ill patients, an IAP between 5 and 7 mm Hg is considered normal,[44] although patients with high body mass index and pregnancy may have higher IAP of up to 10 to 15 mm Hg without any untoward effects.[45] Typically, intraabdominal hypertension is defined as a sustained IAP of 12 mm Hg or higher and ACS is defined by a persistent elevation in IAP of 20 mm Hg or higher with associated end-organ dysfunction.[45,46] The primary renal mechanism of ACS is renal vein compression resulting in an increase in resistance that impedes renal venous drainage.[47,48] Similar to other prerenal states, spot urine sodium and chloride levels are decreased, whereas plasma renin activity, aldosterone, and antidiuretic hormone levels are increased.[49] With progressively higher IAPs, there is a further decrease in urine volume.[50] The progressive renal effects, if left untreated, are a decrease in renal perfusion followed by oliguria, anuria, and AKI. There is general consensus that surgical decompression is indicated for ACS.[51]

Postrenal Acute Kidney Injury

Urinary tract obstruction refers to an interference of normal urine flow anywhere along the genitourinary system from the renal pelvis extending to the urethral meatus. The classification is often based on the location of the obstruction—either intrinsic (occurring within the urinary tract and encompassing both intramural and intraluminal etiologies) or extrinsic (obstruction from external compression)—as well as whether the etiology is an upper tract (above the level of the bladder) or lower tract obstruction. There are no large published epidemiologic data on the incidence of obstructive uropathy in the ICU. Differing demographics often affect the likely potential etiologies for obstructive uropathy. In older men, prostate enlargement is the most common cause. Adenocarcinoma of the prostate is second only to carcinoma of the cervix as the leading cause of extrinsic compression secondary to tumors. In women, pregnancy is the most common cause of extrinsic compression with ureteral dilatation typically observed in the third trimester, more commonly involving the right ureter and with typical spontaneous resolution after delivery. The second most common cause of urinary obstruction in women is carcinoma of the cervix, with urinary obstruction seen in up to 30% of cases.[52] Other etiologies of extrinsic compression in women include prolapsed uterus, pelvic inflammatory disease, and endometriosis.

Obstructive uropathy may also be seen with neurogenic bladder dysfunction (from diabetes mellitus or spinal cord injury), vascular syndromes (from abdominal aortic aneurysms or rarely vasculitis), or certain medications with anticholinergic effects. Retroperitoneal fibrosis (RPF) may lead to an obstructive uropathy. It is characterized by inflammatory and fibrous tissue that encases the ureters and other intraabdominal organs. RPF is typically classified as idiopathic versus secondary, with idiopathic RPF accounting for up to 70% of cases.[53] Idiopathic RPF is an immune-mediated disease that more recently has been associated with a fibro-inflammatory process called immunoglobulin (Ig) G4-mediated disease (IgG4-RD). Secondary forms of RPF are numerous with multiple associations, including radiation therapy for testicular carcinoma, medications, malignancies, and retroperitoneal hemorrhage.

Urinary tract obstruction is typically reversible when diagnosed early. If left untreated, it can lead to urinary tract infection (UTI), urosepsis, and ESRD in patients with prolonged bilateral obstructive uropathy or unilateral obstruction in a solitary functioning kidney. The primary pathologic lesion in the medulla and papilla is ischemic atrophy associated with flattening and atrophy of the tubular epithelium and interstitial fibrosis.

The clinical presentation of patients with obstructive uropathy is quite variable and is often dependent on the site, acuity, etiology, and degree of obstruction. Hyperkalemic renal tubular acidosis may be suggestive of an obstructive uropathy[54] but typically laboratory studies such as urinalysis and degree of creatinine elevation are nondiagnostic. Radiographically, a renal ultrasound (US) is the initial preferred test for screening for most patients with suspected obstructive uropathy, unless an obstructing stone is considered likely; then a noncontrast computed tomography (CT) should be the initial diagnostic study. Magnetic resonance imaging (MRI) is an alternative, but gadolinium should be avoided with advanced

renal insufficiency given the potential for nephrogenic systemic fibrosis. Unilateral obstruction from calculi typically presents with acute flank pain; however, pain is typically absent with external compression from tumors secondary to a slowly progressive course. Urine volume is often variable as well. Complete bilateral obstruction causes anuria, whereas partial bilateral obstruction often does not result in a change in urine volume secondary to the tubular injury causing impaired concentrating ability and sodium reabsorption. Complete unilateral obstruction in the setting of a normal contralateral kidney often does not alter urine volume.

Treatment of obstructive uropathy is dependent on the etiology. For bladder outlet obstruction, placement of a bladder catheter typically relieves the obstruction. In patients with ureteral or other upper tract disease, placement of ureteral stents or percutaneous nephrostomy tubes may be indicated. Recovery of renal function is typically dependent on the duration of the obstructive uropathy.

Intrinsic Acute Kidney Injury

The causes of intrinsic AKI are typically categorized by the primary area of renal pathology: tubulointerstitial, glomerular, vascular, and tubular obstruction. At times, the associated clinical manifestations such as polyuria in patients with lithium-induced nephrogenic diabetes insipidus correlate with the expected area of tubulointerstitial renal involvement. However, there is often an overlap between pathologic categories. For example, patients with lupus nephritis and glomerular involvement have a worse prognosis if there is significant tubulointerstitial disease on renal biopsy.[55,56] Additionally, secondary focal segmental glomerulosclerosis mediated by structural-functional adaptations to glomerular hyperfiltration can be seen in a variety of disease entities including reflux nephropathy.

Acute Tubular Necrosis

The most common cause of intrinsic AKI in the ICU is ATN, accounting for up to 90% of cases.[57,58] There are three major causes of ATN: renal ischemia, sepsis, and nephrotoxins. All causes of severe prerenal azotemia, especially when associated with hypotension, can also lead to ATN. Sepsis-induced ATN is typically secondary to decreased renal perfusion in the setting of hypotension. There are many nephrotoxins that can also cause ATN, including antimicrobials, chemotherapeutic agents, and radiocontrast media. ATN frequently occurs with many underlying comorbidities. The history, physical examination, and certain laboratory findings may provide diagnostic clues to ATN, but a definitive diagnosis can only be made by renal biopsy. Most often, a renal biopsy is not performed when the clinical diagnosis is most consistent with ATN because establishing a pathologic diagnosis concordant with the clinical diagnosis would not alter treatment. The pathophysiology of ischemic ATN involves a complex process of renal hemodynamics, tubular and endothelial cell injury, and inflammatory processes.[59] The histologic changes of ATN include denuding of the epithelium, focal areas of proximal tubular dilatation, and occlusion of the tubular lumen by casts and cellular debris.[60] Clinically, the decrease in GFR in patients with ATN is not always correlative with a decreased urine output. Patients are typically nonoliguric, although anuria may occur. Although it has been shown in several prospective multicenter observational studies that positive fluid balance is an independent risk factor for increased mortality in ATN,[61–63] a nonoliguric ATN has not been routinely associated with a uniformly better outcome.[64] As such, the use of diuretics in patients with ischemic ATN should be used only to treat volume overload and their use for the sole oliguric state is not recommended.[6,65,66]

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a common cause of AKI in the ICU manifested by an inflammatory interstitial infiltrate and tubulitis in the kidney causing renal insufficiency. The glomeruli and blood vessels are typically spared. Various etiologies have been identified with drug-induced causes accounting for up to 71.1% of cases; of these cases antibiotics account for up to one-third of cases.[67] AIN may be idiopathic, but infections (such as leptospirosis and *Legionella*), autoimmune disorders (such as sarcoidosis, Sjögren syndrome), and tubulointerstitial nephritis uveitis syndrome are additional potential etiologies. The classic clinical triad of sterile pyuria, rash, and peripheral eosinophilia[68] may not be seen with certain causative agents such as proton pump inhibitors (PPIs) and NSAIDs.[69,70] A renal biopsy remains the only way to make a definitive diagnosis of AIN. The pathogenesis of drug-induced AIN is a type B idiosyncratic non–IgE-mediated immune reaction.[71] The classic histologic finding on renal biopsy includes a tubulitis, interstitial inflammation, and edema. The interstitial infiltrate is often composed of mononuclear cells, predominantly $CD4^+$ T lymphocytes, macrophages, monocytes, plasma cells, and eosinophils.[72] A less common histologic drug-induced interstitial nephritis caused by certain anticonvulsants, antibiotics, and diuretics is a granulomatous interstitial nephritis manifested by the presence of hypersensitivity granulomas composed of multinucleated giant cells and reactive epithelioid histiocytes.[73] It is imperative to consider AIN in the differential for any unexplained AKI in the ICU as once the acute interstitial inflammation occurs, it can progress to a fibrogenic process marked by tubular atrophy and interstitial fibrosis.[74,75] Because the chronic injury to the tubulointerstitial compartment has been shown to be a major determinant in the development of CKD,[76] an early diagnosis for drug-induced AIN with appropriate treatment is warranted. The primary intervention and treatment for drug-induced AIN is identification and removal of the offending agent. Although corticosteroids are most often used to treat drug-induced AIN even after the offending agent has been stopped, there are no prospective randomized controlled trials to support its use. Despite several retrospective studies showing discordant results with both select benefit[68,77–81] as well as no clear benefit,[82,83] it has been suggested that corticosteroids are a reasonable treatment option for patients whose renal function does not rapidly improve within 3 to 5 days after stopping the offending agent.[84]

Acute Glomerulonephritis

Acute glomerulonephritis (GN) is an unusual cause of AKI in the ICU. However, if undiagnosed, the potential morbidity and mortality is markedly increased because a delay in diagnosis often leads to irreversible renal injury. Because sepsis is a common cause of AKI in the hospital setting, one needs to consider a postinfectious GN in the differential diagnosis of any unexplained AKI. Postinfectious GN used to be referred to as a poststreptococcal GN. With the general improvement in treating streptococcal infections, the incidence of poststreptococcal GN has been decreasing. In contrast, with the rise of antibiotic-resistant *Staphylococcus* strains such as methicillin-resistant *Staphylococcus aureus,* the incidence of *S. aureus*–related acute GN has increased.[85] Clinically, patients with *S. aureus*–related GN typically present with a concurrent infection as opposed to poststreptococcal GN, in which the infection has typically resolved by the time the GN is diagnosed.[86] The site of

infection for *Staphylococcus* GN is typically not an upper respiratory tract infection, and these patients typically present with signs of an acute GN, including hypertension, edema, proteinuria, and an active urine sediment demonstrating microscopic hematuria and red blood cell casts. Many other forms of GN may occur in hospitalized patients with complications requiring ICU care. IgA nephropathy is the most common GN in the world[87,88] and commonly presents with a synpharyngitic microscopic or gross hematuria after an upper respiratory tract infection. There are no reliable blood or urine tests to make a diagnosis of IgA nephropathy and a renal biopsy is required for definitive diagnosis. The pathognomonic finding on renal biopsy is prominent deposits of IgA in the mesangium.[89] AKI often occurs during episodes of gross hematuria and has been attributed to both ATN[90,91] and tubular obstruction from red blood cell casts.[92] Patients with a higher baseline creatinine, heavier proteinuria, and underlying hypertension have a higher risk to progress to ESRD.[93] Rapidly progressive GN (RPGN) is a clinical syndrome often used to describe a rapid deterioration in renal function over days to weeks with an associated renal biopsy finding of crescents.[94] Crescents develop in response to glomerular capillary wall injury.[95] There are typically three broad mechanisms of glomerular injury leading to crescent formation; an anti–glomerular basement membrane antibody (anti-GBM Ab)-mediated disease, a pauci-immune process, or an immune complex–mediated disease. Patients with renal biopsies demonstrating less crescents involving the glomeuruli have been shown to have a better prognosis.[96] Anti-GBM Ab disease is a disorder involving circulating antibodies directed against an antigen in the glomerular basement membrane leading to an RPGN. When associated with pulmonary hemorrhage, it is often termed Goodpasture syndrome, and when the anti-GBM Ab, pulmonary hemorrhage, and renal failure are all present, the entity is typically referred to as Goodpasture disease. Patients with Goodpasture disease typically present with AKI, alveolar hemorrhage in approximately 50% of cases,[97] and a nephritic urine sediment. Approximately 30% to 40% of patients have an associated antineutrophil cytoplasmic antibody (ANCA),[98,99] which is typically anti–myeloperoxidase-specific (MPO-ANCA).[97] As with most causes of RPGN, Goodpasture disease has a better outcome with earlier diagnosis[100] and treatment involves a combination of plasmapheresis, prednisone, and cyclophosphamide.[101] Pauci-immune RPGN refers to a necrotizing GN in which immune deposits in the glomeruli are absent on renal biopsy. ANCA-positive serology is noted in 96% of patients,[102] and they clinically develop a systemic symptom complex of either microscopic polyangiitis or granulomatosis with polyangiitis, formerly called Wegener granulomatosis. The clinical presentation for both of these disorders has significant overlap but generally involves older adults with constitutional symptoms of fatigue, weight loss and anorexia,[103,104] sinusitis and nasal crusting,[103,105] cough and dyspnea,[106] and active GN, including hematuria, red blood cell casts, subnephrotic proteinuria, and renal insufficiency.[107] RPGN disorders with immune complex generation include IgA nephropathy, postinfectious GN, and systemic disorders such as systemic lupus erythematosus (SLE).

Acute Vascular Syndromes

Acute renal vascular disorders causing AKI can affect both the arterial and venous circulation. With increased diagnostic and therapeutic interventional vascular procedures used in daily hospital practice, atheroembolic renal disease (AERD), also known as cholesterol crystal emboli, is a diagnostic consideration in any patient with unexplained AKI who has undergone recent vascular interventions. AERD generally occurs when portions of a cholesterol plaque break off and embolize into distal renal arteries or glomerular arterioles, causing partial or total occlusion with resulting ischemic atrophy rather than acute total renal infarction. Although AERD can occur spontaneously, most cases are iatrogenic.[108] The most common procedure causing AERD has been coronary angiography occurring in up to 1.4% of cases[109]; renal angiography has reported an even higher incidence rate up to 2%.[110] The classic triad is a precipitating vascular procedure, a subacute or AKI, and skin manifestations such as livedo reticularis, blue toe syndrome, or digital gangrene.[111] The typical clinical renal manifestations are a gradual worsening of renal function[112] associated with an inactive urine sediment. Eosinophiluria,[113] peripheral eosinophilia,[114] and hypocomplementemia[115] in the acute phase may also be seen. A definitive diagnosis can only be made by renal biopsy. The diagnostic renal pathologic lesion is cholesterol clefts. There is no definitive treatment for AERD. Anticoagulation with warfarin has been suggested to potentially worsen the clinical course. As opposed to AERD, clot embolism tends to embolize to larger arteries, which is more likely to lead to renal infarction. The primary causes of renal infarction are patients with atrial fibrillation,[116] renal artery dissection,[117] and hypercoagulable states.[116] Less common etiologies include fibromuscular dysplasia and cocaine use.[118] In one series, 30.1% of cases were classified as idiopathic.[116] Patients often report flank and abdominal pain.[119] Laboratory abnormalities may include an elevated serum lactate dehydrogenase level, microscopic hematuria, and mild leukocytosis.[120] Diagnosis is often made by CT with contrast. Treatment options are variable based on etiology and may include anticoagulation, thrombolytic agents, and open surgery.

Intratubular Obstruction

Intratubular obstruction is a cause of AKI in certain clinical syndromes. It may reflect a mechanism of renal injury rather than an actual clinical syndrome. For example, the two heme pigment–containing proteins myoglobin and hemoglobin may be released from muscles or hemolyzed red blood cells (RBCs), causing myoglobinuria or hemoglobinuria, respectively. Both of these pigments are filtered in the glomerulus and subsequently degraded in the urinary space releasing heme pigment. One of the main mechanisms of tubular injury is a tubular obstruction.[121] Patients with rhabdomyolysis often develop red to brown urine and have associated pigmented granular casts and a urinalysis positive for dipstick heme despite an unremarkable urine microscopy with markedly elevated blood creatine phosphokinase levels.[122] Patients with hemolysis and AKI have the same urinary findings in addition to having a low haptoglobin.[123] Patients with ATN from rhabdomyolysis or hemolysis both typically have a fractional excretion of sodium of less than 1%, possibly reflecting vasoconstriction.[124]

Intratubular obstruction can also be a cause of AKI in tumor lysis syndrome, an oncologic emergency typically occurring after initiation of cytotoxic agents. The tumor lysis results in overwhelming release of cellular contents, such as nucleic acids, potassium, and phosphorus, into the circulation. Nucleic acids are metabolized to uric acid, resulting in hyperuricemia. Renal injury is primarily due to urate crystals and calcium phosphate deposition in renal tubules.[125]

Marrow infusion toxicity has been implicated in the pathogenesis of AKI among patients undergoing hematopoietic stem cell transplantation.[126] The pathogenesis is believed to be harvested stem cells exposed to cryoprecipitants such as dimethyl sulfoxide during the hematopoietic stem cell transplantation procedure, resulting in precipitation of heme proteins in the renal distal tubule

causing obstruction.[127] In ethylene glycol intoxication, the renal failure is primarily due to glycolate tubular injury but tubular obstruction from calcium oxalate crystals is often contributory.[128] A similar pathogenesis of calcium oxalate tubular obstruction can be seen with primary hyperoxaluria, rare inborn errors of glyoxylate metabolism,[129] or secondary forms of hyperoxaluria such as patients undergoing gastric bypass procedures.[130] Acute phosphate toxicity has been described in patients using bowel purgatives that contain oral sodium phosphate or sodium phosphate–containing enemas. In response to this recently described entity, certain commercial forms of oral sodium phosphate are no longer sold. The most likely mechanism of renal injury is from severe hyperphosphatemia resulting in calcium phosphate deposition in the tubular lumen[131,132] and causing luminal obstruction.[132] Crystal-induced nephropathy can be caused by several drugs and toxins, resulting in an intratubular precipitation of crystals causing tubular obstruction. Patients are usually asymptomatic. The urinalysis is variable including microscopic hematuria, mild proteinuria, and crystalluria. Although a clinical diagnosis is often made with the temporal relationship of an offending agent with subsequent AKI, definitive diagnosis requires a renal biopsy. Agents reported to cause AKI via crystalluria include acyclovir,[133] protease inhibitors including indinavir[134] and atazanavir,[135] sulfonamide antibiotics,[136] methotrexate,[137] ciprofloxacin,[138,139] amoxicillin,[140] and orlistat.[141,142] Treatment for crystalluric AKI is generally intravenous fluid (IVF) and, in certain cases, bicarbonate-rich IVF. Paraproteinemias often cause renal failure through intratubular obstruction. Light-chain cast nephropathy, formerly termed myeloma kidney, can result in an AKI or CKD by intratubular cast deposition and obstruction.[143] Intratubular amyloid cast nephropathy is a rare mechanism of renal injury.[144]

Clinical Manifestations

The manifestations of AKI vary among patients. Many patients are asymptomatic despite laboratory abnormalities demonstrating significant renal injury. At some point in the continuum of progressive renal failure that does not improve, patients may become symptomatic. Clinical manifestations may include edema, hypertension, and oliguria. Laboratory abnormalities often include elevated BUN and creatinine levels, and an abnormal urinalysis, including hematuria and proteinuria with potential additional metabolic derangements, including an elevated anion gap, metabolic acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. The clinical diagnosis of AKI is often made when oliguria occurs or when the patient develops or presents with an elevated BUN or creatinine level above baseline. However, the GFR rate may significantly decline before this rise in BUN or creatinine occurs and this often delays the therapeutic interventions to alleviate and treat the cause of AKI.

Retention of Filtration Markers and Formulas as an Assessment of Glomerular Filtration Rate

The GFR varies depending on age, sex, and body size and is equal to the sum of filtration rates of all functioning nephrons and is generally 130 mL/min per 1.73 m^2 and 120 mL/min per 1.73 m^2 for men and women, respectively.[145] Estimation of the GFR is often used clinically to address the degree of renal insufficiency, assess worsening renal function, and to clinically map out the planned therapeutic intervention. However, GFR serves to depict the degree of renal insufficiency and does not define etiology, which ultimately guides treatment recommendations. Even when the GFR is defined accurately, it has limitations in regard to predicting stable disease. For example, compensatory hypertrophy typically occurs in patients with a nephrectomy and thus there is not a direct linear relationship between loss of renal mass and loss of GFR.

GFR cannot be measured directly and as such, it is often estimated by using an ideal filtration marker. Inulin has been used as the gold standard but it is expensive and cumbersome to use and as such, not clinically adopted.[146] Nuclear radiographic agents such as iothalamate and iohexol are sparingly used given their limitations.[147] The most common methods to assess GFR use creatinine as the filtration marker and include creatinine clearance, as well as the following estimating equations: the Cockcroft-Gault equation, the Modification of Diet in Renal Disease (MDRD) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Because the individual variability of creatinine production can be calculated based on both demographic and clinical variables, such as gender, race, weight, and age, the use of creatinine in these estimating equations was deemed reasonable. Creatinine clearance is determined by measuring 24-hour urine creatinine excretion; shorter collections provide less accurate results. The major limitations of creatinine clearance are inaccurate collections and secretion of urinary creatinine, leading to overestimation of GFR. The estimating equations also have limitations and are not accurate when used in AKI. The Cockcroft-Gault equation is not adjusted for body surface area and was developed before standardized creatinine assays and thus can overestimate creatinine clearance by up to 40%. Normalization for body surface area increases the accuracy of this equation in patients, especially with renal insufficiency.[148] However, most pharmacokinetic studies for drug dosing in renal disease have used this formula for guidelines.[149] The MDRD equation in estimating GFR is more accurate in patients with CKD[150] and less accurate in patients with a normal GFR.[151] Conversely, the CKD-EPI equation is more accurate in assessing GFR in patient populations with normal or near-normal GFR.[152]

Creatinine

Creatinine is derived primarily from metabolism of creatine in skeletal muscle in addition to dietary meat intake. Creatinine is generally released at a constant rate from skeletal muscle; it is not metabolized by the kidney and there is no tubular reabsorption. Urinary creatinine primarily is derived from its filtration at the glomerulus, but 10% to 40% is derived from a tubular secretion in the proximal tubule in patients with renal insufficiency.[153] As such, because a decrease in GFR is accompanied by an increase in tubular excretion of creatinine, an initial reduction in GFR may not be correlated to an equally reciprocal rise in creatinine. Creatinine can be used to estimate GFR only when renal function is stable. In the steady state, a rise in serum creatinine reflects a decrease in GFR. However, in AKI there can be a significant decrease in GFR before creatinine has time for accumulation. This has potential therapeutic implications. Limitations in using creatinine in assessing GFR include variations in creatinine secretion and production, extrarenal creatinine excretion, and serum measurement of creatinine.

Creatinine production varies among people over time and with different muscle mass. Patients with a higher muscle mass produce more creatinine and patients with a decreased muscle mass secondary to small body frames or those with amputations may have lower creatinine values. Creatinine production may also be reduced in sepsis.[154] Certain disease states such as rhabdomyolysis may have

exaggerated increases in creatinine above the expected range. Creatinine secretion can increase in the proximal tubule with an initial decrease in GFR, possibly blunting a rise in the serum creatinine. However, the proximal tubular secretion is saturated above a creatinine of 1.5 to 2.0 mg/dL and subsequently any rise in creatinine reflects a decrease in GFR.[153] Creatinine secretion may also be inhibited by competition with certain medications such as trimethoprim and cimetidine, leading to a pseudohypercreatininemia (a rise in serum creatinine without any decrease in renal function). Extrarenal excretion of creatinine by intestinal bacterial creatininase activity may result in a lower than expected creatinine value but is often difficult to quantify clinically.[147] Differences in both methods and equipment in creatinine measurement can also account for variable creatinine values.[155] Attempts by the National Kidney Disease Education Program to standardize the assay have limited this variation. Additionally, a dilutional blunting of a creatinine rise may occur with aggressive fluid resuscitation.[156] Given the many potential variables affecting the serum creatinine value and its use in the estimating equations of assessing GFR, these equations are not considered reliable for estimating GFR in critically ill patients with AKI.

Urea

Urea is the chief end product of nitrogen metabolism. Blood urea concentration, measured in blood as BUN, is dependent on the balance between hepatic production and renal excretion of urea. BUN, similar to serum creatinine, varies inversely with GFR. BUN production is not constant and can vary quite significantly based on protein intake, gastrointestinal hemorrhage, protein loading with parenteral nutrition, and hypercatabolic states, such as trauma, sepsis, and glucocorticoid administration. Normally, filtered urea is passively absorbed in the proximal tubule. In prerenal states such as dehydration, CHF, and cardiomyopathy, there is an associated decreased renal perfusion that often results in BUN rising out of proportion to the level of serum creatinine. Secondary to this variability in both production and excretion, it is considered less valuable than creatinine in assessing GFR. However, the one clinical scenario in which measuring urea clearance for assessing renal function has shown potential benefit is in patients with advanced renal failure. In this subset, urea clearance significantly underestimates GFR and creatinine clearance overestimates GFR. The 2005 European best practice guidelines recommended averaging the creatinine and urea clearance to achieve the best results in assessing GFR in patients with advanced renal impairment.[157]

Cystatin C

Given the limitations of both creatinine and BUN in accurately assessing GFR, there is continued interest in finding a more reliable endogenous laboratory marker for GFR assessment. The best studied is cystatin C, which is a low–molecular-weight protein produced by all nucleated cells, is filtered at the glomerulus, and is not reabsorbed. It has a shorter half-life than creatinine; initially studies showed it as a more sensitive marker for assessment of GFR in ICU patients.[158] However, its limitations as an endogenous substance to adequately reflect GFR have recently been elucidated. Cystatin C is metabolized in renal tubules, increases with age,[159] gender, height, and weight,[160] thyroid disease,[161] diabetes mellitus,[162] and body size. Similar to creatinine, there have also been quite variable cystatin C values despite using the same instruments and reagents in the same laboratory.[163] Similar to the creatinine assay standardization, certified reference materials for cystatin C assays were created. It was also proposed that cystatin C–based equations would be more accurate than creatinine-based equations in assessing GFR in certain populations, such as the elderly, renal transplant recipients, and patients with cirrhosis, but results have been variable.[164] There have been several published reports, however, demonstrating that combining the serum creatinine and cystatin C into a single equation may better estimate GFR than equations that use creatinine or cystatin C singularly,[165] especially in patients with CKD.[166] Despite these potential benefits, few have routinely adopted the measurement of cystatin C in clinical practice.

Markers of Tubular Injury and Novel Biomarkers

Given the limitations of creatinine, BUN, and cystatin C in detecting an early change in GFR, there has been continued interest in the development of early biomarkers of renal tubular injury. An ideal biomarker should have several properties, including universal ease of measurement, earlier detectability than the rise in serum creatinine to allow an earlier diagnosis of AKI, adequate specificity to distinguish functional prerenal azotemia from a tubular injury or CKD, identification of the location of renal injury, allowing prediction of renal and patient outcomes and potentially offering pharmacologic response to therapy.[167] Several biomarkers have been reported to be early predictors of AKI, including neutrophil gelatinase-associated lipocalin (NGAL),[168–170] kidney injury molecule-1,[171] *N*-acetyl-β-D-glucosaminidase,[172] retinol-binding protein,[173] micro–ribonucleic acid molecules,[174] cytokine interleukin 18,[175] as well as others. NGAL serum and urinary levels have been shown to have better sensitivity than serum creatinine in patients with ischemic AKI.[176] Urinary NGAL has been shown to be a predictive biomarker for delayed graft function after kidney transplantation[177] as well as a predictor of AKI in patients with septic shock.[178] In adult patients undergoing cardiac surgery, urinary kidney injury molecule-1 could predict the development of AKI better than NGAL.[179] Several of these biomarkers have been shown to have improved utility to current measures in earlier diagnosis of AKI. However, studies have reported variable results in the predictability of AKI with many of these biomarkers.[180] As such, despite certain biomarkers showing superior and earlier detection of AKI in specific patient cohorts, further validation of these benefits with large multicenter prospective studies is needed before any single biomarker replaces the current laboratory studies that are currently universally used.

Oligoanuria

Oligoanuria is one of the three clinical parameters used by KDIGO in defining AKI.[6] Oliguria is generally defined as urine output less than 400 mL/day and anuria as less than 50 mL/day. In patients who become oligoanuric, the creatinine and BUN will rise to help diagnose and define AKI. However, many patients in whom AKI develops in the ICU are nonoliguric. The absence of oligoanuria does not define a less critical attention to AKI. There are many severe forms of intrinsic AKI that are nonoliguric and without appropriate diagnostic and therapeutic responses, AKI will worsen. However, in patients who are anuric, this often is a sign of a severe form of renal injury that requires immediate diagnostic and potentially therapeutic intervention. Unilateral obstruction in a solitary functioning kidney, bilateral ureteral obstruction, cortical necrosis from profound ischemic ATN or in pregnancy-related AKI,[181,182] pigment nephropathy, acute renal vascular events, or active proliferative GN can all initially manifest with anuria. In a prospective cohort study in a single tertiary care hospital over a 2-year period, septic and postoperative AKI were the primary causes

of anuric AKI.[183] Oligoanuria does not necessarily narrow the differential in regard to the etiology but it does signify a nephrologic emergency requiring immediate evaluation.

Detection of Clinical Complications of AKI

At times, patients may seek medical attention secondary to complications of AKI in which oligoanuria or an elevated BUN and creatinine level are not the initial diagnostic abnormality prompting evaluation. Patients with nephrotic syndrome may present with new-onset edema or anasarca. Uremic encephalopathy may be a presenting sign but is less common with the advent of routine diagnostic laboratory screening for renal insufficiency. A pericardial friction rub may develop in patients with advanced renal failure.[184] At times, electrolyte abnormalities, such as hyperkalemia, hyponatremia, metabolic acidosis, hyperuricemia, and hyperphosphatemia, may be the presenting laboratory abnormality signifying an AKI.

Diagnostic Approach

General Aspects

The initial step in evaluating and assessing the cause of AKI in the ICU is to follow a diagnostic algorithm. As the treatment of AKI is dependent on the etiology, it is incumbent upon the provider to use all appropriate and available diagnostic testing to narrow the differential. A history and physical examination often assist in the differential diagnosis by outlying potential etiologies. A patient with prerenal azotemia in whom AKI develops after an intravenous contrast study is more likely to have contrast nephrotoxicity if additional history does not suggest other potential etiologies. Patients with severe hypotension and previous recent normal renal function who require multiple pressors often have ischemic ATN as a leading diagnosis in the latter ICU setting. AKI that develops after the patient receives potentially nephrotoxic medications may provide a diagnostic clue. Obtaining a urinalysis with microscopy at the time of the AKI will potentially help narrow the differential diagnosis. Oftentimes, the urine microscopy provides diagnostic clues. A bland urinalysis lacking cellular components such as RBCs, white blood cells, or RBC casts makes an active proliferative GN less likely. Radiographic imaging may also be helpful. A bladder scan is now often used to screen for a bladder outlet obstruction, especially in the current hospital environment to limit catheter-associated UTIs. A renal US with or without Doppler of the renal vasculature, a CT scan of the renal collecting system, and an MRI of the urinary tract all have potential utility in providing diagnostic aid in certain clinical scenarios. In some patients, a renal biopsy is necessary for a definitive diagnosis. In the ICU, this often becomes relevant when patients develop AKI from presumed ischemic ATN after a prolonged hypotensive episode. Although not often clinically required, a renal biopsy often provides the only method for establishing a definitive cause of the AKI. Some patients in the ICU have a prolonged AKI after a clinical scenario of associated oligoanuria with ATN as the clinical diagnosis. Many of these patients receive multiple medications and antimicrobials, which raises the possibility of an associated alternative diagnosis such as an AIN. The only way to make the latter diagnosis is by renal biopsy. Certainly, if an AIN were the cause of AKI in the ICU, either removing the offending agent versus administering steroids would be warranted at times. It is not uncommon for critically ill patients to have related coagulopathies, often making renal biopsy not feasible. An empiric course of steroids is sometimes used in the latter scenario.

Patient History and Physical Examination

The initial step in evaluating a patient with AKI in the ICU is to review the patient's pertinent medical history and perform a physical examination to help narrow the differential (Table 52.1). Reviewing the clinical scenario prompting their ICU presentation may identify potential etiologies. For example, NSAID use or other potentially nephrotoxic medication administration before the development of AKI may provide diagnostic clues in the correct clinical context. A history of benign prostatic hypertrophy or prostate cancer in men or a gynecologic malignancy in women with known retroperitoneal lymphadenopathy should raise the suspicion for an obstructive uropathy. A history of nephrolithiasis, especially in the setting of a superimposed unilaterally functioning kidney, with either renal colic or gross hematuria, should alert the provider to screen for obstructive uropathy. Recent administration of chemotherapeutic agents in a patient with a high tumor burden should suggest the possibility of either tumor lysis syndrome or a tubular or glomerular toxicity. Identifying events even before admission may prove diagnostic. A history of diarrhea, vomiting, decreased fluid intake, severe cardiomyopathy, heart failure, or cirrhosis may certainly suggest some component of prerenal azotemia. Associated other primary organ involvement in the disease state such as pulmonary infiltrates may suggest a pulmonary-renal syndrome. Jaundice suggests liver disease with a broad differential, including hepatorenal syndrome or a potential secondary GN from known primary liver disease. Constitutional symptoms such as poor appetite, fever, and weight loss may suggest the development of a systemic disorder such as a primary GN. Administering antimicrobials when patients have a superimposed rash and fevers may alert the physician to the possibility of an AIN. Obtaining a history of over-the-counter medication use such as a PPI may suggest an AIN, or the ingestion by the patient of excess amounts of the herb star fruit (carambola) would suggest the possibility of a calcium oxalate kidney stone in a patient who had acute sepsis from nephrolithiasis in the latter setting. Reviewing the medical record should also focus on indices such as frequent weights, accurate intake and outputs, blood pressure, and heart rate measurements that would help assess the volume status of the patient. An extensive review of all medications is required with the knowledge of their potential nephrologic side effects. As previously outlined, urine output may help in the differential as anuria does signify a likely severe nephrologic emergency requiring immediate evaluation.

The physical examination should initially focus on the volume status of the patient, in particular, the intravascular volume. Even with evidence of total body water excess on examination, the intravascular volume often dictates therapeutic interventions. If the intravascular volume is decreased, expansion with IVFs fluids or colloid is often the initial approach. To help evaluate intravascular volume, assessing orthostatic changes in heart rate and blood pressure from a supine to standing position and evaluating skin turgor and mucous membranes may all offer additional physical examination clues to accurately identify the patient's fluid balance. A consensus statement defining orthostatic hypotension was published in 2011.[185] Diagnosing orthostatic hypotension requires rest in the supine position for 5 minutes, subsequent standing for 2 to 5 minutes, and observing one or both of the following: a drop in systolic blood pressure of at least 20 mm Hg or a drop in the diastolic blood pressure of at least 10 mm Hg. Although the presence of orthostatic hypotension suggests an intravascular volume depletion, it is not specific.

TABLE 52.1 Steps for Diagnosing Acute Kidney Injury in the Intensive Care Unit

1. History
   1. Identify any chronic renal failure component
   2. Review for nephrotoxic agents (e.g., contrast, antibiotics, NSAIDs, chemotherapy)
   3. Identify risk factors for obstruction:
      a. Nephrolithiasis
      b. Prostate cancer
      c. Retroperitoneal lymphadenopathy
      d. Gynecologic malignancy
   4. Identify surgical history (e.g., nephrectomy)
   5. Presence of constitutional symptoms suggestive of prerenal etiology (e.g., vomiting, diarrhea, decreased oral intake, cardiomyopathy, cirrhosis)

2. Physical examination
   1. Assess volume status
      a. Measure blood pressure, heart rate
      b. Check for othostatic hypotension
      c. Assess skin turgor, mucous membranes
      d. Assess for edema suggestive of total body water excess, possible nephrotic syndrome, cardiomyopathy
   2. Lung examination
      a. Crackles may reflect congestive heart failure
   3. Abdominal examination
      a. Ascites may indicate liver disease or hepatorenal syndrome
   4. Skin assessment
      a. Rash may be suggestive of AIN
      b. Purpura may reflect cutaneous vasculitis
   5. Ophthalmologic examination
      a. Papilledema may be associated with hypertensive emergency/crisis
   6. Cardiac examination
      a. Valvular murmurs may be indicative of renal perfusion abnormalities
   7. Extremity examination
      a. Livedo reticularis reflective of atheroembolic renal disease

3. Laboratory Findings

Laboratory	Potential Causes
Urine	
Gross Assessment	
Turbid urine	UTI
Gross hematuria	Urologic cause, glomerulonephritis, rhabdomyolysis
Brown urine	Rhabdomyolysis
White urine	Chyluria
Dipstick	
Heme	Urologic causes, glomerulonephritis, rhabdomyolysis
Protein	Primary glomerulonephritis, paraproteinemia, diabetes hypertension
Urine Microscopy	
RBC	Glomerulonephritis, urologic cause
RBC casts	Glomerulonephritis
Acanthocytes	Glomerulonephritis
WBC	Infection, AIN, CIN, TB, malignancy
WBC casts	Infection
Urine eosinophils	AIN, AERD
Other cellular casts	
Broad	CRF
Fatty	Nephrotic syndrome
Granular	ATN
Urine Electrolytes	
Decreased spot sodium	Prerenal azotemia
Fe_{Na}, percent	Prerenal azotemia (<1%) vs. ATN (>2%)
Decreased spot urine chloride	Prerenal azotemia with metabolic alkalosis
Increased spot urine potassium	Hyperaldosteronism/secondary hypertension
Blood	
Hypercalcemia	Multiple myeloma, paraproteinemia, sarcoidosis, humoral hypercalcemia of malignancy
CPK	Rhabdomyolysis
Hyperphosphatemia	Phosphate nephropathy, tumor lysis syndrome, AKI, CKD
Hyperuricemia	Uric acid nephropathy, tumor lysis syndrome
Prolonged PTT	Lupus anticoagulant, SLE
Peripheral eosinophilia	AIN
Thrombocytopenia, elevated LDH, bilirubin	Hemolytic uremic syndrome, TTP
Serologies: ANA, dsDNA, C3, C4, ANCA, anti-GBM antibody, cryoglobulin, hepatitis, HIV, ENA	Vasculitic syndromes

4. Radiographic Testing

Radiographic Tests	Significance of Findings/Diagnostic Screen
Renal ultrasound	Enlarged kidneys may suggest obstruction, infiltrative disorders, renal vein thrombosis, HIV, diabetes mellitus Small kidneys suggest CRF
CT scan	Nephrolithiasis, obstruction and malignancy
MRI	Obstruction and renal infarcts
MRA	Renal artery stenosis
MRV	Renal vein thrombosis
Renal angiography	Polyarteritis nodosa
Nuclear scan	Renal infarcts

AERD, Atheroembolic renal disease; *AIN,* acute interstitial nephritis; *AKI,* acute kidney injury; *ANCA,* antineutrophil cytoplasmic antibody; *ATN,* acute tubular necrosis; *CIN,* chronic interstitial nephritis; *CKD,* chronic kidney disease; *CKR,* chronic kidney disease; *CPK,* creatine phosphokinase; *CRF,* chronic renal failure; *CT,* computed tomography; *dsDNA,* double-stranded DNA; *ENA,* extractable nuclear antigen; *FENa,* fractional excretion of sodium; *GBM,* glomerular basement membrane; *HIV,* human immunodeficiency virus; *LDH,* lactate dehydrogenase; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *MRV,* magnetic resonance venography; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PTT,* partial thromboplastin time; *RBC,* red blood cell; *SLE,* systemic lupus erythematosus; *TB,* tuberculosis; *TTP,* thrombotic thrombocytopenic purpura; *UTI,* urinary tract infection; *WBC,* white blood cell.

Common alternative causes of orthostatic hypotension include aging,[186] medications,[187] cardiovascular etiologies such as aortic stenosis,[187] and neurally mediated etiologies.[188] A cardiopulmonary examination may certainly help in establishing a diagnosis of heart failure. Evaluation for the presence of jugulovenous distention, pulmonary basilar rales, and presacral and lower extremity edema may all be suggestive of the presence of CHF. In certain cohorts such as the morbidly obese, critically ill, or cirrhotic patients, these clinical findings may be difficult to define. Therefore additional radiographic tests such as a chest radiograph and laboratory studies such as an elevated brain natriuretic peptide may be ordered to aid in the clinical assessment. Central venous catheters are oftentimes in place, allowing for monitoring of the central venous pressure assessment, which can help determine a patient's volume status. Unfortunately, the central venous pressure measurement does not predict whether an IVF challenge will increase stroke volume and cardiac index.[189] Pulmonary artery catheter use has fallen out of favor over the past several years owing to the lack of improvement in mortality benefit or the ICU length of stay with lack of cost benefit.[190] The pulmonary artery catheter still remains a potential diagnostic tool in assessing the different types of shock (hypovolemic, distributive, cardiogenic, obstructive), which may be difficult to discern on clinical assessment alone.[191]

Assessment for ascites, jaundice, or scleral icterus in the setting of an AKI may suggest the presence of underlying liver disease. Palpation of abdominal masses or bladder distention may signify an obstructive uropathy or bladder outlet obstruction, respectively. A rectal and pelvic examination may also provide clues of an obstructive uropathy. A retinal examination may demonstrate the presence of papillary edema, which is nondiagnostic but may be indicative of an untreated hypertensive emergency from a primary proliferative GN, renovascular-induced uncontrolled hypertension, or even an illicit drug ingestion such as cocaine. The presence of Hollenhorst plaques would suggest an atheroembolic event. Presbycusis could signify aminoglycoside toxicity or Alport syndrome in the correct clinical context. Skin manifestations such as a rash may be suggestive of an AIN, livedo reticularis suggestive of atheroembolic renal disease, or palpable purpura possibly reflecting a cutaneous vasculitis, such as Henoch-Schönlein purpura or the presence of a microangiopathic process typical for a hemolytic uremic syndrome or a thrombotic thrombocytopenic purpura.

Urinalysis and Urine Indices

The first application of urine microscopy to clinical practice is generally attributed to a French nephrologist, Pierre Rayer, in the early 1800s.[192] Since that time, the evolution of evaluating urine in providing diagnostic clues to assist in narrowing the differential diagnosis or specifically defining the etiology of the renal failure has continued to evolve. The three primary components of a complete urinalysis include gross assessment, dipstick analysis, and urine microscopy. Various findings on urinalysis may suggest specific categories of renal disease and in certain circumstances be pathognomonic, but these findings need to be interpreted in the appropriate context of the history, physical examination, and other laboratory data. The gross assessment of a turbid and cloudy urine with associated dysuria is often indicative of a UTI or pyelonephritis. The color of urine may also provide diagnostic clues. Gross hematuria could be secondary to bleeding anywhere in the urinary system, including the urethra, bladder, ureters, or the kidneys. Certain etiologies of GN such as IgA nephropathy can often present with gross hematuria in up to 45% of cases.[87] Hematuria can also result when only the supernatant of a centrifuged urine is red, such as in myoglobinuria in the setting of rhabdomyolysis or hemoglobinuria, which can occur with hemolysis. Milky white urine may be a manifestation of chyluria,[193] whereas purple urine may suggest a catheter-related UTI.[194] Orange urine may be seen with use of certain medications such as pyridium, and green urine may be seen with propofol use.[195] The urine dipstick typically provides analysis for heme, nitrite, leukocyte esterase, albumin, hydrogen ions, specific gravity, and glucose. A urine dipstick result largely positive for heme with no significant RBCs on urine microscopy often suggests rhadomyolysis. A dipstick result positive for nitrite or leukocyte esterase is often indicative of a UTI. Dipstick albuminuria is suggestive of a potential glomerular injury, although non-albumin proteins such as immunoglobulin light chains seen in multiple myeloma are often not positive on urine dipstick. A 24-hour urine collection for protein is the initial step in quantifying the degree of dipstick albuminuria because nephrotic range proteinuria would suggest a differential for AKI different than in patients who have minimal proteinuria. Overall, albuminuria has been associated with worse cardiovascular morbidity and mortality.[196–198] The urine hydrogen ion concentration, measured as urine pH, is typically used in evaluating different forms of renal tubular acidosis. Glyosuria is typically seen in the setting of uncontrolled diabetes mellitus, but it may be a manifestation of a proximal renal tubular injury seen with Fanconi syndrome.[199]

The third component of a urinalysis evaluation is performing a urine microscopy that primarily evaluates for cells, casts, and crystals, all of which can often help to identify certain causes of AKI, and at times, specific microscopic findings are essentially pathognomonic for the disease state causing the AKI. The presence of RBCs on urine microscopy raises concern for a GN but the latter needs to be differentiated from urologic causes. Distinguishing between glomerular and non-glomerular bleeding is the key initial step in identifying the source of hematuria. To help differentiate between glomerular versus urologic causes of hematuria, the presence of dysmorphic RBCs known as glomerular RBCs on urine microscopy often suggests a glomerular etiology.[200] In a subset of glomerular RBCs known as acanthocytes there are characteristic membrane protrusions with increased specificity for GN.[201] The presence of RBC casts on urine microscopy is often a nephrologic emergency requiring a renal biopsy for definitive diagnosis. Although RBC casts have been primarily identified with an active proliferative GN, they have been described in up to nearly 30% of cases of AIN.[202] White blood cells identified on urine microscopy are often associated with bacteriuria but when an infection is not present, the differential is broad and should include an AIN, a chronic tubulointerstitial nephritis, nephrolithiasis, tuberculosis, and malignancy.[203] Urine eosinophils are best identified using Hansel stain.[204] Eosinophiluria has been traditionally ordered in the workup for AKI in hospitalized patients as a potential diagnostic aid for defining an AIN. However, eosinophiluria can be seen in many disorders, including atheroembolic renal disease, cystitis, pyelonephritis, transplant rejection, and in patients with ileal conduits.[113,205–207] In a recent study, the sensitivity and specificity for urine eosinophils in the setting of renal biopsy-proven AIN was quite low—30% and 68%, respectively. As such, its diagnostic accuracy and clinical use needs to be revisited and interpreted with caution.[208] Casts are generally divided into two categories: cellular and noncellular. Urine casts are cylindrical structures that are formed in the tubular lumen and are composed primarily of Tamm-Horsfall mucoprotein. Cellular casts have cellular components within a

matrix and are diagnostic of an intrarenal origin. RBC casts are generally consistent with a glomerular etiology, white blood cell casts suggest an interstitial inflammation, and broad casts are generally seen in CRF. The presence of fatty casts, oval fat bodies, or free fat on urine microscopy suggests nephrotic syndrome. Noncellular casts include hyaline, waxy, broad, granular, and renal tubular. Hyaline casts are usually not indicative of renal pathology. Granular casts are a typical microscopic finding in ischemic ATN, which is the leading cause of AKI in hospitalized patients.[209] Despite general adoption and concordance between automated and manual microscopy in identifying certain cellular components in the urinalysis such as white blood cells and RBCs, manual microscopy is often required in AKI to evaluate for the presence of cellular casts.[210] In addition, those providers most familiar with microscopy interpretation such as nephrologists are best at defining cellular components on the urinalysis.[211] An observation of crystals on urine microscopy may identify or suggest a certain stone composition that may lead to screening for an obstructive uropathy.

Urine electrolytes may also be helpful in narrowing the differential for AKI, such as in differentiating between prerenal azotemia and ATN. In patients with ATN, renal tubular cells are damaged and this affects the proximal tubular reabsorption of sodium. In prerenal azotemia, the physiologic response of the proximal renal tubule remains intact and urine sodium reabsorption is typically increased. Thus in prerenal states the urine sodium is expectedly low, but with ATN the spot urine sodium is often elevated. The fractional excretion of sodium (FE_{Na}) is more accurate than the spot urine sodium alone in differentiating prerenal azotemia from ATN because FE_{Na} directly measures sodium handling. The FE_{Na} measures the percent of filtered sodium excreted in the urine and is calculated by

$$\text{FENa}\ (\%) = \frac{U_{Na} \times S_{Cr}}{S_{Na} \times U_{Cr}} \times 100,$$

where U_{Na} is the spot urine sodium concentration, U_{Cr} is the spot urine creatinine concentration, S_{Na} is the serum or plasma sodium concentration, and S_{Cr} is the serum or plasma creatinine concentration. Several studies have identified a benefit of the FENa in differentiating prerenal azotemia from ATN[212–214] with other reported studies demonstrating less clinical utility.[215] Overall, a FENa less than 1% is generally expected in prerenal states, a value greater than 2% is typically seen with ATN, and a value between 1% and 2% can be seen with either disorder. However, these urinary indices have several limitations. The FE_{Na} may be greater than 1% despite prerenal azotemia in patients with active diuretic tubular effects, in patients with CKD who have a delayed response to maximizing urine sodium reabsorption, or in patients with metabolic alkalosis with resultant bicarbonaturia. Conversely, the FE_{Na} may be less than 1% in several settings other than prerenal azotemia, including radiocontrast media,[216] myoglobinuric or hemoglobinuric ATN,[217] certain forms of ATN,[214,218] AKI from AIN,[219] and even with the absence of kidney disease such as cirrhosis.[220] Given the potential limitations of FE_{Na} in certain clinical situations, the fractional excretion of urea (FE_{Urea}) has been proposed as an alternative assessment of tubular function and to add clinical utility in assessing for prerenal azotemia. A FE_{Urea} of 50% to 65% or less than 35% has been proposed in differentiating ATN from prerenal azotemia, respectively. The FE_{Urea} is calculated by

$$FE_{Urea}\ (\%) = \frac{U_{Urea} \times S_{Cr}}{S_{Urea} \times U_{Cr}} \times 100,$$

where U_{Urea} is the spot urine urea concentration, U_{Cr} is the spot urine creatinine concentration, SUrea is the serum or plasma urea concentration, and the S_{Cr} is the serum or plasma creatinine concentration. The FE_{Urea} has been shown to be potentially useful in differentiating prerenal azotemia, especially in patients receiving diuretics,[221,222] although discordant results have been noted.[223] The fractional excretion of other urine molecules such as uric acid[224,225] and lithium[225] have also had limited study but this measure is not clinically used.

In the subset of patients with metabolic alkalosis caused by vomiting or nasogastric tube suctioning, the assessment of intravascular volume is better assessed by obtaining a spot urine chloride (UCl) rather than a spot UNa, including in the ICU setting.[226] In patients with metabolic alkalosis, bicarbonaturia develops with a subsequent rise in UNa, which may result in a normal or even high spot UNa finding despite an intravascular volume depletion. Thus the spot UCl in the latter cohort of patients is always appropriately low and typically less than 20 mEq/L and is a better marker for intravascular volume depletion. Similar to other spot urine electrolytes, a spot UCl may be affected by other clinical scenarios. An elevated spot UCl level may be present despite intravascular volume depletion in settings such as persistent diuretic effect. Patients with metabolic alkalosis from laxative abuse or cystic fibrosis with excess sweating[227] may have a low UCl. Patients with metabolic alkalosis, hypovolemia, and a spot UCl level that is not low and often high can be seen in disorders such as excess licorice ingestion, primary hyperaldosteronism, and Liddle syndrome.

Urine potassium excretion may also be helpful in identifying certain causes of hypertension that may present with hypertensive urgency or emergency and even renal insufficiency. Patients with hypokalemia not caused by urinary losses are expected to have an appropriate decrease in urinary potassium excretion to less than 30 mEq/day,[228] a spot urine potassium of less than 15 mEq/L,[229] and a spot urine potassium-to-creatinine ratio of less than 13 mEq/g.[230] Because spot urine potassium concentration is affected by urine volume, a spot urine potassium-to-creatinine ratio is preferred to a spot urine potassium value alone, especially if a 24-hour urine collection is not available or cannot be performed. In patients with both hypokalemia and hypertension with inappropriately elevated urinary potassium excretion, secondary causes of hypertension such as primary aldosteronism and renovascular disease should be considered.

Radiologic Imaging

Several radiographic studies are often utilized in the workup of AKI (see Table 52.1). A renal US is typically the first radiographic test ordered when AKI is unexplained and obstructive uropathy is considered.[231] A renal US with false-negative results for obstructive uropathy may be seen with early obstruction, RPF, or with malignancy, and thus a CT scan of the urinary system without contrast is sometimes required to rule out obstructive uropathy. Nonobstructive findings may occasionally be useful in defining causes of AKI. An enlarged kidney on renal US may be indicative of a renal vein thrombosis,[232] especially in the clinical setting of flank pain and severe nephrotic syndrome. The average size of kidneys on renal US is 10 to 11 cm in length.[233] At times, patients present with renal insufficiency with no prior laboratory studies for many years. Renal US findings suggestive of CKD include shrunken kidneys less than 10 cm in length and an increased renal echogenicity often indicative of fibrous tissue associated with CKD.

Patients with ATN may also present with increased echogenicity on renal US.[234] Therefore a renal US cannot be used to distinguish AKI from CKD. Enlarged kidneys on US can occur with acute renal vein thrombosis, obstructive uropathy, malignancy and infiltrative disorders, human immunodeficiency virus, and diabetic nephropathy. Intravenous radiocontrast administration may worsen or delay renal recovery in AKI and should be avoided whenever possible. MRI is sometimes useful in screening for an obstructive uropathy or diagnosing renal infarction.[235] Magnetic resonance angiography has been extensively used to screen for renal artery stenosis[236,237] and magnetic resonance venography for renal vein thrombosis.[238] However, using gadolinium-containing contrast agents should be avoided if possible in AKI and in patients with CRF with a GFR of 30 mL/min or less given the concern for the development of nephrogenic systemic fibrosis.[239] Nephrogenic systemic fibrosis has been associated with all five of the most common gadolinium agents used in the United States and the Food and Drug Administration has issued updated boxed warnings with their administration.[240] Renal arteriography is sometimes necessary to diagnose polyarteritis nodosa.[241] Nuclear renal scans may also be useful in diagnosing renal infarction.[242]

Other Laboratory Testing

Certain specific laboratory results are nearly diagnostic for certain causes of AKI such as a positive anti-GBM Ab in Goodpasture syndrome. However, most often a final diagnosis is achieved by using and reviewing many associated laboratory findings that may help narrow the differential and result in a diagnosis; at times, a renal biopsy is required for definitive diagnosis. For example, AKI with associated anemia, hypercalcemia, a normal anion gap metabolic acidosis, an elevated total serum protein, and rouleaux formation on peripheral smear all suggest multiple myeloma. AKI with microangiopathic hemolytic anemia, an elevated lactate dehydrogenase and bilirubin level, a negative Coomb test result, and thrombocytopenia suggest a thrombotic thrombocytopenic purpura or a hemolytic uremic syndrome. A markedly elevated creatine phosphokinase with AKI suggests rhabdomyolysis. Bicytopenia or pancytopenia with an elevated sedimentation rate and a prolonged prothrombin time suggests the presence of a lupus anticoagulant with possible associated SLE. Peripheral eosinophilia with AKI suggests the possibility of an AIN. Hypercalcemia and AKI would warrant a workup for a paraproteinemia, malignancy, sarcoidosis, or tuberculosis in the appropriate clinical setting. Marked hyperphosphatemia and AKI suggest acute phosphate nephropathy. Hyperphosphatemia, hyperuricemia, and severe hyperkalemia raise the possibility of a tumor lysis syndrome. Severe hyperuricemia alone with AKI suggests an acute uric acid nephropathy. Overall, additional specific laboratory testing is often required to narrow the differential for AKI. Certain specific serologic tests ordered to screen for vasculitides include antinuclear antibody, anti–double-stranded DNA, extractable nuclear antigen, complements including C3 and C4 levels, ANCAs including antimyeloperoxidase, anti-proteinase 3, anti-GBM antibody, hepatitis B and C antibodies, cryoglobulins and cryocrit, human immunodeficiency virus, antiphospholipid, and anticardiolipin antibodies.

Renal Biopsy

The most common causes of acute renal injury such as prerenal azotemia and ATN do not require a renal biopsy. Renal biopsy is indicated for any cause of renal failure that is indeterminate and where tissue diagnosis may alter treatment.[243] Renal biopsy is sometimes considered for critically ill patients who develop unexplained AKI and have been exposed to multiple offending nephrotoxic agents with either incomplete or no renal recovery. Cortical necrosis may develop in some patients with prolonged and profound ischemic ATN requiring multiple pressor agents in the setting of severe hypotension. This is an essentially irreversible form of AKI that is likely a continuum of ATN, and although rare, is often diagnosed on renal biopsy. The presence of a nephritic syndrome with dipstick hematuria and proteinuria and a urine microscopy demonstrating RBCs, RBC casts, and acanthocytes all suggest an active proliferative GN that often requires a renal biopsy for definitive diagnosis. Considerations of performing a renal biopsy in the critically ill patient is often confounded by comorbid conditions (such as infections, coagulopathy, respiratory failure requiring ventilator support) and certain medications (such as antiplatelet agents and other anticoagulants). Absolute contraindications to renal biopsy initially included uncontrolled severe hypertension, uncooperative patients, a bleeding diathesis, and a solitary kidney.[244] More recently, it has been suggested that with better techniques and procedures, a percutaneous renal biopsy can be performed in patients with a solitary kidney.[245] Renal biopsy has also been shown to be safe in ventilated ICU patients.[246] The primary risk of renal biopsy is bleeding[247–249] into the collecting system resulting in hematuria, underneath the renal capsule essentially causing a renal tamponade, or into the perinephric space. Most clinically significant bleeding occurs within the first 24 hours and thus most patients are observed for one day after a renal biopsy.[250]

Prevention

The prevention of AKI in the ICU setting should be aimed at changing or altering those modifiable risk factors that have been shown to increase the risk of AKI. These modifiable risk factors include appropriate dosing of medications, avoidance of potentially nephrotoxic agents, optimizing volume status to maintain renal perfusion, and avoiding hypotension. Certain preventative measures for AKI are also disease, agent, and medication specific.

Maintenance of Renal Perfusion

Prerenal azotemia and ATN account for the majority of causes of AKI in the hospital and ICU setting. ATN is often multifactorial with several confounding factors often potentially contributing, including ischemia, sepsis, and nephrotoxic agents. The first step in preventing ATN is to identify patients with comorbidities that increase the risk of ATN; these include patients with CKD, diabetes mellitus, obesity, malignancy, and coronary artery disease.[251–253] Patients in the hospital setting at risk for ATN should also be identified, including patients requiring intravenous contrast studies, patients with sepsis, or patients at high risk for developing hypotension, including those with hemorrhagic and cardiogenic shock and severe dehydration.

For all patients at increased risk for ATN, optimizing volume status and hemodynamic status to improve or maintain renal perfusion is a prudent first step in AKI prevention. Perioperative optimization of hemodynamic status in surgical patients undergoing both elective and emergent surgical procedures has been shown to decrease the risk of AKI.[254] Most published data exist for preventative strategies with IVF administration that is specific for the clinical scenario

of the patient. Intravascular volume expansion has been shown to decrease the risk of AKI for radiocontrast-induced nephrotoxicity,[255,256] myoglobinuric and hemoglobinuric AKI,[257–259] cisplatinum,[260] aminoglycoside,[261,262] amphotericin nephrotoxicity,[263,264] and the tumor lysis syndrome.[265] Given the complex nature of AKI development in the setting of sepsis, the role of volume administration in its prevention in this cohort is more challenging. Proposed mechanisms of renal injury in patients with sepsis have included renal ischemia owing to hypoperfusion and hypoxemia,[266] but newer evidence suggests other multiple contributing factors, including renal macrocirculatory and microcirculatory disturbances, surge of inflammatory markers and oxidative stress, coagulation cascade activation, and bioenergetic adaptive response with controlled tubule cell-cycle arrest.[267] Patients with sepsis have now been shown to have normal or even elevated renal blood flow, which has been shown to be associated with a redistribution of blood flow from the cortical to medullary regions. Septic shock with resulting hypotension is secondary to a combination of factors, including diffuse vasodilatation, a redistribution of intravascular fluid, and myocardial depression.[268,269] Despite these complex and interrelated systemic factors in the setting of sepsis, such as an increased cardiac output in the setting of hypotension and a depressed myocardium, the use of IVFs and goal-directed therapy have been advocated in the setting of sepsis with some reduction in AKI incidence.[270] The optimal volume of resuscitation is unknown; however, in a prior study, the mean volume of resuscitation was 5 L within the first 6 hours[271] with more recent studies using 2 to 3 L within the first 6 hours.[272,273] Careful monitoring of these patients is crucial. Although IVF boluses are intended to prevent hypotension and maintain renal perfusion, patients with sepsis are at increased risk for developing CHF and noncardiogenic pulmonary edema (ARDS). Excess amounts of fluid given to patients with sepsis have been shown to prolong ventilator dependency.[274]

The choice of fluids for intravascular volume expansion in patients with hypovolemic shock and septic shock include crystalloid solutions (such as saline solution and buffered solutions such as Ringer lactate and bicarbonate-buffered 0.45% saline solution), colloid-containing solutions (such as albumin), and blood products (including packed RBCs or their substitutes).

For hypovolemic shock not caused by bleeding, crystalloid solutions, particularly saline solution, are preferred to colloid-containing solutions because no mortality benefit has been attributed to colloids over crystalloid solutions[275–277]; additionally, colloids are much more expensive. The use of synthetic colloids has been thought to provide a better intravascular volume expansion than colloid solutions; however, hyperoncotic starch solutions should be avoided as they have an associated increased risk of AKI, need for RRT, and even death.[278–281] Similar to intravascular volume depletion, in the setting of sepsis, crystalloids are preferred to colloids because no definitive mortality benefit has been observed with albumin versus crystalloids[282,283] and synthetic colloids should similarly be avoided.

Multiple pharmacologic agents have been studied in an attempt to decrease the risk of AKI and maintain renal perfusion. Dopamine has been shown to be ineffective in preventing AKI[284–286] and in some cases has demonstrated deleterious renal effects.[287] The use of fenoldopam, a dopamine receptor-1 agonist, has also had discordant results with both positive protective effects[288,289] and results demonstrating no benefit.[290] Natriuretic peptides such as atrial natriuretic peptide (ANP) have been studied but similar discordant results have limited its use.[291] Diuretics have also not demonstrated any preventive AKI effects.[292,293] Overall, as such none of these pharmacologic agents has shown reproducible beneficial protective AKI effects and therefore cannot be advocated.[6]

Avoidance of Nephrotoxicity

A major function of the kidney is the concentration and excretion of potentially toxic medications, many of which are used to treat critical illness in hospitalized ICU patients. The kidney is a frequent site of drug toxicity because medications can damage cells within all compartments of the kidney, including the renal tubules, the interstitium, or most commonly, a combined tubulointerstitial injury. Medication-induced glomerular injury is less common. Drug-induced nephrotoxicity has been reported to cause between 8% and 60% of in-hospital AKI.[294] Common nephrotoxins include NSAIDs, aminoglycosides, radiocontrast agents, antibiotics, ACE inhibitors and ARBs, PPIs, chemotherapeutic agents, lithium, interferon, acyclovir, colistin, methotrexate, and nucleoside inhibitors.

The prevention of nephrotoxicity from certain medications requires several approaches, including early recognition of their potential nephrotoxicity, because stopping the offending agent often leads to renal recovery. As in the case for certain causes of AIN, the use of steroids has shown some potential benefit in renal recovery. Additional considerations in preventing medication-induced nephrotoxicity include avoiding combined nephrotoxic agents that may have additive nephrotoxicity, identifying high-risk cohorts, using nephrotoxic agents for the shortest interval possible, using alternative nonnephrotoxic medications when available, monitoring renal function closely, and following measurable blood levels when appropriate.

NSAIDs including selective cyclooxygenase inhibitors (COX-2) can cause renal insufficiency via several mechanisms in up to 5% of patients,[295,296] with the most common being a hemodynamically mediated etiology. Risk factors for NSAID-induced AKI include CKD, volume depletion, heart failure, hypertension, older age, and concomitant use of certain medications including ACEs, ARBs, and diuretics.[297–299] The mechanism of the hemodynamically mediated AKI is inhibition of cyclooxygenase enzymes with subsequent decrease in prostaglandin-mediated afferent vasodilatation, which can lead to reversible renal ischemia.[300] The combination use of NSAIDs with other potential nephrotoxic medications or agents such as radiocontrast media should be avoided given the increased risk of nephrotoxicity.[301,302]

Prevention of NSAID nephrotoxicity should be aimed at avoiding their use in high-risk patients. Other potential manifestations of NSAID-induced renal effects include interstitial nephritis, minimal change disease, membranous nephropathy, papillary necrosis, and electrolyte abnormalities such as hyperkalemia and hyponatremia. NSAID-induced AIN typically occurs after a more prolonged course of treatment than in β-lactam–induced AIN.[303]

PPIs have been used for the treatment of acid reflux disorders for many years. Several studies have demonstrated their role in causing AIN.[304–307] Typically patients with PPI-induced AIN lack the triad of symptoms typically associated more with antibiotic-induced AIN. More recently, PPI use has been associated with an increased risk of incident CKD, progression of CKD, and ESRD.[308,309] Whether the mechanism of increased incident CKD is related to an increased AIN incidence or other mechanism is unknown.

Aminoglycosides have been commonly used in the treatment of multiple infections in the hospitalized patient and rates as high as 24% in vascular surgery patients have been described.[310] The

proximal renal tubule is the typical site of injury. Renal insufficiency typically occurs 5 to 7 days after treatment with creatinine typically returning to baseline approximately 21 days later after allowing for regeneration of healthy proximal renal tubular cells. Risk factors for aminoglycoside toxicity include prolonged use, elevated plasma drug levels, increased age, associated concomitant comorbid conditions (such as leukemia and diabetes mellitus), decreased intravascular volume, endotoxins and sepsis, concomitant use of certain medications (such as furosemide [Lasix], ACE inhibitors, and vancomycin), as well as the type of aminoglycoside.[311–318]

Preventive strategies to minimize aminoglycoside nephrotoxicity include selecting the least nephrotoxic agent, a once-daily dosing regimen, and avoiding their use either in a prerenal state or with other potentially nephrotoxic medications. Gentamicin has been reported as the most nephrotoxic aminoglycoside[311] with tobramycin less nephrotoxic than gentamicin.[319,320] Once-daily dosing of aminoglycosides versus standard dosing has shown comparable bacteriologic cure rates with lower rates of AKI.[321,322] ACE inhibitors and ARBs are extensively used because their use has shown benefits in multiple clinical cohorts, including the slowing of kidney disease progression in patients with diabetic nephropathy,[323] as well as improved mortality in patients with cardiomyopathy[324] and acute myocardial infarction.[325] ACE inhibitors can also cause an acute decrease in GFR in patients with CKD, bilateral renal artery stenosis, and hypertensive nephrosclerosis.[326,327] Typically many patients using an ACE inhibitor already have a reduction of their intrarenal perfusion pressure. GFR is partially maintained via an angiotensin II–induced increase in resistance of the efferent arteriole, which helps maintain intraglomerular pressure and GFR. Blocking this physiologic response with ACE inhibitors by relaxing the efferent arteriole results in a lower intraglomerular pressure and a subsequent reduction in GFR. ACE inhibitor use in intravascular volume–depleted states such as vomiting and diarrhea may cause AKI and should be avoided.[328] The rise in creatinine can be acute but generally occurs 3 to 5 days after initiation of an ACE or ARB. The most common electrolyte abnormality associated with ACE inhibitors is hyperkalemia.[329]

Many other medications occasionally used in the ICU may cause nephrotoxicity. Colistin has been reported to cause AKI in up to 43% of patients.[330–333] Intravenous vitamin C, secondary to possible antioxidative effects, has been shown to have potential renoprotective effects for colistin-induced AKI[334] but study results have been discordant.[335] As previously described, most medications cause nephrotoxicity through a tubulointerstitial process but glomerular injury can occur. Various exogenous interferons are associated with minimal change disease and focal segmental glomerulosclerosis.[336] Oral bisphosphonates are considered nonnephrotoxic, whereas intravenous bisphosphonates are potentially nephrotoxic; pamidronate is associated with nephrotic syndrome and a collapsing form of focal segmental glomerulosclerosis[337,338] and zoledronic acid is associated with a tubular toxicity.[339] A thrombotic microangiopathy (TMA) is associated with certain antiangiogenesis medications such as vascular endothelial growth factor inhibitors[340] and certain chemotherapeutic agents such as gemcitabine[341,342] and mitomycin C.[341,343] There is no clear evidence for prevention of TMA in the above settings and treatment primarily consists of stopping the offending agent if TMA develops.

Prevention of Contrast Nephrotoxicity

The use of iodinated contrast studies is often unavoidable in the care of critically ill patients. As early as the 1960s, intravenous contrast was described as causing AKI[344] with multiple subsequent studies linking contrast media with AKI.[345–349] The incidence of contrast-induced AKI (CI-AKI) in critically ill patients has been reported to be 2% to 18% with multiple factors contributing to this wide variation, including the variable study population and the definition of AKI.[350] The simple daily variation of serum creatinine values in critically ill patients who have not even received intravenous contrast has been reported to also complicate the interpretation of CI-AKI in the critically ill population,[351] for which small rises in creatinine are often used to define AKI. Typically the creatinine rises within 24 to 48 hours after the contrast is administered. The pathophysiology of contrast nephrotoxicity is not completely understood but primarily involves a tubular injury inducing ATN. The proposed mechanisms of ATN include renal vasoconstriction and direct cytotoxic effects.[352–355] Risk factors for CI-AKI include CKD, diabetes mellitus, increasing age, type of ionic contrast agent used, CHF, hypovolemia, and multiple myeloma.* The risk of CI-AKI in patients who do not have these associated risk factors is low.[347] Because the clinicians caring for patients are responsible for the timing of the patient receiving iodinated contrast, preventive strategies to minimize AKI risk should be pursued as there is no specific treatment once CI-AKI develops. Certainly, using alternative diagnostic modalities with avoidance of iodinated contrast in the higher-risk populations should be considered whenever possible. Although not widely used, carbon dioxide has been given in angiographic procedures as an alternative diagnostic interventional radiographic agent.[358] However, if intravenous contrast is required, other preventive strategies are required. Lower doses of iodinated contrast should be used wherever possible as the risk of AKI is less with lower administered doses.[359,360] The type of iodinated contrast also affects risk of CI-AKI as the nonionic low osmolal or iso-osmolal agents have a lower risk of AKI than the first-generation hyperosmolal ionic contrast agents.[347,361] The primary therapeutic intervention in preventing CI-AKI is administering periprocedure isotonic IVF when it is not clinically prohibitive, such as in patients who have CHF. The type of IVF used to prevent CI-AKI has been shown to be important as isotonic saline solution has been shown to be superior to one-half isotonic saline solution.[256] Because alkalinization may protect against free radical injury, using isotonic bicarbonate has been compared with isotonic saline solution but results have been conflicting.[362–365] Thus as there are no clear superiority benefits of isotonic bicarbonate solutions over isotonic saline solution, periprocedure isotonic saline solution for 6 to 12 hours both before and after the procedure is generally used as a preventive strategy in the hospitalized patient when clinically appropriate.

In addition to IVF serving to prevent CI-AKI, multiple additional agents, either administered alone or in combination with other pharmacologic agents, have been studied but most have not demonstrated a clear benefit with some agents actually demonstrating increased risks of nephrotoxicity. The use of diuretics and mannitol with IVF[366,367] has not shown benefits in preventing CI-AKI and has shown potential harm; thus it has been recommended to consider holding oral diuretics before any contrast periprocedure study.[365] Forced diuresis with matched saline solution infusion has shown some renoprotective effect[368,369] but further studies are needed before wider adaptation given concerns regarding arrhythmia risk and volume administration. Oral hydration compared with IVF in preventing CI-AKI has demonstrated discordant results.[370,371]

*See references 345, 346, 348, 352, 356, 357.

Dopamine infusion and ANP use have been reported as having an increased risk of CI-AKI.[372] The use of ascorbic acid has also had variable results in preventing CI-AKI.[371,373] N-acetylcysteine (NAC), a thiol compound with both antioxidant and vasodilatory properties, is available in both oral and intravenous formulations, and its favorable side effect profile and relative low cost have prompted its study for potential prophylactic benefits in preventing CI-AKI. Multiple studies, however, have shown discordant results[374–377] and thus even practice guidelines have had variable recommendations with KDIGO suggesting using NAC and IVF in high-risk patients,[6] whereas the American College of Cardiology and American Heart Association guidelines do not recommend its use.[378]

The potential of removing the iodinated contrast from the circulation to limit CI-AKI after contrast has been administered has prompted several studies evaluating the potential benefit of hemofiltration and hemodialysis (HD). A meta-analysis from 2012 consisting of 11 published studies concluded that periprocedural RRT did not decrease the incidence of CI-AKI, with HD potentially increasing CI-AKI risk.[379]

Management of Established Acute Kidney Injury

General Aspects

Once AKI develops, the specific management is generally tailored to the etiology of the AKI, carefully monitoring volume status, and managing the clinical manifestations associated with AKI, including electrolyte and organ-specific complications. Patients with prerenal azotemia should have intravascular deficits replaced. Those with cardiorenal syndrome (CRS) should have cardiac function optimized. The early descriptions and definitions of CRS focused more on a unidirectional etiology in that CRS was defined as a condition in which therapy to relieve CHF was affected by a decrease in the GFR. More recent definitions have focused on the bidirectional interactions between the heart and the kidney. Five types of CRS were initially proposed by Ronco and colleagues.[380] Type 1 was acute heart failure causing AKI, whereas type 2 was chronic heart failure causing renal insufficiency. Types 3 and 4 bring attention to the primary role of kidney disease potentially worsening heart failure, and type 5 CRS describes systemic disorders worsening both cardiac and renal function.[380] Defining renal failure as secondary to heart failure can be clinically difficult because there are no specific diagnostic tests, but typically patients lack proteinuria and have an inactive sediment unless the patient has underlying CKD. In 2012, the 11th Consensus Conference of ADQI group developed a work group to better review the pathogenesis of type 1 CRS. Potential mechanisms of CRS type 1 in causing AKI included low cardiac output, activation of vasoactive substances resulting in decreased renal perfusion, increased IAP, and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[381] Further studies are necessary, however, to better define the pathophysiology of these different types to improve evaluation of the treatment of patients clinically within these different categories of the CRS.

Patients with an obstructive uropathy should have all reasonable attempts undertaken to relieve the obstruction. Patients with an AIN should have the offending agent stopped and, although not conclusive, initiating steroids has shown some benefit. Typically an acute GN is treated dependent on the specific syndrome but generally involves immunosuppressive agents including steroids. Rhabdomyolysis is often treated with IVF. The ACS is often treated surgically by decompression. The best treatment for the hepatorenal syndrome is to treat the underlying etiology of the liver failure. For critically ill patients, norepinephrine, vasopressin, and albumin have shown effectiveness.[382–385] Overall, many AKI complications are not unique to the specific cause of renal failure and thus treatment of AKI is always initially driven by the specific cause.

Management of Volume Status

After optimizing volume status, the use of diuretics to treat AKI should be based on the volume status of the patient. Oliguria is typically defined as urine volume less than 400 mL/day and anuria as urine volume less than 50 mL/day. Some data suggest that critically ill patients with nonoliguric AKI have better outcomes with overall lower morbidity and mortality and lower incidence of dialysis than patients with nonoliguric ATN[386–388]; however, some studies have shown discordant results with increased in-hospital mortality in patients with nonoliguric ATN that could possibly be secondary to delayed initiation of dialysis secondary to diuretic use.[64] Overall, there is a lack of evidence supporting the use of diuretics in attempting to convert an oliguric AKI to a nonoliguric AKI. Thus use of diuretics in this clinical scenario should be dependent on the volume status of the patient; if the patient does not have intravascular volume expansion or total body water excess, diuretics should be avoided.[6,65] However, there are data to suggest that patients with positive fluid balance after AKI have higher mortality.[61–63,385] Thus in the latter cohort of patients, a trial of diuretics as short-term treatment for volume control would seem appropriate.

Prophylactic use of other medications with renal vasodilatory properties to prevent ATN or treat AKI, such as fenoldopam, dopamine, and atrial natriuretic peptide, has been studied with overall lack of evidence supporting their general use. Fenoldopam, a dopamine receptor-1 agonist, has shown discordant results.[288–290,389–392] In a recent large multicenter randomized, placebo-controlled parallel-group study of fenoldopam use in early AKI after cardiac surgery, fenoldopam showed no effect on the need for RRT or mortality at 30 days.[392] In a recent meta-analysis of fenoldopam use in the perioperative setting of patients undergoing cardiothoracic surgery, partial nephrectomy, or liver transplantation, fenoldopam use was associated with a reduction in postoperative AKI but, similar to many previous studies, its use had no impact on RRT or hospital mortality.[393]

Dopamine has natriuretic effects on the proximal tubule as well as vasodilatory properties on both the afferent and efferent arterioles.[394–396] As such, low dose dopamine has been extensively studied as a prophylactic agent in ATN. However, many studies have shown that it is ineffective in preventing ATN.[284–287,397] ANP, a natriuretic peptide, has both diuretic and natriuretic effects. It inhibits tubular sodium reabsorption and causes vasodilatation of afferent arterioles. Some small studies regarding ANP use in preventing AKI have shown some potential benefit,[398–400] but its use has not been clinically endorsed.[6]

Preventing, Monitoring, and Treating Complications

Complications of AKI include the development of several electrolyte abnormalities, such as hyperkalemia, hyponatremia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperuricemia,

hypercalcemia, and hypermagnesemia. At times, certain preventive approaches can prevent these complications such as a low-potassium diet to help prevent hyperkalemia. In certain clinical scenarios, hypercalcemia may occur. AKI is also associated with an increased risk of infections and hematologic disturbances including bleeding and anemia. There are several organ-specific associations, including neurologic disturbances, respiratory failure, cardiac dysfunction, and gastrointestinal complications. (A detailed discussion of these complications can be found in the online supplement at www.expertconsult.com.)

Hyperkalemia

The incidence of hyperkalemia has increased among hospitalized patients[401] and is a potentially serious complication of AKI that has been associated with increased all-cause and in-hospital mortality.[402,403] Among patients with AKI, hyperkalemia is considered the most serious electrolyte abnormality given its potential for increased cardiac arrhythmias. Potassium is primarily an intracellular cation with a cellular concentration of 140 mEq/L compared to 4 to 5 mEq/L in the extracellular space. This difference in concentration is maintained by the sodium-potassium-adenosine triphosphatase (Na-K-ATPase) pump and is the main determinant of the resting membrane potential. Hyperkalemia reduces the resting membrane potential and electrocardiographic (ECG) changes can occur. Although a specific serum potassium level does not correlate with precise ECG manifestations, the typical progression of ECG changes with progressive hyperkalemia include peaked T waves, atrial asystole, prolongation of both the PR and QRS intervals with eventual sine wave, ventricular fibrillation, and asystole. Although muscle weakness and paralysis can occur with severe hyperkalemia, most patients are initially asymptomatic. The treatment of hyperkalemia often includes treatment of the precipitating risk factors, preventing life-threatening cardiac arrhythmias by administering calcium-based salts, shifting of potassium from the extracellular to the intracellular space, and enhancing potassium elimination by inducing a kaliuresis or using cation exchange resins.[404] Patients with oliguric or anuric AKI and associated hyperkalemia often require a more emergent treatment approach. Unless patients have a readily reversible cause of AKI producing hyperkalemia (such as bladder outlet obstruction where placement of an indwelling catheter can relieve the obstruction and improve solute clearance relatively rapidly), treatment options may be limited and the patient may require HD. HD removes potassium more rapidly versus peritoneal dialysis (PD) and thus HD is preferred to PD in treating patients with severe hyperkalemia.[405]

The first assessment in the treatment of hyperkalemia is to address whether effective removal of potassium from the body can be achieved. Options include attempted kaliuresis with IVFs in the setting of prerenal azotemia with expectant recovery of solute clearance and improved urine output with intravascular volume replacement. Loop diuretics may be helpful in inducing kaliuresis in hypervolemic patients or in euvolemic patients with mild hyperkalemia receiving IVF, but they are not recommended as a sole treatment of severe hyperkalemia with advanced renal failure. Gastrointestinal losses of potassium by administration of cationic exchange resins are available but should be avoided in postoperative patients and those with suspected bowel obstruction given the higher risk for intestinal necrosis. Two widely used cation exchange resins are patiromer and sodium polystyrene sulfonate. The active moiety of patiromer is a nonabsorbed polymer that binds potassium in exchange for calcium predominantly in the distal colon.[406] Sodium polystyrene sulfonate may also lower the serum potassium and may be given orally or as a retention enema. Removal of potassium from the body may not always be feasible, and especially with hyperkalemic-induced ECG changes, medications to shift serum potassium intracellularly are often used. Insulin administration can help lower the serum potassium by enhancing the activity of Na-K-ATPase pump in skeletal muscle, which helps drive potassium intracellularly.[407] Glucose is often administered simultaneously to prevent hypoglycemia. The serum glucose should be monitored closely after insulin administration to check for potential development of hypoglycemia. Sodium bicarbonate can also lower serum potassium by raising the serum pH, which results in hydrogen ion release from cells and compensatory movement of potassium intracellularly to maintain electroneutrality. The overall clinical benefit of the effect of sodium bicarbonate in lowering serum potassium has been variable and often is the least effective of the available potential treatment interventions.[408] Albuterol, a β_2-adrenergic agonist, can also be used to help drive potassium intracellularly by also activating the Na-K-ATPase pump in skeletal muscle. Its effect can be additive with insulin and glucose in lowering serum potassium.[409] Use of intravenous calcium to antagonize and stabilize cardiac membrane excitability in patients with severe hyperkalemia will have effects that typically last only up to 60 minutes. One of the major concerns of intravenous calcium use is that many of these AKI patients have associated hyperphosphatemia and intravenous calcium may cause precipitation of calcium and phosphate in cardiac, vascular, and soft tissues. After initial treatment of moderate to severe hyperkalemia, guidelines suggest that a repeat serum potassium level be checked 1 to 2 hours later.[410]

Hyponatremia

Hyponatremia is commonly seen with AKI and becomes more prevalent as AKI worsens. The etiology is usually secondary to an inability to excrete free water. As renal failure worsens, the lowest urine osmolality that can be achieved often rises to 200 to 250 mOsm/kg despite a decrease in antidiuretic hormone, whereas in patients with normal renal function, the urine osmolality can be lowered to 50 mOsm/kg. This defect in free water excretion can lead to accumulation of free water with resultant hyponatremia. Typically patients with hyponatremia have a proportional reduction in the serum osmolality, but this may not occur with advanced renal failure because the rise in BUN can counteract the fall in serum osmolality induced by the hyponatremia. Patients are often asymptomatic but mental status changes and seizures can occur if the hyponatremia becomes severe. Treatment includes water restriction, avoidance of medications that can worsen hyponatremia, and occasionally dialysis is indicated.

Calcium, Phosphorus, and Magnesium Disorders

Hyperphosphatemia is a known complication of AKI and is often associated with hypocalcemia. The kidney has a major influence on phosphate balance, and thus hyperphosphatemia in AKI results from a decreased urinary phosphorus excretion. In normally functioning kidneys, only 5% to 20% of filtered phosphorus is excreted in the urine because most of the filtered phosphorus is absorbed in either the proximal tubule (60%–70%) or distal tubule (10%–20%).[411] With a decrease in GFR that accompanies AKI, there is both a decrease in filtration and excretion of phosphorus. Phosphorus homeostasis can be maintained by the phosphaturic response of increased secretion of both parathyroid hormone (PTH) and phosphatonins such as fibroblast growth factor 23. In the setting of hyperphosphatemia, this adaptive decrease in proximal tubular phosphate reabsorption can be generally maintained until

the GFR falls below 25 to 40 mL/min. Once phosphate tubular reabsorption is maximally suppressed and the increased urinary excretion can no longer keep pace with phosphate intake, the serum phosphate level will rise. As the serum phosphorus level increases, the calcium level often decreases. Mild elevations in serum phosphorus can usually be treated by preventive measures such as limiting phosphate intake[412] or by using phosphate binders with meals to prevent dietary absorption of ingested phosphate.[413] Phosphate binders are generally divided into calcium-containing binders such as calcium carbonate and calcium acetate and noncalcium-containing binders such as sevelamer, lanthanum carbonate, sucroferric oxyhydroxide, and aluminum hydroxide. The optimal choice of phosphate binder remains controversial; however, aluminum-containing phosphate binders should be avoided for any prolonged use to avoid aluminum toxicity. In severe hyperphosphatemia, standard HD is usually ineffective in removing lowering serum phosphorus, but prolonged nocturnal HD does provide much better phosphate control and often obviates the need for phosphate binders.[414–416]

Hypocalcemia in AKI is often multifactorial in etiology. Hyperphosphatemia often leads to chelation with calcium, leading to hypocalcemia and the potential for calcium-phosphate salt deposition in soft tissues. Another contributory factor to hypocalcemia in AKI is the skeletal resistance of bone to PTH. This skeletal resistance to PTH may result from the inability of the kidney in AKI to convert the inactive form of 25-(OH)-vitamin D to the active 1,25-$(OH)_2$-vitamin D. Low levels of this active form of vitamin D are typically seen with AKI. Typically patients with hypocalcemia in AKI are asymptomatic, although with more severe hypocalcemia, symptoms such as carpopedal spasm, tetany, and seizures may occur. Treatment is generally aimed at lowering the serum phosphorus level, which often results in improved serum calcium levels. Treatment with intravenous calcium is usually reserved for the rare occurrence of symptomatic hypocalcemia.

When hypercalcemia occurs in the setting of AKI, the pathophysiology may be multifactorial and includes primary hyperparathyroidism secondary to PTH–mediated osteoclast activation, multiple myeloma via osteoclast activating factors, humoral hypercalcemia of malignancy via PTH-related protein effects, and in the recovery phase of rhabdomyolysis secondary to release of calcium into the circulation from prior deposition of calcium into injured muscle.

Hypermagnesemia may be seen in AKI. Even small amounts of ingested daily magnesium can result in hypermagnesemia with AKI. Medications with any magnesium content should generally be avoided in patients with renal failure. Treatment options for mild hypermagnesemia include IVF and diuretics when clinically feasible, but in more severe hypermagnesemia, intravenous calcium[417] and HD may become necessary.

Hyperuricemia

Many epidemiologic studies and meta-analysis have linked hyperuricemia as a risk factor for AKI development in several settings, including hospitalized patients, those undergoing coronary artery bypass grafting, contrast studies, or cisplatin therapy.[418–423] The kidneys account for approximately two-thirds of uric acid excretion with gut elimination accounting for the other one-third under normal physiologic circumstances. In the kidney, approximately 90% to 95% of the filtered urate is absorbed in the proximal tubule. Uric acid may cause AKI through several mechanisms, including direct tubular toxicity from crystal-induced injury or indirectly through potential vasoconstriction, oxidative stress, and inflammatory changes.[418] In AKI, the GFR is usually quite low with small amounts of uric acid filtered and thus intratubular precipitation of uric acid does not occur. Uric acid nephrolithiasis and acute gouty flares are not typically seen with AKI. Hyperuricemia, however, is common with AKI but is mostly asymptomatic and the level is often less than 12 mg/dL. However, in those patients who are prerenal secondary to intravascular vole depletion or are receiving loop and thiazide diuretics when proximal reabsorption of sodium and urate are increased, higher serum uric acid levels may be seen. One disorder in which uric acid is nephrotoxic is in acute uric acid nephropathy (UAN). UAN typically develops in patients treated for leukemia, lymphoma, or bulky tumors with radiation or chemotherapy that results in a marked overproduction and excess excretion of uric acid. Patients generally have associated oligoanuria and marked hyperuricemia. The serum uric acid level is usually greater than 15 mg/dL. The urinalysis in patients with UAN often demonstrates uric acid crystals but the latter are nondiagnostic. Another potential clue for the diagnosis of UAN is an elevated spot urine uric acid/creatinine ratio that is typically greater than 1 with UAN, whereas it is less than 0.6 to 0.75 with other forms of AKI.[424,425] Although treatment of asymptomatic AKI-induced hyperuricemia is usually not initiated, in patients with UAN a combination of preventative and therapeutic modalities, including aggressive IVF, recombinant urate oxidase, and xanthine oxidase inhibitors, is often used.

Metabolic Acidosis

The kidney plays a major role in acid-base regulation. The relatively fixed daily nonvolatile acid production rate is approximately 50 to 100 mEq of hydrogen ions (H^+)/day. Elimination of this acid load and maintenance of acid-base homeostasis is maintained by the urinary excretion of hydrogen ions, both as titratable acidity and as ammonium. Metabolic acidosis begins to develop in AKI when either a combination of the damaged kidney to generate new bicarbonate or an inability of the kidney to further increase ammonium excretion results in the accumulation of plasma organic acids and other unmeasured ions. This typically occurs when the GFR decreases below 40 to 50 mL/min. Much of the acid secreted by the kidney is the product of daily metabolism and as such, the metabolic acidosis in AKI is typically mild and usually does not require treatment with alkali. The decline in plasma bicarbonate concentration is usually 0.5 to 1.0 mmol/L per day.[426] However, many patients with AKI have contributing factors that result in worsening acidosis, such as hypotension, sepsis, and multiorgan failure, or even superimposed toxic ingestions that can often lead to generation of lactic acid and ketoacids and a more severe metabolic acidosis. The latter acidemia that develops is typically a high anion gap metabolic acidosis. As there are no official guidelines or general consensus to suggest the optimal timing of administering alkali therapy or initiating dialysis in patients with severe metabolic acidosis and AKI, the treatment strategies are based on the individual clinical situations.

Hematologic Complications: Anemia and Bleeding

Anemia is frequently associated with AKI in critically ill patients[427] and has been associated with worse outcomes in ICU patients.[428] Some degree of anemia often occurs with AKI, and the etiology is often multifactorial; causes include reduced RBC production secondary to erythropoietin deficiency, frequent phlebotomy, bone marrow suppression from certain medications, systemic disorders affecting both the kidney and the hematopoietic system (such as hemolytic uremic syndrome and SLE), gastrointestinal bleeding,

and blood loss from dialyzers. The anemia in AKI is typically mild, slowly developed, well tolerated, and asymptomatic; treatment using erythropoietin has not been associated with a decrease in transfusion requirements or enhanced renal recovery.[427] A restrictive strategy of blood transfusions using a threshold of 7 g/dL in hemodynamically stable ICU patients without ischemic heart disease had similar 30-day mortality rates compared to liberal transfusion, and in certain subgroups such as those younger than 55 years of age and with Acute Physiology and Chronic Health Evaluation (APACHE) II scores less than 20, the mortality rates were actually lower in the restrictive strategy cohorts.[429] The overall relationship between anemia and AKI and the effect of anemia on long-term mortality in critically ill patients is unresolved. In a recent retrospective analysis of 2145 ICU patients with anemia and AKI with long-term follow-up of 10 years, a hemoglobin level less than 10.5 g/dL was associated with both an increased 10-year mortality and AKI risk.[430]

Similarly, in a study of 3472 patients undergoing transcatheter aortic valve implantation for severe aortic stenosis, both preprocedural and postprocedural anemia were significantly associated with AKI and 1-year mortality.[431]

Bleeding

Overt bleeding in the setting of AKI and uremia can be manifested by gastrointestinal bleeding, active bleeding after procedures such as percutaneous renal biopsies, spontaneous bleeding directly into the skin or joints, oropharyngeal bleeding, or bleeding in the respiratory system.[432] The mechanism by which AKI and uremia affect bleeding risk is multifactorial and includes platelet dysfunction, uremic toxins, anemia, and nitric oxide. Impaired platelet function secondary to impaired platelet aggregation and adhesiveness is considered the major cause of uremic bleeding.[433] Mixing studies have shown that uremic toxins can cause platelet dysfunction. Correction of anemia has also demonstrated improved platelet dysfunction.[434] Nitric oxide has been shown to be an inhibitor of platelet aggregation, and nitric oxide synthesis has been shown to be increased in uremic patients.[435] In addition to these specific AKI-induced potential contributory factors that may result in clinical bleeding, other comorbid conditions such as liver disease, thrombocytopenia associated with sepsis, disseminated intravascular coagulation, or disorders such as thrombotic thrombocytopenic purpura may all additionally contribute to the increased risk of bleeding in AKI. Certain medications such as aspirin have been shown to have a cyclooxygenase-independent prolongation of the bleeding time that is greater than that seen in normal subjects taking aspirin.[436] Generally, patients with AKI without active bleeding do not require specific treatment. With uremia, the platelet count, prothrombin time, and partial thromboplastin time are generally normal. The bleeding time, however, is generally prolonged in uremia.[437] Some patients with AKI may develop a bleeding diathesis secondary to abnormalities of primary hemostasis which require treatment. Several therapeutic options to improve and possibly correct the bleeding time in AKI are available. Desmopressin, an analog of antidiuretic hormone, has been shown to shorten the bleeding time in uremia.[438] Desmopressin can be administered intravenously or intranasally and the bleeding time begins to correct within 1 hour of administration. Its effects are short-lived and last only 4 to 8 hours and tachyphylaxis is common. Cryoprecipitate can also be used to shorten bleeding time in uremia[439] and its effects on shortening bleeding time begin in 1 hour and last 4 to 24 hours. Although the specific mechanism of action of these agents in reducing bleeding time is unknown, it is thought that cryoprecipitate results in direct infusion of multimeric forms of factor VIII. Von Willebrand factor aggregates and desmopressin induces the release of large factor VIII; von Willebrand factor multimers from endothelial cells which enhance the binding of platelets to endothelial surfaces.[440,441] Conjugated estrogens have been shown to control bleeding in uremic patients with normalization of the bleeding time.[442] Intravenous administration of estrogens has been studied with its effects noted within 1 day of administration and lasting up to 1 week or longer after the last administered dose.[443] Short courses of estrogens have safely been used in men. The specific mechanism of action is unknown but is possibly related to decreased generation of nitric oxide.[444] Lastly, both PD and HD have been shown to shorten the bleeding time in uremic patients.

Infectious Complications

Although large epidemiologic surveys have clearly described increased mortality associated with AKI, there are few data available on the proximate cause of death among patients with AKI. Infectious complications, however, remain a leading cause of death in patients who develop AKI in the ICU. In a cohort study of 3930 hospitalized patients prospectively identified as having AKI via AKIN criteria, the in-hospital mortality rate was 21.9% and data on the primary cause of death were available for 93.4% of the deceased patients. Death from sepsis was listed as the primary cause of death in 41.1% of patients, whereas AKI was listed as the primary cause of death in only 3.1% of patients.[445]

In a study of CI-AKI, the frequency of sepsis after AKI was 45%.[446] Common sources of infection include intravenous vascular access, including dialysis and triple-lumen catheters; indwelling urinary catheters; operative sites; and skin and respiratory infections. Many ICU patients with AKI are treated with antibiotics for these superimposed infections and are therefore at risk for development of infection with *Clostridium difficile*, the causative agent for antibiotic-associated colitis. Patients with AKI in the ICU may not mount the typical expected response of fever and leukocytosis in the setting of infection compared to those patients with normal renal function[447] and thus careful clinical vigilance is required to monitor for infection. To reduce the risk of infection, all preventive and clinical interventions should be considered to prevent, diagnose, and treat infections early. A careful physical examination with particular attention to central line exit sites should be performed routinely. In addition, central venous and arterial lines and indwelling urinary catheters should be removed as soon as possible. Tailored antibiotic usage with assistance from the antibiotic stewardship program should be used whenever possible to optimize the antibiotic regimen and prevent drug resistance.[448]

Cardiovascular Complications

Cardiovascular complications are frequently encountered in AKI. This organ-organ interaction, also referred to as organ crosstalk, has led to defining the CRS.[449] Type 3 CRS is specifically characterized as worsening of kidney failure leading to heart disease, including acute coronary syndrome, decompensated heart failure, and arrhythmias. Patients with oligoanuria are at risk of developing total body water excess secondary to sodium and water retention, which clinically can be manifested as peripheral edema and ascites. This positive fluid balance can also lead to pulmonary edema and hypertension. Both volume overload and hypovolemia are associated with increased morbidity and mortality in critically ill patients.[450] Thus accurate assessment of the intravascular volume status of these patients is critical to the treatment strategies of either using

diuretics for nonoliguric AKI with volume overload versus IVF for intravascular volume depletion or renal replacement therapies for patients with intractable total body water excess and oligoanuria. Given the heterogeneity of the patient population in the ICU with AKI, goal-directed fluid therapy should be individualized and include serial monitoring using physical examination findings and clinical tools, such as oxygenation, chest radiographs, body weights, urine output, and central hemodynamic monitoring. In addition, use of bedside echocardiography to measure the diameters of both the inferior and superior vena cava may help guide fluid resuscitation in mechanically ventilated patients.[451,452] Several additional cardiovascular complications, such as fatal arrhythmias, myocardial infarction, and pericarditis, can complicate AKI. Hyperkalemia secondary to AKI often requires immediate treatment in the setting of oligoanuria because fatal arrhythmias such as ventricular fibrillation, ventricular tachycardia, and sine wave can develop in patients with severe hyperkalemia.[453] Hypocalcemia often accompanies AKI and can result in prolongation of the QT interval on the ECG and generalized myocardial dysfunction. Uremia itself may also cause myocardial contractility and promote pericardial effusions and pericarditis.[454]

Pulmonary Complications

Volume overload with associated pulmonary edema is a known complication of AKI. This results in impaired gas exchange, and mechanical ventilation often is required in up to 50% of patients with severe AKI. Mechanical ventilation is a risk factor for increased mortality in patients with AKI[20] and is also considered a proinflammatory intervention that contributes to the increased inflammatory load of critically ill patients.[455] Some of the pulmonary alterations in AKI include increased vascular permeability, alveolar edema formation, neutrophil extravasation, and pulmonary microhemorrhages.[456] Avoiding mechanical ventilation whenever possible in patients with AKI in the ICU would seem prudent because this cohort of patients has significantly longer requirements for mechanical ventilation even without oliguria.[457] The development of respiratory failure with AKI has been shown to have additive effects on mortality. In a retrospective, observational cohort study of data of 217,994 patients who underwent high-risk intraabdominal general surgical procedures, in patients in whom both respiratory failure and AKI developed, the 30-day mortality rate was 65.2% versus a 30-day mortality rate of 7.24% and 10.8%, respectively, if only AKI or respiratory failure developed.[458]

Excess volume and infection are major components and etiologies of respiratory failure in AKI, but vigilance is needed for other potential etiologies. In particular, the respiratory system is often involved in patients with the anti-GBM Ab–mediated syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis, SLE, and, less likely, cryoglobulinemia.

Gastrointestinal Complications

Gastrointestinal symptoms, such as nausea, vomiting, dyspepsia, gastroparesis, and poor appetite, are common in advanced AKI and may be the precipitating symptoms that cause RRT to be initiated. Whether CRF and ESRD are associated with an increased risk of peptic ulcer disease has revealed discordant results.[459,460] As such, prophylactic treatment for prevention of peptic ulcer disease in patients with AKI is not recommended. In addition, use of aluminum- and magnesium-containing antacids should be avoided with advanced renal failure given the potential for toxicity in the latter cohort of patients. Many systemic disorders can cause AKI and often have associated gastrointestinal symptomatology. Gastroparesis is common in patients with long-standing diabetic nephropathy and systemic sclerosis. Polyarteritis nodosa is associated with hepatitis B infection and often presents with constitutional gastrointestinal symptoms of nausea, vomiting, abdominal pain, and diarrhea. Henoch-Schönlein purpura is associated with abdominal pain and gastrointestinal bleeding.[461] SLE is associated with mesenteric vasculitis and gastrointestinal bleeding is common with systemic amyloidosis.

Intestinal consequences of AKI have recently been described.[456] During AKI the intestinal integrity is disrupted, potentially causing increased mucosal permeability and translocation of either endotoxin or live microorganisms that can further aggravate the inflammatory process.[462] This loss of barrier function of the intestine may partially explain the increased potential for liver injury in AKI as endotoxins and inflammatory mediators drain into the portal circulation, resulting in Kupffer cell activation and further cytokine release.[463,464] Liver injury may clinically be evident by abnormal liver function test results or physical examination findings such as scleral icterus and jaundice. Jaundice was reported in one prospective study in up to 28% of patients during their ICU course.[465] The mechanism of liver injury and jaundice is usually multifactorial, including sepsis, hypotension, medications, and hepatic congestion. Although AKI often accompanies acute pancreatitis, it is important to note that AKI itself can cause elevations in both serum amylase and lipase without clinical pancreatitis but the elevations typically do not exceed three times the upper limits of normal.[466]

Neurologic Complications

Neurologic complications of AKI are variable and early clinical symptoms may include lethargy, irritability, confusion, and disorientation. Tremors, asterixis, and myoclonus may be noted on physical examination with coma and seizures much less common. The degree of encephalopathy generally is concordant with the degree of renal failure, although variability exists and older patients are generally symptomatic earlier than younger patients. The most common electroencephalographic finding is a prominence of slow waves. Dialysis is indicated for the treatment of uremic encephalopathy and symptom resolution may improve acutely; however, several days are often needed for mental status to resolve to baseline.

Medication Dosing Considerations

Most medications and pharmacologic agents are either metabolized or removed from the circulation by either the liver or the kidney. In patients with AKI, all prescribed medications need to be assessed for appropriate dosing to avoid nephrotoxicity or accumulation of the active drug or its metabolites that could have other organ-specific complications. Certainly, all unnecessary medications should be stopped. Measuring drug levels when available to help prevent nephrotoxicity such as in aminoglycoside use should be performed. Certain cohorts of patients such as the elderly are at increased risk for requiring medication adjustments for renal insufficiency.[467] Multiple resources exist to help practitioners adjust medication dosing in renal failure.[468] Many medications used in the perioperative setting also have been demonstrated to cause AKI and therefore dosing adjustment may deserve special attention.[469] For patients receiving IHD, PD, or continuous RRT, knowledge of pharmacokinetic principles in the latter setting can be challenging but it is important to avoid toxicity and ensure appropriate therapeutic dosing to maintain maximum clinical effect.[470–473]

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TABLE 52.2 Nutritional Provisions in Critically Ill Patients With Acute Kidney Injury

Type of Enteral Formulation	Standard, Polymeric Fluid-Restricted Formula[a]
Energy requirements	25–30 kcal/kg per day (actual body weight)
Protein requirements	1.2–2 gm/kg per day (up to 2.5 g/kg per day with frequent continuous renal replacement therapy)

[a]Specialized formulations with reduced electrolyte content may be necessary in patients with electrolyte abnormalities.

Nutritional Considerations

Nutritional support in the critically ill patient with AKI refers to the appropriate administration of calories, protein, electrolytes, vitamins, and fluid to alter the course of critical illness. The optimal nutritional support in critically ill patients with AKI is often influenced by associated multiple comorbidities. Whenever feasible however, enteral nutrition is preferred to parenteral nutrition because enteral nutrition is believed to preserve gut immune function and prevent translocation of gut bacteria.[474] Direct comparisons of enteral versus parenteral nutrition in the critically ill patient have shown that enteral nutrition may be associated with a lower rate of infection but does not reduce mortality.[475,476] However, guidelines discourage enteral nutrition in hemodynamically unstable or prerenal patients given the concern for bowel ischemia.[477,478] Nutritional requirements must be determined once it has been determined that nutritional support will be required in the critically ill patient with AKI (Table 52.2). Although the appropriate goal for critically ill adult patients is unknown, caloric intake is generally recommended to be initially 8 to 10 kcal/kg per day[479] with a goal of 25 to 30 kcal/kg per day but not to exceed 35 kcal/kg per day.[480] Because protein requirements increase with the severity of illness, critically ill patients with AKI are often hypercatabolic and therefore the recommended protein requirement is 1.2 to 2 kcal/kg per day.[481,482] In regard to volume administration with parenteral nutrition, careful examination of the patient is continually warranted to optimize fluid balance by treating intravascular volume depletion yet avoiding excess volume administration. The goals of prescribing parenteral nutrition are to optimize clinical outcome and address electrolyte abnormalities and volume status in the critically ill patient; this requires advanced understanding and training in nutrient metabolism as well as solute compatibility. As such, guidelines have been developed to ensure proper ordering, compounding, labeling, and dispensing of parenteral nutrition.[483] Similarly, a framework to help guide institutions in ensuring and maintaining competency in prescribing parenteral nutrition has also been published.[484]

Renal Replacement Therapy

In patients with severe AKI, RRT is the cornerstone of supportive management (Box 52.3). The goal of RRT is to permit the removal of fluid and solutes that accumulate in renal failure, thereby restoring the composition and volume of the extracellular fluids and preventing the complications of uremia, hyperkalemia, and acidosis.

A detailed technical guide to the performance of RRT is beyond the scope of this chapter. The following discussion provides an overview of RRT with a focus on the key management issues of selection of modality, timing of initiation of dialysis, and appropriate intensity of therapy.

• BOX 52.3 Indications for Renal Replacement Therapy

Hyperkalemia
Volume overload
Acidosis
Uremia (altered mental status, pericariditis)
Certain drug and alcohol intoxications

Modalities of Renal Replacement Therapy

Different modalities of RRT include conventional IHD, PD, continuous RRT (CRRT), and hybrid therapies such as sustained low-efficiency HD (SLED) or extended-duration dialysis or prolonged intermittent renal replacement therapy (PIRRT). The various forms of CRRT include continuous venovenous HD (CVVHD), continuous venovenous hemofiltration (CVVHF), and continuous venovenous hemodiafiltration (CVVHDF).

Solute removal during RRT may occur by diffusion down a concentration gradient from blood, across a semipermeable membrane, into dialysate, or by convective transport of solute across the membrane during ultrafiltration. Fluid removal occurs by ultrafiltration, driven by either a hydrostatic or osmotic pressure gradient across the semipermeable dialyzer or filtration membrane.

IHD is a process of solute clearance by diffusion across the dialysis membrane driven by the concentration gradient between blood and the dialysate. It requires a large-bore double-lumen venous catheter typically inserted in the internal jugular, subclavian, or femoral vein. Because an episode of AKI requiring dialysis may not recover renal function, a subclavian venous catheter should always be avoided whenever possible owing to the risk of subclavian stenosis that would affect functioning of an arteriovenous fistula. Treatment duration and frequency of IHD are variable and usually dependent on factors such as the patient's planned volume removal and metabolic needs.

CRRT is a modality intended to run 24 hours/day in the ICU setting. It provides slower per unit time clearance compared with intermittent therapies. Solute removal is achieved by diffusion (HD), convection (hemofiltration), or both (hemodiafiltration).

CRRT includes CVVHD, CVVHF, and CVVHDF. CRRT is considered to cause less hemodynamic stress than IHD in patients with severe AKI. CRRT was initially described using an arteriovenous extracorporeal circuit (continuous arteriovenous HD) with inflow through a large-bore arterial catheter and return through a venous catheter. It used the patient's own cardiac output to drive blood through the dialysis circuit. It has now been replaced by CVVHD that allows higher blood flow rates and is independent of mean arterial pressure and thus avoids the complications of prolonged arterial cannulation.

As in IHD, CVVHD solute removal occurs by diffusion across the concentration gradient with hydrostatic forces driving ultrafiltration. In addition to the duration of therapy, the other major difference between CVVHD and IHD is the dialysate flow rate. With IHD, the typical dialysate flow rate is 500 to 800 mL/min, which is greater than or equal to the typical blood flow rate allowing for rapid solute clearance. In CVVHD, dialysate flow rate is typically 1 to 2 L/hr, which is slow compared with a blood flow rate of 200

to 300 mL/min, allowing for virtual equilibration of low–molecular-weight solutes between the blood and dialysate. Although CRRT provides slower solute clearance per unit time compared with intermittent therapies, CRRT is typically prescribed over 24 hours and therefore the overall solute clearance with CRRT may even exceed the typical clearances obtained with IHD.

In CVVHF, a high ultrafiltration rate is generated and physiologic replacement fluid is administrated at a rate equal to the difference between the high ultrafiltration rate and the desired rate of fluid removal. Solute removal is achieved by convection and clearance is equal to the ultrafiltration rate. No dialysate is used. In continuous hemodiafiltration, the dialysate flow of continuous HD is added to the convective ultrafiltration of continuous hemofiltration.

Prolonged intermittent RRT is a modification of conventional IHD, using lower blood and dialysate flow rates while prolonging the treatment duration to 8 to 16 hours compared with the usual 3 to 4 hours of IHD. As with CRRT, by prolonging the treatment duration and decreasing the rate of net ultrafiltration, the hemodynamic stress on the patient is minimized.

PD uses the peritoneum as a natural semipermeable membrane through which solute transport and fluid removal occurs via diffusion from the blood to the dialysate. The dialysate is a highly concentrated, typically dextrose-based solution instilled in the peritoneum via a peritoneal catheter. In adults, acute PD is not widely used for many reasons. Acute PD requires surgical placement of a PD catheter, which may not be appropriate for patients with recent abdominal surgery or with an acute intraabdominal process. Solute clearance with PD is not optimal in patients with a hypercatabolic state. Other limitations include the potential for compromising lung volumes in mechanically ventilated patients owing to increased IAP or the development of glucose intolerance from the high dextrose concentration within the dialysate.

Theoretically, CRRT and SLED may provide advantages over IHD such as providing better hemodynamic tolerability, improving control of fluid removal, and offering improved efficiency of solute clearance. However the data do not support either modality as superior to IHD in regard to patient survival or recovery of renal function.

Comparing outcomes of CRRT with IHD has been reported in observational studies and case series.[485–488] However, conclusions from these studies are confounded by a selection bias for an increased number of hemodynamically unstable and higher-acuity patients in the CRRT group. After adjusting for the severity index, there appears to be no survival benefit between patients receiving CRRT or IHD.[486,487]

In a multicenter, randomized, controlled trial comparing continuous hemodiafiltration and IHD, continuous hemodiafiltration was associated with increased ICU mortality (59.5% vs. 41.5%) and in-hospital mortality (65.5% vs. 47.6%). Despite randomization, there was a significant difference in severity scores between the two groups. After adjustment, the odds of death with continuous hemodiafiltration were nonsignificant.[489]

In the Hemodiafe Trial, the largest prospective, randomized, multicenter study consisting of 360 patients, patients were randomly assigned to receive either IHD versus CVVHDF. The primary endpoint was 60-day survival; there was no statistically significant difference in 60-day survival between the two groups: 32% in the IHD group versus 33% in those patients receiving CVVHDF.[490]

Similarly, in another multicenter prospective randomized controlled trial involving 316 patients with AKI, patients were randomly assigned to receive intermittent renal replacement therapy (IRRT, defined as daily dialysis during 4–6 hours per session with a blood flow of 100–300 mL/min and a dialysate flow of 300–500 mL/min) or CRRT (CVVH continued during 24 hours per day with a blood flow rate of 100–250 mL/min, an ultrafiltration rate of 1–2 L/hr). The randomly assigned treatment modality of IRRT or CRRT had to be continued daily for at least 3 consecutive days. Thereafter treatment could be continued according to the needs of the patients. Results demonstrated that duration of ICU stay, hospital stay, and renal recovery at the time of discharge were also comparable between the two groups.[491]

In the CONVINT trial, 252 critically ill patients in the ICU were randomly assigned to receive IHD versus CVVH. The primary outcome measure was survival at 14 days after the end of RRT. Results demonstrated survival rates at 14 days after RRT were not statistically significant (39.5% IHD vs. 43.9% CVVH).[492]

Recent systemic reviews and meta-analyses have confirmed the absence of differences in mortality rate or recovery of renal function across different dialysis modalities.[493–495] Advocates of CRRT claim that it offers better hemodynamic tolerability and greater volume control in critically ill patients.[62,496] In patients with acute brain injury or hepatic liver failure, CRRT is associated with better preservation of cerebral perfusion than IHD and seems to be a more appropriate modality of RRT.[497–501] Based on these data, the KDIGO Clinical Practice Guideline for AKI suggests using intermittent and continuous RRT as complementary therapies in patients with AKI and have suggested that CRRT be used preferentially in hemodynamically unstable patients.[6]

Studies comparing PIRRT and CRRT show similar outcomes. In a prospective, randomized clinical study, 12-hour SLED was compared to 24-hour CVVH. The primary outcome, 90-day mortality, was similar in both groups, although the SLED cohort had reduced nursing time and lower costs.[502] Other studies have shown that SLED demonstrated similar hemodynamic stability and metabolic control compared to CRRT.[503–505] A systematic review and meta-analysis comparing CRRT with extended daily dialysis showed no difference in mortality or recovery of kidney function between the two groups.[506] There are only limited studies comparing PIRRT and IHD.[507]

PD has long been used as a dialytic therapy in AKI, although its use has declined as the use of CRTT has become more common. Single studies have compared PD efficacy with hemofiltration favoring hemofiltration; however, this was not replicated in a larger study demonstrating similar metabolic control, mortality rate, and renal function recovery between both groups.[508–510]

In the absence of data suggesting better survival or recovery of renal function with one particular modality over another, these modalities should be considered complementary. In general, CRTT and PIRRT modalities are more optimal therapies for patients who are hemodynamically unstable but are more expensive.[511] The choice of modality should be based on the local availability, and expertise of practitioners prescribing RRT, and nursing staff delivering the therapy.

Timing of Initiation of Renal Replacement Therapy

The urgent indications to initiate dialysis in patients with AKI include refractory hyperkalemia, fluid overload, severe metabolic acidosis, pericarditis, uremic encephalopathy, and certain drug and alcohol intoxications. In the absence of these acute indications, the timing of initiation of dialysis in AKI is unclear. However, common practice is to start dialysis in patients before the development of these acute indications in severe AKI in whom imminent recovery of renal function is unlikely. Although starting early dialysis

may have benefits, it also exposes patients to RRT risks related to the procedure including increased risk of catheter-related infections.

A number of retrospective and observational studies have suggested that earlier initiation of dialysis may be associated with better survival.[512–523] A recent meta-analysis including 15 studies compared 28-day mortality for early versus late initiation of renal support. An odds ratio of 0.45 was associated with early initiation; however, the methodologic quality of the included studies was low.[524] There was a significant statistical heterogeneity as well as evidence of publication bias toward smaller studies in which early initiation of RRT was associated with a survival benefit.

A recent randomized controlled trial of 620 patients randomly assigned patients to either an early or delayed strategy. In the early group, RRT was initiated immediately after randomization, whereas in the delayed group, RRT was not initiated until at least one of the following criteria was met: oliguria for more than 72 hours, BUN of more than 112 mg/dL, or any of the acute indications for RRT. No significant difference in mortality at 60 days was demonstrated between the two groups. The rate of catheter-related blood infections was significantly higher in the early strategy group and diuresis occurred earlier in the delayed-strategy group, possibly suggesting recovery of renal function.[525] A prospective, open label, randomized trial consisting of 208 patients with AKI in India showed similar results that do not support early initiation of dialysis among patients with AKI.[526]

In contrast, investigators from the ELAIN trial randomly assigned patients to one of three groups: early, late, or no initiation of dialysis. In the early group, dialysis was initiated within 8 hours of diagnosis of KDIGO stage 2 AKI. In the delayed group, dialysis was initiated within 12 hours of stage 3 AKI, whereas 11 patients never initiated dialysis in this group. The primary endpoint was mortality at 90 days, which was significantly lower in the early initiation group compared with the delayed group (39% vs. 54%). More patients with early initiation of RRT had renal recovery (53% vs. 38%) as well as a significantly shorter duration of RRT and length of hospital stay.[527]

The severity of volume overload as an indication for initiation of RRT has gained considerable attention in recent years. Observational studies have shown that fluid overload is associated with increased mortality in patients with AKI in which early initiation of replacement therapy has shown benefit.[63] In another prospective multicenter observational study consisting of 618 patients, fluid overload, defined as more than 10% increase in body weight relative to baseline, was independently associated with mortality in patients with AKI with an odds ratio for death at dialysis initiation of 2.07.[528] Similar results were shown in another observational study from Beijing in which a higher cumulative fluid balance was associated with a higher 28-day mortality after AKI.[529] Although these data provide a strong caution regarding overly aggressive volume administration in patients with AKI, the hypothesis that earlier initiation of RRT to prevent or reverse volume overload still needs to be tested in prospective clinical trials.

Intensity of Renal Support in Acute Kidney Injury

Assessment of the dose of both IHD and PIRRT is dependent on the intensity and the frequency with which these therapies are provided. Intensity of a treatment is usually quantified in terms of urea reduction ratio or the fractional clearance of urea. In one study of 160 patients, daily IHD was beneficial compared with alternate-day intermittent dialysis.[530] However, this result was not reproduced in the large Veterans Affairs (VA)/National Institutes of Health (NIH) Acute Renal Failure Trial Network (ATN) study, a randomized controlled trial involving 1124 patients randomly assigned to either an intensive or less intensive treatment group. In the intensive treatment group, patients received IHD and sustained low-efficiency dialysis 6 times per week and CVVHDF at 35 mL/kg of body weight per hour. In the less intensive treatment group, patients received the corresponding treatments 3 times a week and at 20 mL/kg per hour. There was no statistically significant difference in either recovery of renal function or 60-day mortality between the two groups.[531]

For CRRT, the dose is usually expressed in terms of the total effluent flow (dialysate plus ultrafiltrate) normalized to body weight. In the Randomized Evaluation of Normal versus Augmental Level (RENAL) study (N = 1508), the high-intensity group received CVVHDF with an effluent flow of 40 mL/kg of body weight per hour, whereas the lower-intensity group received CVVHDF with an effluent flow of 25 mL/kg per hour. Ninety-day mortality was similar (44.7%) in both groups.[532] Two meta-analyses confirmed the same results.[533,534] High-dose CVVH was not beneficial in prospective randomized controlled trials in patients with AKI from either septic shock[535] or after cardiac surgery.[536]

These studies show that more intensive renal support does not result in improved outcomes. The 2012 KDIGO guideline for AKI[6] recommends delivering a fractional clearance of urea of 3.9 per week for patients undergoing intermittent therapy. However, more frequent IHD may be necessary for fluid management in extremely hypercatabolic patients and for control of severe hyperkalemia. For CRRT, the recommended delivered dose of therapy is an effluent flow rate of 20 to 25 mL/kg per hour. Achieving this target dose often requires the prescription of a slightly higher dose (25–30 mL/kg per hour) with careful attention to minimization of interruption of therapy.

Prognosis and Outcomes

AKI increases the risk of hospital mortality, development of CKD and ESRD, pulmonary complications, cardiovascular events, and readmission rates. This association is even stronger among patients in whom recurrent and more severe AKI develop.

Many studies have focused on short-term morbidity and mortality rates of AKI in hospitalized patients. Hospital-acquired AKIs have reported mortality rates as high as 62%,[537] and these rates are higher than even those for patients in whom acute lung injury or myocardial infarction develops. Recent studies have focused on long-term outcomes of patients with AKI and results demonstrate that AKI has clearly been associated with development of CKD.[538,539] In a meta-analysis by Coca and colleagues with pooled data involving 13 studies in patients with AKI, the pooled incidence of CKD and ESRD was 25.8 per 100 person-years and 8.6 per 100 person-years, respectively. The more severe the AKI, the greater the risk of adverse outcomes.[537] Similarly, in a large VA health care system study, 20% of patients in whom an episode of ATN developed rapidly progressed to stage 4 CKD.[540] In addition, in a retrospective study by the VA system in hospitalized diabetic patients, the development of each AKI episode up to three doubled the risk of developing stage 4 CKD.[541]

The KDIGO AKI guideline recommends that patients should be evaluated 3 months after AKI for resolution of AKI or worsening of preexisting kidney disease with management according to CKD guidelines for those at increased risk of CKD as appropriate.[6] Despite the potential benefits in optimizing proteinuria reduction, glycemic and blood pressure control in potentially slowing CKD

progression, close follow-up of patients in whom AKI develops has been lacking. Follow-up care should include laboratory assessment of kidney function and referral to a nephrologist. Recent published studies from the U.S. Department of Veterans Affairs demonstrate the need for strategies to ensure closer follow-up. In a retrospective study by Matheny and colleagues of nearly 11,000 patients admitted with AKI and discharged with an estimated GFR less than 60 mL/min per 1.73 m^2, 69% and 85% of patients had a serum creatinine level obtained at 90 days and 365 days, respectively. However, during outpatient follow-up at 90 days and 365 days, only 6% and 12% had quantitative proteinuria; PTH and phosphate were measured in only 10% and 15% of patients, respectively.[542] Siew and colleagues also reported that only a minority of at-risk survivors of an AKI episode in whom an estimated GFR less than 60 mL/min per 1.73 m^2 developed within 30 days of peak stage of AKI were referred to a nephrologist (8.5%) over 12 months.[543] Similarly, the U.S. Renal Data System reported only 13.2% of patients in whom AKI developed saw a nephrologist at 3 months, and only 18.1% of patients saw a nephrologist after a recurrent AKI episode.[544] Given the increased incidence of AKI worldwide with its associated long-term sequelae, more comprehensive and updated strategies to ensure appropriate follow-up will be necessary.

AKI in hospitalized patients is associated with both direct and indirect health care costs and prolonged hospitalization, which increases resource utilization. Despite secular trends demonstrating that AKI-associated mortality may be decreasing,[545] the mortality rate remains exceedingly high. AKI is associated with greater diagnostic monitoring, longer ICU stays, prolonged hospitalization, and an increased risk of early rehospitalization.[544] AKI that is not associated with critical illness has been shown to add $2600 (U.S. dollars) in attributable costs and increased the length of stay by 5 days.[546] Increased health care costs of AKI were also reported by Chertow and colleagues in hospitalized patients with KDIGO stage 2 AKI; there was a 6.5-fold increased odds ratio for death, as well as a $9000 (U.S. dollars) increase in hospital costs and more than 3.5 days of increased length of stay.[547] The development of KDIGO stage 1 AKI after cardiac surgery resulted in a 1.6-fold increase in total postoperative costs compared with patients without AKI.[548] Rehospitalization rates have also been shown to be increased in patients in whom AKI develops but who did not require RRT.[549]

Health-related quality of life (HRQL) and residual disability have been increasingly reported and recognized as patient-centered outcomes after acute illness complicated by AKI. Several small and mostly single-center studies have evaluated HRQL and concentrated on functional disability in patients with critical illness. Overall, HRQL is lower in survivors of AKI requiring RRT compared with the age- and sex-matched general population at both hospital discharge and at 6 months after AKI onset. Older age, greater comorbid disease, higher illness severity, longer durations of ICU and hospital stays, and dialysis dependence are all associated with significantly lower HRQL.[544]

Key Points

- There is general consensus that a standardized definition of AKI has both epidemiologic and clinical benefits.[7]
- The worldwide incidence of AKI in the ICU has been reported to be greater than 50%.[34]
- The most common cause of AKI in the ICU is acute tubular necrosis.[58]
- The MDRD equation in estimating GFR is more accurate in patients with CKD and less accurate in patients with a normal GFR.[151]
- Anuria does signify a likely severe nephrologic emergency requiring immediate evaluation.
- Granular casts are a typical microscopic finding in ischemic ATN, which is the leading cause of AKI in hospitalized patients.[209]
- Intravascular volume expansion has been shown to decrease the risk of AKI for radiocontrast-induced nephrotoxicity.[256]
- Drug-induced nephrotoxicity has been reported to cause between 8% and 60% of in-hospital AKI.[294]
- Medications such as PPIs have been associated with an increased risk of incident CKD, progression of CKD, and ESRD.[309]
- Patients with positive fluid balance after AKI have a higher mortality.[62]
- Infectious complications, however, remain a leading cause of death in patients who develop AKI in the ICU.[445]
- Critically ill patients with AKI are often hypercatabolic; therefore the recommended protein requirement is 1.2 to 2 kcal/kg per day.[481]
- After adjusting for the severity index, there appears to be no survival benefit between patients receiving CRRT and those receiving IHD.[487]
- Development of AKI has clearly been associated with development of CKD.[538]

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Review Questions

1. A 25-year-old male pedestrian was struck by a car while riding his bicycle. He was brought to the emergency department by ambulance. Physical examination reveals blood pressure of 130/80 mm Hg, pulse rate of 70 beats/min, and that the patient was afebrile. Cardiac examination reveals S_1, S_2, no S_3, and a I/VI systolic ejection murmur at the left sternal border. Lungs were clear; the abdomen was nontender; extremities revealed tenderness of the left lower extremity but not tense; and pulses in the lower extremity were normal. The patient was not taking any medications at presentation. Laboratory study results included urinalysis: trace protein, large blood; urine microscopy: 0–1 white blood cells (WBCs) per high-power field (HPF), 0–1 red blood cells (RBCs)/HPF, no casts; urine osmolality 295 mOsm/kg H_2O; serum creatinine 2.5 mg/dL; blood urea nitrogen 32 mg/dL; sodium 144 mEq/L; potassium 5.1 mEq/L; bicarbonate 22 mEq/L; glucose 92 mg/dL; aspartate aminotransferase 98 IU/L; alanine aminotransferase 78 IU/L.

What is the best initial management for this patient?

a. Obtain an immediate (stat) renal ultrasound
b. Stat vascular surgical consult
c. Intravenous fluids
d. Obtain urine for eosinophils
e. Obtain a spot urine myoglobin

Answer: c. This patient presented with a history concerning for rhabdomyolysis. The laboratory criteria consistent with the latter diagnosis are urinalysis with no RBCs on microscopy but large dipstick blood as well as elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and associated renal failure. An elevated creatine phosphokinase level would be expected (value not given). The best initial treatment is intravenous fluids (IVF), normal saline solution with a goal urine volume of 200 mL/hr. At some point, a renal ultrasound will likely be required but the initial treatment is IVF. There is no need to obtain a urine eosinophil level in this setting because the latter is often ordered when there is concern regarding the possibility of acute interstitial nephritis. A urine myoglobin study may help in the diagnosis but results can be normal at initial presentation. A stat vascular surgery consultation is not yet indicated in view of normal lower extremity pulses, but continued vigilance would be necessary to observe for the possibility of a compartment syndrome.

2. A 25-year-old female with a 14-year history of type 1 diabetes mellitus (DM) presents to your office for routine follow-up. She has no new complaints except that her mother, who is a nurse, took her blood pressure on two occasions over the past month and it was elevated at 146/92 mm Hg and 156/98 mm Hg. The patient admits to poor compliance to diabetic control for many years and her hemoglobin A_{1c} is often above 9.0%. One year ago the patient had microalbuminuria and was prescribed an angiotensin-converting enzyme (ACE) inhibitor but she never filled the prescription. On review of systems, the patient denied recent rashes, illicit drug use, shortness of breath, chest pain, or headaches. Physical examination shows blood pressure of 142/98 mm Hg, pulse rate of 88 beats/min, and the patient is afebrile. Results of fundoscopic, cardiac, and pulmonary examinations were normal and there was no lower extremity edema. The patient was not using any medications. Laboratory study results were creatinine 0.9 mg/dL, blood urea nitrogen 24 mg/dL, sodium 140 mEq/L, potassium 4.2 mEq/L, chloride 94 mEq/L, bicarbonate 24 mEq/L, hemoglobin 13.0 gm/dL, WBCs $5.0 \times 10^3/\mu L$, platelets $345{,}000 \times 10^3/\mu L$, aspartate aminotransferase 14 IU/L, alanine aminotransferase 22 IU/L. Chest x-ray and electrocardiogram results were normal. The urinalysis showed 2+ protein, 1+ dipstick blood; urine microscopy showed 3–5 WBCs/HPF, 5–10 RBCs/HPF, 2 dysmorphic RBCs/HPF, 1 RBC cast/HPF, 1 to 3 hyaline cast/HPF. The prothrombin time is PT 12.5 seconds and the partial thromboplastin time is 25 seconds. Renal ultrasound shows normal echogenicity; right kidney 11.0 cm, left kidney 11.6 cm.

Which of the following is the most appropriate first step in caring for this patient?

a. Schedule a renal biopsy.
b. Obtain a renal artery Doppler.
c. Obtain a serum renin/aldosterone ratio.
d. Begin an ACE inhibitor and low-sodium diet with close follow-up in 4 weeks.
e. Refer the patient to a urologist.

Answer: a. This patient has a long-standing history of DM that has been poorly controlled. She has dipstick proteinuria and was not compliant with prescribed ACE inhibitors and is therefore at risk for progressive DM nephropathy. However, the patient has new-onset hypertension in the setting of an active sediment (RBCs, RBC casts, dysmorphic RBCs, and worsening proteinuria). This patient has a normal serum creatinine level *but* her urinalysis is consistent with an active proliferative glomerulonephritis. This essentially is a nephrologic emergency. Any delay in treatment is likely to be harmful to the patient and may result in irreversible renal failure. The first step is to schedule a renal biopsy for definitive diagnosis. Starting the ACE inhibitor (assuming she is not pregnant [i.e., or screening for latter first]) and a low-sodium diet would also be reasonable, but having the patient return in 1 month is not appropriate because an emergent renal biopsy is indicated. The urine sediment is concerning for glomerular injury and therefore urologic evaluation is not indicated. Although new-onset hypertension raises the possibility of fibromuscular dysplasia or other potential secondary causes such as primary hyperaldosteronism to explain her hypertension, her active urine sediment reflects an acute glomerulonephritis and as such, a renal Doppler and renin/aldosterone ratios are not indicated.

3. Which one of the following estimating equations for measurement of glomerular filtrate rate (GFR) is most accurate in patients with normal or near-normal renal function?

a. Cockcroft-Gault formula
b. Modification of Diet in Renal Disease (MDRD) study Eq. (4 variable)
c. MDRD study Eq. (6 variable)
d. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
e. Iothalamate clearance

Answer: d. The measurement of an accurate GFR in clinical practice is complex and can be cumbersome with many potential variables that can interfere with the results. The gold standard for measuring GFR is an inulin clearance but it is difficult to perform and mostly not available. The most common methods

to measure GFR are the 24 hour urine for creatinine clearance and three "estimating" equations to assess GFR. Of the clinically used estimating equations, the CKD-EPI equation is the most accurate in those with near-normal GFR. The MDRD equation is more often used in patients with CRF. The Cockcroft-Gault equation has been historically used to assess GFR for drug dosing guidelines and often overestimates the GFR. Iothalamate clearance, which provides a more accurate assessment of GFR than creatinine clearance, is not an estimating equation but rather a measured GFR (using iothalamate).

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Chronic Kidney Disease

CHRISTOPHER B. MCFADDEN

CHAPTER OUTLINE

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- Definition and Etiology
- Diagnosis

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- Hypertension
- Electrolyte Disorders in Chronic Kidney Disease
- Metabolic Acidosis
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Summary

Introduction

Chronic kidney disease (CKD) is a common diagnosis in adult medicine.[1–6] To properly identify patients at risk for adverse outcomes and disease progression, extensive work has focused on early and appropriate classification over the past 10 years. In particular, the National Kidney Foundation proposed a classification system for CKD in 2002 using estimated glomerular filtration rate (eGFR) as a method to categorize patients.[7,8] Table 53.1 describes current NKF guidelines of CKD. CKD patients have higher mortality after critical illnesses.[9,10] Understanding this population's physiology and underlying disease state may aid caregivers in attempting to improve outcomes.

This chapter aims to define CKD and discuss the physiology of CKD in terms of blood pressure, electrolytes, mineral disorders, and anemia. An emphasis is given to the ICU management of these problems. When available, evidence-based guidelines are reviewed and discussed. The ICU management of patients with CKD is often not guided by evidence-based therapy.

Definition and Etiology

As shown in Table 53.1, CKD is staged in a five-tier system based on eGFR. The diagnosis relies on abnormal kidney function or urinalysis findings for 3 months or more. The serum creatinine level and age, sex, gender, and race are used to generate an eGFR from a quadratic equation derived from the Modification of Diet in Renal Disease Study (MDRD).[7] Most patients with CKD do not progress to end-stage renal disease (ESRD), however, because of the very high cardiovascular and noncardiovascular mortality associated with this at-risk population.[11–14] Proposals exist to more clearly define elderly subjects with CKD stage 3 disease at risk for disease progression, though this has not become standard.[15–17] In particular, stage 3A CKD (eGFR 45–60 mL/min per 1.73 m^2) does not progress toward ESRD in most elderly subjects if proteinuria is absent, whereas stage 3B CKD (eGFR 30–44 mL/min) may progress.[18]

Etiologies for CKD are broad and often multifactorial. However, frequently diabetes mellitus and hypertension play a major role. Hypertension may lead to kidney damage in the form of nephrosclerosis or chronic renal ischemia owing to atherosclerotic vascular disease. An important recent development is the recognition that the higher prevalence of nondiabetic kidney disease in the African American population may be due to genetic risk conferred by inherited variants in the apolipoprotein L1 gene (*APOL1*).[19] Additional causes of kidney disease in the general population include immune-mediated glomerular diseases, such as systemic lupus erythematosus, immunoglobulin (Ig) A nephropathy, membranous nephropathy, or other previous glomerulonephritides that often are present. Glomerulonephritis may be active as evidenced by hematuria and proteinuria, or it may have occurred in the patient's past, leading to abnormal kidney function but a relatively bland urinalysis. Alternatively, primary tubulointerstitial diseases could exist owing to reflux nephropathy, sarcoidosis, chronic infections, allergic reactions, or side effects from medications such as cyclophosphamide (Cytoxan) and lithium. In general, the diagnosis of CKD should warrant a higher index of suspicion for concurrent, and potentially undiagnosed, cardiovascular disease.

The population with CKD is at risk for deterioration in kidney function during a hospitalization stay, particularly if a critical illness is present. Potential causative factors for this are listed in Box 53.1. Importantly, acute tubular necrosis may occur without obvious hypotension and patients with reduced kidney function are more at risk for this complication.[20]

Diagnosis

Intrinsic to the eGFR formula, as well as other estimates of renal function from the serum creatinine level, is the presumption that a patient's serum creatinine level is stable. This may not be the case in patients in the intensive care unit (ICU); as a result, imprecision should be expected in kidney function estimation in ICU patients.[21] The serum creatinine level is now recognized as potentially providing an underestimated level of renal function in a large population of patients, particularly those with low weight,

TABLE 53.1 Chronic Kidney Disease Stages

Chronic Kidney Disease Stage	eGFR (mL/min per 1.73 m^2)	Urinalysis Findings
1	≥90	Hematuria, proteinuria, or abnormal imaging >3 months
2	60–89	Hematuria, proteinuria, or abnormal imaging >3 months
3	30–59	Above or normal
4	15–29	Above or normal
5	0–14	Above or normal

eGFR, Estimated glomerular filtration rate.

• BOX 53.1 Factors Leading to Deterioration in Kidney Function During Hospitalization in Patients With Chronic Kidney Disease

Volume depletion (prerenal, including "normotensive" sepsis, renal vasoconstriction owing medications or hypercalcemia)
Obstruction
Acute tubular necrosis
Renal vascular disease (atherosclerotic with volume depletion, thrombotic, and/or embolic disease)
Upper urinary tract infection (bilateral or unilateral with single kidney, including a kidney transplant)
Nephrotoxic medications (allergic inflammation, tubular injury)
Glomerular disease (immunoglobulin A or postinfectious related to infection)

• BOX 53.2 Factors That May Alter Serum Creatinine Level

Endogenous Impact on Creatinine Level
Reduced muscle mass
Reduced hyperbilirubinemia

Exogenous
Increased medications inhibiting tubular secretion (trimethoprim and cimetidine)

Medications Interfering With Laboratory Assays[a]
Increased flucytosine and cefoxitin
Reduced catecholamines

[a]*Varies by type of assay used.*

small muscle mass, and liver disease.[22] In addition, both endogenous and exogenous factors can influence the measurement of serum creatinine.[23–26] Box 53.2 describes situations in which serum creatinine measurements may not adequately reflect kidney function. Importantly, some vasoactive substances can impart a negative interference on creatinine values if the creatinine sample is obtained from a central line used for vasopressors.[27] Nonetheless, creatinine variation has improved since values have been standardized to reference values.[28,29]

In general, current guidelines recognize the importance of stage 3 through 5 kidney disease for prognostication in outpatient and inpatient outcomes. Proteinuria is now associated with increased cardiovascular risk at all levels of GFR, including normal GFRs.[30] Even mild kidney dysfunction, defined typically as a serum creatinine level as low as 1.5 mg/dL, is associated with worse outcomes after coronary artery bypass grafting and cardiac valvular and general surgery.[31–35]

Concern exists about the accuracy of the MDRD equation at higher GFRs. For example, the newer creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula equation leads to a lower prevalence rate of stage 3 CKD than the MDRD equation as more patients have an eGFR above 60 mL/min.[36–38] The CKD-EPI formula has been reported to better predict vancomycin dose requirements compared with the eGFR formula.[39]

Measurement of serum cystatin C levels, a protein produced by all nucleated cells and freely filtered by the glomerulus, may provide more accurate estimates of kidney function than creatinine-based equations, particularly when kidney function is close to normal.[40] Cystatin C may also provide prognostic information about future cardiovascular events.[13] In fact, cystatin C has been proposed as a marker of "preclinical" kidney disease based on worse cardiovascular outcomes in elderly subjects with higher cystatin C levels.[41] Despite a growing body of literature, use of cystatin C is not routine in clinical practice.

When the serum creatinine level is stable and the eGFR formula is considered to inaccurately measure kidney function, creatinine clearance can be measured by using a 24- hour urine collection through the following formula:

$$\text{Creatinine clearance (dL/24 hr)} = (\text{Urine creatinine (mg/dL)} \times \text{volume of urine (dL)}) / \text{Plasma creatinine (mg/dL)}$$

In this equation, units will need to be converted from deciliters per 24 hours to milliliters per minute by a conversion factor of 0.0694.

If this measure is pursued, clinicians are counseled to pay close attention to units as well as the expectation that men excrete 1500 to 2500 mg/day of creatinine and women excrete 1000 to 1500 mg/day of creatinine.[42] If a lower amount of urinary creatinine is obtained, the possibility of an undercollection should be considered. It is also worthwhile to note that, historically, drug dosing has been determined by creatinine clearance and *not* estimated GFR.

In summary, estimating kidney function in ICU patients may be challenging owing to the absence of steady-state conditions and irregularities in body size and fluid compartments. Critical care providers need to understand the strengths and weaknesses of measuring kidney function in these patients.

Physiology of Chronic Kidney Disease

Hypertension

More than 80% of CKD patients with eGFRs less than 60 mL/min have hypertension.[5] This has several important impacts on the management of ICU patients. First, long-standing hypertension, if uncontrolled, leads to adaptations in autoregulation. Autoregulation refers to the ability of blood vessels to constrict and dilate in

the presence of hypertension and hypotension, respectively. Consequently, patients become acclimated to blood pressures near their "typical" blood pressure and may not immediately tolerate lower blood pressures, despite these apparent lower values being in the normal range. A consequence of this may be hypoperfusion to the kidneys as well as the brain, heart, intestine, and other critical organs at blood pressure levels that appear normal. If a history of poorly controlled hypertension is obtained, an astute clinician should aim to keep blood pressure close to a patient's prior level. This very much requires individualized attention and thorough history taking.

Second, CKD leads to sodium retention.[43,44] The most notable ICU impact this will have is the potential for volume retention and the need for diuretics to manage hypertension in the CKD population.[45–47] Several mechanisms lead to the development of hypertension in the CKD population. They include upregulation of the renin-angiotensin system, increased sympathetic nervous system activity, and impairment of endothelial-dependent arterial smooth muscle relaxation.[48–54] Owing to these mechanisms, patients with CKD may develop more edema and volume overload with equivalent amounts of intravenous fluids. One worthwhile consideration, however, is that sodium retention associated with CKD may be counterbalanced by sodium loss from excessively high blood pressure levels. This phenomenon, known as pressure natriuresis, may explain the rapid drops observed in blood pressure in hypertension emergencies once excess sympathetic activity is controlled. Finally, volume management may be confounded by the presence of pulmonary hypertension, which is now recognized to occur more frequently is patients with CKD.[55]

Electrolyte Disorders in Chronic Kidney Disease

Sodium

Sodium homeostasis in patients with CKD is abnormal.[56] Although patients with CKD are sodium "avid" and tend toward states of volume overload, they are less able to increase sodium retention in times of need and subsequently are also at risk for volume depletion. In comparison, subjects with normal renal function can quickly increase sodium absorption and avoid volume-depleted states.[57] Patients with tubulointerstitial disease and obstructive uropathy may be particularly at risk for episodes of volume depletion because of their recognized inability to increase sodium reabsorption in times of volume depletion.[58]

Patients with CKD thus are a group at risk for both volume depletion and volume overload. ICU illnesses may confound this because of irregularities in physical examination findings in this population. Specifically, elevated blood pressure and edema in the CKD population are frequently present but may not represent states of intravascular volume overload. In summary, close attention to assessment of volume status and need for supplemental fluids or diuresis is warranted in the CKD population.

When volume overload is present, iatrogenic sources may be playing a role. Potential sources of sodium include maintenance intravenous fluids (including bicarbonate), antibiotics, and nutritional sources including total parenteral nutrition. Tracking fluid intake and output does not clearly differentiate between the electrolyte makeup of the various sources. Consequently, volume overload may develop insidiously. When volume overload develops, the standard approach involves minimizing sodium-containing sources and initiating a diuretic regimen.

Diuretics range from the gentler thiazide diuretics, which are less effective with a GFR below 30 mL/min, to more potent loop diuretics. In general, if significant volume removal is desired, a twice-daily or every 12-hour loop diuretic regimen should be prescribed to avoid excess sodium reabsorption in the period after the major diuretic effect.[59] Chronic administration of diuretics before ICU admission may lead to adaptive processes necessitating higher diuretic doses, combination therapy, or alternative approaches to volume overload states.[60–63] Torsemide is the loop diuretic that may be closest to lasting 24 hours.[64] Doses of loop diuretics need to be increased as renal function declines. Significant variability in loop diuretic kinetics exists; if a dose does not yield an increase in urine output within 2 hours, consideration should be given to increasing the dose. Alternatively, continuous infusion of loop diuretics may provide a better diuresis with less toxicity.[65,66] Typically infusion rates of furosemide are 10 to 40 mg/h. When a loop diuretic drip is ordered, a bolus should be given before initiating therapy to avoid a significant delay in efficacy.

Diuretic failure is common in the CKD population. Potential explanations in an ICU population include acute kidney injury, inadequate dosing, and distal tubular hypertrophy as the result of chronic diuretic use. When high-dose loop diuretics do not achieve adequate diuresis, the addition of metolazone may improve urine output. Historically, metolazone is given 30 minutes before the loop diuretics, although it may be efficacious if given at other times as well. Finally, isolated ultrafiltration or dialysis may be required for volume removal. Recently intraabdominal hypertension has been recognized as a disorder that may negatively affect kidney function as well as response to diuretics.[67–72]

Water

Water concentration and dilution are abnormal in patients with CKD. Normal patients can dilute and concentrate urine within a range of 40 to 1400 mOsm/kg.[73] CKD leads to a narrower range of urine osmolality. Specifically, patients with advanced CKD have a urine osmolality much closer to 300 mOsm/kg; the ability to adjust urine osmolality declines as kidney function worsens.[74] Consequently, patients with CKD are prone to both hypernatremia and hyponatremia. Loop diuretics may further worsen the kidneys' ability to concentrate and dilute urine.[75]

The approach to hypernatremia and hyponatremia is similar to that of other patients. In hypernatremia cases, concurrent illnesses often lead to patients being unable to obtain water for themselves; a high urine output owing to hyperglycemia or a high urea concentration may worsen this. Elevated urea, similar to high serum glucose levels, functions as an osmolar agent in the tubular lumen and creates a state of relative resistance to antidiuretic hormone with the potential for substantial free water loss.[76]

Hypernatremia can lead to significant agitation and should be treated aggressively with increased water either intravenously, in the form of hypotonic intravenous fluids, or enterally. When severe, an estimation of free water deficit is appropriate. Unexplained polyuria with a low urine osmolality, hypernatremia, and CKD in an ICU patient with an unclear history should warrant an investigation for previous lithium use.[77]

Hyponatremia reflects irregularities in water excretion in the vast majority of cases. Patients with CKD are less able to excrete water owing to the inability to lower urine osmolality.[78] Sources of water include intravenous fluids, medications mixed in dextrose, and enteral sources. Patients often are not aware of or not forthcoming about the amount of water they drink, although this is less an issue in ICU patients. The approach to hyponatremia in most patients with CKD is similar to the non-CKD population: looking for and reducing causes of increased water intake. Mild to moderate

CKD is not a contraindication to using antagonists to antidiuretic hormone. Importantly, sodium abnormalities in the patient with CKD, both with and without congestive heart failure, are associated with worse mortality.[79]

Potassium

Potassium (K^+) regulation is an essential function of the kidneys in normal states. Patients with CKD routinely maintain serum potassium in the normal range despite losing up to 90% of renal function.[80,81] Mechanisms underlying the maintenance of normal serum K^+ in advanced CKD include increased K^+ excretion per functioning nephron, increased gastrointestinal elimination of K^+, and increased uptake of K^+ by cells.[82] Diabetes mellitus, however, may exacerbate the development of hyperkalemia owing to the presence of a distal tubular acidosis (type IV) from aldosterone resistance. Hypokalemia may also be present as the result of current diuretic use or renovascular hypertension.[83] Its presence is associated with a higher risk of death and future ESRD needs in the CKD population.[84]

ICU patients with CKD represent a population prone to irregularities in K^+ homeostasis, in particular hyperkalemia.[85,86] Potential causes of hyperkalemia include insulin deficiency, hypoaldosteronism, and a loss of normal intestinal function that plays a role in increased potassium excretion in patients with CKD. Decreased blood flow to muscle and intestines in times of critical illness may impede potassium cellular uptake and excretion, respectively. Tissue ischemia from trauma, hypoxia, or tumor lysis is associated with an elevation in K^+, which may occur quickly.[87] One additional clinical consideration is that patients with CKD who are fasting may develop surprising levels of hyperkalemia without any apparent cause owing to low levels of insulin.[88] Glucose-containing intravenous fluids may avoid this.

The evaluation of hyperkalemia in patients with CKD begins with assessing the cause. Typically, this includes close scrutiny of medications, intravenous fluids, and types of nutritional support. Frequently, ICU patients receive nutrition very different from what the body is accustomed to and cannot manage a higher load of K^+, especially in states of relative tissue perfusion. Importantly, many patients with CKD are using diuretics as part of their routine outpatient medications; simply stopping these medications may lead to states of hyperkalemia. Hyperosmolality leads to a K_+ shift out of cells owing to solvent drag; in its most common presentation, hyperglycemia, this can be reversed quickly with the use of insulin. Metabolic acidosis may be associated with hyperkalemia, although organic acidosis states appear to cause less hyperkalemia than non-organic acid–induced states.[89]

Medications are an important and growing cause of hyperkalemia. Congestive heart failure and proteinuric renal disease remain as indications for possible combination therapy of an aldosterone antagonist with either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. In this setting, hyperkalemia may occur and may be severe.[90] Box 53.3 lists some common causes of hyperkalemia in the CKD population and the associated mechanism.[91] The presence of hyperkalemia should warrant close attention to affected patients as its presence is associated with increased mortality.[92]

Metabolic Acidosis

The kidneys and lungs regulate acid balance in the body. Kidney excretion of acid occurs through two mechanisms: as protons bound to anions such as phosphate and through ammoniagenesis. As kidney function declines below a GFR of 30 mL/min, the excess excretion of protons by each remaining functional nephron is no longer able to keep serum bicarbonate in the normal range. As a result, bicarbonate levels in patients with CKD are frequently in the range of 18 to 22 mmol/L, owing to a modest increase in the serum anion gap.[93] A recent trial showed sodium bicarbonate, supplemented orally, could delay kidney disease progression (Fig. 53.1).[94]

In ICU patients with CKD, serum bicarbonate and anion gaps are often further worsened by concurrent conditions, including lactic acidosis, ketoacidosis, or dilution, as the result of aggressive volume resuscitation. In the latter case, dilutional acidosis, may present with a worsening serum bicarbonate in the days after admission to the ICU and institution of intravenous fluids; the anion gap should not change significantly. In general, an anion gap above 20 mEq/L should warrant a workup for other causes of increased acid generation. Medications may also worsen acidosis in the CKD population because of disturbances in ammonia

• BOX 53.3 Causes of Hyperkalemia in Patients With Chronic Kidney Disease in the Intensive Care Unit

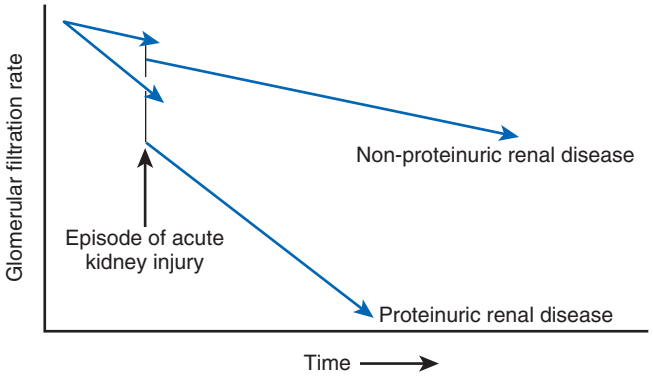
Medications

Trimethoprim—Reduced renal K^+ excretion[141,142]
NSAIDs, ACE inhibitors, ARBs—Decreased renal K^+ excretion
Heparin—Decreased aldosterone synthesis[143]
β-Blockers, nonselective—Decreased cellular K^+ uptake[144]
Triamterene, spironolactone, amiloride—Decreased renal K^+ excretion
Digoxin overdose—Decreased cellular K^+ uptake[145]
Succinylcholine use with trauma/critical illness—Increased K^+ release from cells[146]
Penicillin G—Increased K^+ load[147,148]

Clinical Conditions

Renal tubular acidosis (associated with diabetes)—Decreased renal K^+ excretion
Thrombocytosis—K^+ release *after* phlebotomy[149]
Insulin deficiency—Reduced cellular K^+ uptake
Cell death (tumor lysis, rhabdomyolysis)—Increased K^+ load

ACE, *Angiotensin-converting enzyme;* ARBs, *angiotensin receptor blockers;* K^+, *potassium ion;* NSAIDs, *nonsteroidal antiinflammatory drugs.*
Superscript numbers indicate references provided online.



• **Fig. 53.1** Rate of decline in renal function over time showing higher rate of decline in patients with proteinuric renal disease *and* potential for episodes of acute kidney injury to hasten kidney disease progression.

production as well as excess acid production in the form of lactic acid, ketoacids, and pyroglutamic acids.[95,96]

Mineral Bone Disorder

Substantial information has developed in the past several years about the mechanisms leading to abnormal calcium and bone metabolism in patients with CKD. Historically, this disorder was named *renal osteodystrophy.* The current preferred term is *CKD mineral bone disorder*.[97] The main developments reflects the growing importance of fibroblast growth factor FGF-23 on phosphate and parathyroid regulation and the relaxation of guidelines for strict parathyroid hormone (PTH) control in the ESRD population.[98]

FGF-23 is a phosphaturic protein produced by bone. Phosphaturia occurs as a result of decreased expression of sodium-phosphate (NaPi)-2a cotransporters in renal proximal tubular cells.[99] In addition, FGF-23 leads to a reduction in 1,25(OH)2D production by the kidney.[100] Its concentration increases earlier in the course of CKD than PTH. These adaptations initially keep calcium and phosphorus levels well maintained through early to middle stages of progressive CKD.

From the perspective of an ICU patient, hypocalcemia will routinely be encountered owing to the previously mentioned developments. Hypocalcemia, in the absence of other causes, suggests renal disease is chronic. Serum phosphorus levels may similarly be elevated as GFR declines. Dietary phosphorus restriction and phosphorus binders are the primary treatments for this. There is limited prospective data evaluating the best management of CKD mineral bone disorder, and therapy is for the most part dictated by nonrandomized studies and consensus guidelines. Elevations of FGF-23 are associated with a higher risk of mortality across multiple levels of kidney function.[101] Important issues for anyone caring for CKD patients with abnormalities of calcium bone deposition in the ICU include the following:

- Avoidance of phosphorus containing gastrointestinal stimulants owing to risk of systemic absorption and acute kidney injury.
- Recognition that hypocalcemia may be chronic; typically patients adapt to this with a normal ionized calcium owing to concurrent metabolic acidosis. Rapidly raising pH may lower serum calcium levels acutely and predispose patients to arrhythmias.[102]
- Consideration for other causes of hypocalcemia and hyperphosphatemia, in particular cell death from rhabdomyolysis and tumor lysis syndrome.

Anemia and Hematologic Disease

Erythropoietin is produced by the kidney and stimulates hematopoiesis in the bone marrow. CKD is associated with a reduction in erythropoietin levels and consequent anemia. As CKD progresses toward ESRD, anemia becomes more severe.[103] As a general rule, most patients with ESRD receive supplemental erythropoietin to increase their hemoglobin (Hgb) level and avoid transfusions.

Two large trials published in 2006 significantly altered the management of anemia of CKD.[104,105] The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trials both showed, in a well-designed format, that randomization to a normal Hgb did not improve outcomes and increased some adverse events. As a result, goal Hgb levels have dropped closer to 10.0 g/dL in general practice and the use of these medications has fallen substantially. These trials reinforced earlier data showing a normal Hgb, achieved through supplement erythropoietin, in the CKD population was dangerous.[106] Similar results were noted with darbepoietin alfa.[107] These studies clearly show adverse events from supraphysiologic Hgb levels in patients with CKD. The impact of relative reductions in Hgb in critically ill CKD patients is not well studied.

In CKD patients with critical illnesses, the problems of anemia are often magnified. How the anemia of CKD affects hospital course is not well understood. The current preference of minimizing transfusions and keeping Hgb levels in a lower range, based on trials for the most part on patients without CKD, has led to a reduction in Hgb in patients with CKD as well.[108–110] It is important to consider that patients with CKD may not be able to recover Hgb after acute illness as the result of reduced erythropoietin production.

Acute drops in the Hgb level in CKD patients in the ICU should be managed similar to patients without CKD. Chronic anemia should not be presumed to be due to CKD, and routine evaluations should still occur, including stool studies and iron status assessment. CKD patients, when blood urea levels increase above 100 mg/dL, are more prone to bleeding as the result of irregularities in platelet functional activity.[111–113] Dialysis may reduce the risk of bleeding related azotemia and "uremic platelets," although variable data on this point exist.[114–116] Additionally, desmopressin stimulate von Willebrand factor release acutely, although tachyphylaxis develops after the first dose.[117,118] Finally, conjugated estrogens may provide a sustained reduction in bleeding complications in patients with CKD who have recurrent gastrointestinal bleeding from arteriovenous malformations.[119] Low-molecular-weight heparin clearance is reduced in patients with low GFRs. Appropriate dose reductions should occur; currently no guidelines exist for dosing with these medications in patients with a GFR below 15 mL/min, and their use in these settings should be avoided. Similarly, new direct oral anticoagulants (thrombin inhibitors, factor Xa inhibitors) have limited information on safety in subjects with advanced kidney disease. Although patients with ESRD consistently fall into high-risk groups for stroke, their potential benefit from anticoagulation may be limited by a higher bleeding risk.[30,120]

End-Stage Renal Disease

Patients with ESRD represent a large and growing percentage of the CKD population. In the United States, 90% of this population receives renal replacement therapy in the form of in-center hemodialysis at the time of dialysis initiation.[5] Efforts are under way to move more of this care to the patient's home in the form of home hemodialysis or peritoneal dialysis.

Patients with ESRD have a higher mortality when admitted to ICUs.[121,122] This is primarily due to comorbid conditions.[123] Indications for admission may be dialysis specific, such as access complications or volume overload, or may be due to other comorbid illnesses. Most commonly, this includes cardiovascular causes including acute coronary syndromes and strokes, other infectious causes, and gastrointestinal hemorrhages. Commonly used ICU prognostic scoring systems such as Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score, and Sequential Organ Failure provide reasonable prognostication of patients with ESRD.[124]

Attention to a dialysis patient's access for ESRD is essential in the care of any hospitalized ESRD patient. Arteriovenous fistulae and arteriovenous grafts (AVGs) may potentially occlude during hypotension.[125] Loss of dialysis access due to complications from hypotension or potential iatrogenic causes such as restraints could

pose a severe hardship for the patient upon recovery from their current illness.[126–128] A relatively recently recognized issue is the need to avoid brachial and subclavian accesses whenever possible in patient who may currently or imminently need an arteriovenous fistula or AVG. The reason is the frequent development of venous stenosis or thrombosis that could hamper future access maturation; studies show a high prevalence of thrombosis—more than 30%—after placement of a peripherally inserted central catheter.[129] Tunneled intrajugular catheters are an appropriate option in this population.[130] Subclavian lines, even temporarily, pose similar complication risks. Currently the Kidney Disease Outcomes Quality Initiative, sponsored by the National Kidney Foundation, recommends not placing peripherally inserted central catheter lines in patients with CKD.[131]

Common causes of infection in the ESRD population are cellulitis, pneumonia, bacteremia, and pycocystitis.[132] In the absence of a clear cause of infections, a high index of suspicion for access infection should be maintained for ESRD patients presenting with unexplained sepsis if a tunneled dialysis catheter is being used. Generally, catheters do not show signs of infection. Initially, antibiotic therapy should broadly cover gram-positive and gram-negative organisms, as these are the most common organisms associated with infection.[133] Vancomycin and gentamicin, prescribed with a loading dose to achieve therapeutic targets based on local sensitivity data, are standard regimens. Considering the prevalence of methicillin-resistant *Staphylococcal aureus*, a cephalosporin only–based regimen may significantly delay effective therapy.[134] An important consideration is the patient undergoing peritoneal dialysis who still produces urine. If feasible, these patients should not receive aminoglycoside therapy to maintain their important residual renal function. Instead, a third-generation cephalosporin should be used. Whenever possible, old culture results should be used to guide initial treatment as antibiotic resistance is commonplace. When a tunnel infection is suspected in a patient receiving dialysis, as evidence by an erythematous track around the course of the catheter or purulent drainage from the tunnel itself, catheter removal should urgently occur. When an AVG is infected, urgent removal or resection should also occur. Old, occluded AVGs may represent a source for chronic indolent infections and inflammation.[135]

Ideal fluid management in ESRD patients with sepsis requires close monitoring and repeat assessments. Limited data exist to guide the clinician and, in states of classic sepsis, appropriate volume resuscitation should occur. Nonetheless, thoughtful consideration as to when to moderate fluid repletion in the intubated ESRD patient with sepsis may improve subsequent ventilator weaning.

Kidney Transplantation

Patients with a functioning kidney transplant constitute an important and growing percentage of the CKD population. Data from the 2008 U.S. Renal Data System survey show that patients with a functioning kidney transplant make up 30% of ESRD patients.[5] Infectious and cardiovascular complications are the most frequent complications requiring admission to an ICU.

The risk of infection in a kidney transplant patient is complex and related to a number of factors, including the health of the allograft, specific donor and recipient factors (such as cytomegalovirus status and time from transplant), adequate prophylaxis, up-to-date and effective vaccination, and the level of immunosuppression.[136] In the early posttransplant period, generally defined as 1 month or less, typical postoperative complications are most common, including *Clostridium difficile*–associated colitis. In months 1 through 6 after transplantation, opportunistic infections and viral infections are the predominant source of infection owing to the residual effects of induction immunosuppression. After 6 months, typical community-acquired organisms remain the primary source of infection. Infection with cytomegalovirus is an important cause of morbidity in the transplant population and may be present outside the first 6 months. Specific guidelines exist regarding prophylaxis, screening, and treatment for cytomegalovirus in the solid organ transplant patient.[137]

Drug Dosing

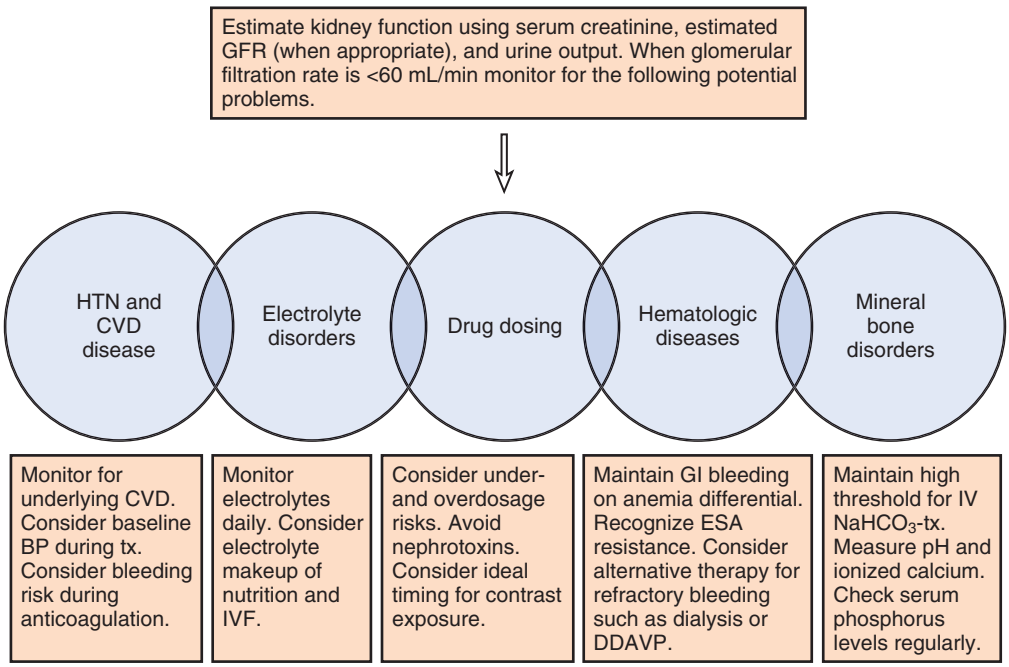
Drug dosing in patients with CKD requires close attention to current levels of kidney function and an understanding of the risks and benefits of the medication prescribed. Two points are worthy of specific attention. First, drug dosing has historically been defined by creatinine clearance and not eGFR.[138,139] The second is that patients with CKD, particularly those with advanced disease, are an understudied population in terms of medication dosing.[140] Antibiotic dosing in the critically ill patient is an area in which the balance between toxicity of overdosage needs to be balanced against the possibility of subtherapeutic dosing. Recognizing that the serum creatinine level may not reflect true GFR is an important part of this process.

Summary

The prevalence of CKD and ESRD in the ICU has increased, and this population is prone to poor outcomes. Ideal care of this population includes the recognition that serum creatinine levels may not reflect GFR, that patients are prone to volume overload and volume depletion, and that abnormalities in Hgb, pH, calcium, and phosphorus may reflect normal and not abnormal physiology. Drug dosing needs to be tailored to individuals with consideration of the risks of both underdosage and overdosage. See Fig. 53.2 for a summary of management principles for CKD.

Key Points

- Patients with CKF frequently die of cardiovascular disease; a high index of suspicion for occult cardiovascular disease should guide caregivers.
- The serum creatinine level frequently does not accurately reflect the current level of kidney function in the ICU patient.



• **Fig. 53.2** Select management principles for patients with chronic kidney disease. *BP,* Blood pressure; *CVD,* cardiovascular disease; *DDAVP,* 1-deamino-8-D-arginine vasopressin; *ESA,* erythropoietin stimulating agent; *GFR,* glomerular filtration rate; *GI,* gastrointestinal; *HTN,* hypertension; *IVF,* intravenous fluid; *$NaHCO^3$*, sodium bicarbonate; *tx,* treatment.

- CKD is associated with sodium retention and a higher prevalence of hypertension. Acute blood pressure control should take into account baseline blood pressure control to avoid tissue under perfusion.
- Electrolyte disorders, particularly hyperkalemia, in the ICU population with CKD, are frequent.
- Acute treatment of chronic metabolic acidosis may lead to iatrogenic falls in serum calcium.
- Brachial and subclavian access is relatively contraindicated in the advanced CKD and ESRD population owing to their future impact on maturing vascular access for dialysis.
- Drug dosing in patients with CKD is poorly studied. Clinicians should be aware of under dosage and over dosage potentials.

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Review Questions

1. In the care of a critically ill individual with an abnormal serum creatinine level, which of the following statements *best* describes the assessment of kidney function?

a. An isolated serum creatinine level can be used to calculate the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation.

b. Stage 3a chronic kidney disease (CKD; e GFR 45–60 mL/min) has a high risk of progressing to end-stage renal disease (ESRD).

c. Proteinuria increases cardiovascular risk even at a normal GFR.

d. Serum creatinine is the most accurate measure of kidney function.

Answer: c. The measurement of kidney function using a serum creatinine level may be misleading. Patient-specific issues (size irregularities) and exogenous substances can lead to situations where serum creatinine may inaccurately reflect kidney function; other measures such as 24-hour creatinine clearance may be helpful at times. Kidney function assessment requires steady-state serum creatinine and a single value may provide an inaccurate result. Patients with stage 3a CKD do not have a high risk of kidney disease progression unless significant proteinuria is present. Proteinuria is now a recognized risk factor for cardiovascular disease at all levels of kidney function.

2. A 56-year-old male with stage 3b CKD owing to diabetic nephropathy is recovering from pneumonia. Through the course of the hospitalization he has accumulated 12 kg in weight and is hypertensive and edematous on examination. You believes he needs aggressive diuresis. An initial regimen of furosemide 40 mg intravenously (IV) twice a day (bid) does not yield a negative fluid balance. In reviewing his record, you note his creatinine level is slightly worse than on admission (currently 3.2 mg/dL; 2.4 before admission) and he was taking furosemide 80 mg bid before admission. What is the best additional step in treating his volume overload?

a. Convert furosemide to a thiazide diuretic such as chlorthalidone 25 mg daily.

b. Increase his furosemide to 80 mg IV bid.

c. Convert his furosemide to 80 mg IV daily.

d. Replace furosemide with metolazone 5 mg daily.

Answer: b. Patients with CKD who use moderate- to high-dose diuretics develop compensatory mechanisms to retain additional sodium. As a result they often require higher-dose diuretics or, on occasion, the addition of metolazone to a diuretic regimen to achieve an adequate diuresis. Thiazide diuretics such as chlorthalidone or hydrochlorothiazide are not as effective at initiating a diuresis as loop diuretics. This case illustrates an example of a volume overloaded state in which diuretics are not achieving an adequate diuresis as the result of worsening kidney function and the need for a higher dose. In a volume-overloaded state, most loop diuretics (the exception being torsemide) should be administered twice daily. Metolazone is rarely used alone.

3. You are caring for a 62-year-old male patient with stage 4 CKD (eGFR 22 mL/min) owing to polycystic kidney disease. He was admitted for sepsis attributed to an infected renal cyst. He will be completing an antibiotic course and you are asked to write orders for him to leave the ICU. Which of the following statements is *true* regarding the care of patients with stage 4 CKD?

a. A peripherally inserted central catheter (PICC) line should not be used.

b. Phosphorus-containing gastrointestinal stimulants may be used if serum phosphorus is in the normal range.

c. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should be avoided.

d. All subjects should follow a renal diet.

Answer: a. In subjects with advanced CKD (all subjects with stage 4 disease) PICC lines are not recommended to avoid damage to the subclavian vein, which may be a site for future vascular access for dialysis. Phosphorus-containing gastrointestinal stimulants should be avoided because of the potential for a large phosphorus load to be absorbed and subsequent acute kidney injury. ACE inhibitors and ARBs are not contraindicated in advanced but stable CKD, although close attention to potassium levels is needed. Although a renal diet may control volume overload and potassium excess states, if subjects are malnourished they may not be necessary.

54

Acid-Base, Electrolyte, and Metabolic Abnormalities

JASON A. KLINE AND LAWRENCE S. WEISBERG

CHAPTER OUTLINE

Metabolic Disorders of Acid-Base Homeostasis
- Normal Acid-Base Physiology
- Metabolic Acidosis
- Metabolic Alkalosis

Disorders of Potassium Homeostasis
- Normal Potassium Physiology
- Disorders of Potassium Homeostasis
- Clinical Manifestations of Potassium Imbalance
- Evaluation of Disorders of Potassium Homeostasis
- Treatment of Potassium Imbalance

Disorders of Water Homeostasis
- Physiology of Water Homeostasis
- Hyponatremia
- Hypernatremia
- Differential Diagnosis

Calcium
- Normal Calcium Physiology
- Plasma Calcium Measurement
- Hypocalcemia
- Hypercalcemia

Disorders of Magnesium Homeostasis
- Normal Magnesium Physiology
- Assessment of Body Magnesium Status
- Hypomagnesemia
- Hypermagnesemia

Phosphorus
- Normal Phosphorus Homeostasis
- Hypophosphatemia
- Hyperphosphatemia

Acid-base, electrolyte, and metabolic disturbances are common in the intensive care unit (ICU). Indeed, critically ill patients often have compound acid-base and electrolyte disorders. Successful evaluation and management of such patients requires recognition of common patterns (e.g., hypokalemia and metabolic alkalosis) and an ability to dissect one disorder from another. This chapter is intended to provide clinicians with the tools they need for diagnosis and treatment of the acid-base, electrolyte, and metabolic disorders encountered in the care of critically ill patients. By reviewing the elements of normal physiology in these areas and presenting a general diagnostic scheme for each condition, we hope to provide readers with a foundation for approaching not only common, but novel and complex disorders.

Metabolic Disorders of Acid-Base Homeostasis

Normal acid-base balance depends on the cooperation of at least two vital organ systems: the lungs and the kidneys. The gastrointestinal (GI) tract also is implicated in many acid-base disturbances. Multiorgan system involvement, therefore, provides the backdrop for the acid-base disorders commonly seen in critically ill patients.

Normal Acid-Base Physiology

Normal biochemical and physiologic function requires that extracellular pH be maintained within a very narrow range. Although the "normal" range of pH in clinical laboratories is 7.35 to 7.45 pH units, the actual pH in vivo varies considerably less.[1] This tight control is maintained by a complex homeostatic mechanism involving buffers and the elimination of volatile acid by respiration.

The principal extracellular buffer system is the carbonic acid/bicarbonate pair. The equilibrium relationships of the components of this system are illustrated as follows[1]:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

From these relationships, the Henderson-Hasselbalch equation is derived:

$$pH = pK + \log_{10} \frac{HCO_3^-}{\alpha_{CO_2} \cdot P_{CO_2}}$$

where CO_2 is carbon dioxide, HCO_3^- is bicarbonate, and Pco_2 is the partial pressure of carbon dioxide. In this equation, α_{CO2} is the solubility coefficient of CO_2 (0.03), and pK is the equilibrium constant for this buffer pair (6.1). Rearrangement yields the Henderson equation:

$$H^+ = 24 \cdot \frac{P_{CO_2}}{HCO_3^-}$$

TABLE 54.1 Expected Compensation for Simple Acid-Base Disorders

Disorder	Primary Disturbance	Compensation	Magnitude	Time to Completion
Metabolic acidosis	↓ $[HCO_3^-]$	↓ PCO_2	1.5 • $[HCO_3^-]$ + 8	12–24 h
Metabolic alkalosis	↑ $[HCO_3^-]$	↑ PCO_2	0.9 • $[HCO_3^-]$ +9	12–24 h
Respiratory acidosis, acute	↑ Pco_2	↑ $[HCO_3^-]$	1 mmol/L/10 torr	<6 h
Respiratory acidosis, chronic	↑ Pco_2	↑ $[HCO_3^-]$	3.5 mmol/L per 10 torr	>5 days
Respiratory alkalosis, acute	↓ Pco_2	↓↓ $[HCO_3^-]$	2 mmol/L/10 torr	<6 h
Respiratory alkalosis, chronic	↓ Pco_2	↓ $[HCO_3^-]$	5 mmol/L per 10 torr	>7 days

HCO_3^-, Bicarbonate; Pco_2, partial pressure of carbon dioxide.

It is apparent from this equation that disturbances in the proton concentration of the extracellular fluid (ECF) (and blood) may be due to perturbation in the numerator, the denominator, or both. Disturbances that affect the Pco_2 primarily are called respiratory disturbances, and those that affect the HCO_3^- primarily are called metabolic.

Acid-base homeostasis depends on compensation for a primary disturbance. Compensation for a respiratory disturbance is metabolic, and compensation for a metabolic disturbance is respiratory. Furthermore, it is clear from the previous equations that to mitigate the change in proton concentration or pH, the direction of the compensation must be the same as the direction of the primary disturbance. Thus consumption of bicarbonate will be accompanied by hyperventilation and a consequent reduction in Pco_2. A simple acid-base disturbance is considered to consist of the primary disturbance and its normal compensation. A complex acid-base disturbance consists of more than one primary disturbance. To detect complex acid-base disturbances, one must be familiar with both the direction and magnitude of normal compensation (shown in Table 54.1).[2] More than one metabolic disturbance may coexist (e.g., metabolic acidosis and metabolic alkalosis), but only one respiratory disturbance is possible at a time.

In this section, we discuss disorders that affect the metabolic component of acid-base homeostasis: metabolic acidosis and metabolic alkalosis. Respiratory disturbances affecting acid-base balance will be discussed elsewhere (see Chapters 9–11, and 34).

Metabolic Acidosis

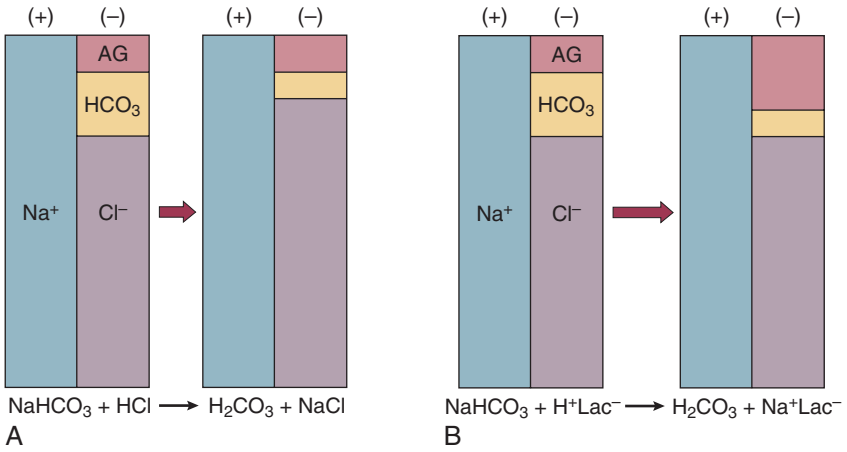
Definition and Classification

A metabolic acidosis is a process that, if unopposed, would cause acidemia (a high hydrogen ion concentration, or low pH, of the blood) by reducing the extracellular bicarbonate concentration. The extracellular bicarbonate concentration may be reduced by either addition of acid and consequent consumption of bicarbonate, or by primary loss of bicarbonate.

An adult eating a normal diet generates 16,000 to 20,000 mmol of acid per day.[3] Almost all of that acid is in the form of carbonic acid, resulting from CO_2 and water generation in the metabolism of carbohydrates and fats. Individuals with normal ventilatory capacity eliminate this prodigious acid load through the lungs, thus the term volatile acid. The remainder of the daily acid load, about 1 mmol/kg body weight per day, derives from metabolism of phosphate- and sulfate-rich protein (yielding phosphoric and sulfuric acid). These nonvolatile, or fixed, acids are buffered primarily by extracellular bicarbonate under normal circumstances. The kidneys are responsible for regenerating the consumed bicarbonate by secreting hydrogen ions (protons) in the distal nephron. These secreted protons must be buffered in the tubule lumen to allow elimination of the daily fixed acid load within the physiologic constraint of the minimum urinary pH. The urinary buffers are composed of the filtered sodium salts of the phosphoric acid, and ammonia, which is synthesized in the proximal tubule and acidified in the collecting duct to form ammonium (NH_4^+). Under conditions of acid loading, the normal kidney reabsorbs all the filtered bicarbonate in the proximal tubule. Urinary net acid excretion therefore consists of phosphoric acid (so-called titratable acidity, because it is quantified by titrating the urine with alkali to pH 7.40) and ammonium, less any excreted bicarbonate.[4]

Many factors modify the kidney's capacity to regulate acid-base balance. For example, renal ammoniagenesis is stimulated by acidemia, and inhibited by alkalemia, and thus participates in a homeostatic feedback loop.[1] Hyperkalemia inhibits and hypokalemia stimulates renal ammoniagenesis. Hypokalemia further stimulates acid secretion by activating the sodium-hydrogen (Na^+-H^+) exchanger in the proximal tubule and the hydrogen ion (H^+), potassium ion–adenosine triphosphatase (K^+-ATPase) in the collecting duct. Finally, aldosterone stimulates both proton and K^+ secretion in the collecting duct. For these reasons, hypokalemia tends to perpetuate a metabolic alkalosis, and hyperkalemia a metabolic acidosis.[1]

Metabolic acidosis can be caused by excessive production of fixed acid, decreased renal secretion of fixed acid, or loss of bicarbonate, either through the kidney or through the intestine.[4] The net effect of any of these processes is a reduction in the blood bicarbonate concentration. The plasma anion gap helps to distinguish among the various causes of metabolic acidosis. Of course, because of charge neutrality, the sum of the concentration of all cations in the plasma is equal to the sum of all the anions. By convention, however, the anion gap is defined as the difference between the plasma sodium concentration and the sum of the bicarbonate and chloride concentrations. It represents the concentration of anions that are normally unmeasured by a basic metabolic chemistry panel.[5] The anion gap normally is about 8 mmol/L, but it varies widely according to the methods used by the clinical chemistry laboratory.[6] The anion gap is composed mainly of albumin, along with phosphates, sulfates, and organic anions.



• **Fig. 54.1** The generation of hyperchloremic and anion-gap *(AG)* acidoses. Blocks represent the ionic composition of the plasma, cations (+) to the left and anions (–) to the right. In each of the panels (A and B), the bar to the left represents the basal or normal state. The anion gap is shown in red. Panel A shows the change in the ionic composition of the plasma when hydrochloric acid *(HCl)* is added. The chloride concentration increases as bicarbonate is consumed. Panel B shows the effect of addition of an organic acid such as lactic acid *(H^+Lac^-),* in which case the bicarbonate is consumed and the AG increases proportionately. *Cl,* Chloride; *H_2CO_3,* carbonic acid; *Na,* sodium; *$NaHCO_3$,* sodium bicarbonate.

There are two important pitfalls in the interpretation of the anion gap. First, because the anion gap is proportional to the plasma albumin concentration, hypoalbuminemia (common in critically ill patients) will lower the "baseline" anion gap (by approximately 2.5 mmol/L for each gram per deciliter decline in the albumin concentration).[7] Thus profound hypoalbuminemia may falsely lower the anion gap, and thus mask a high anion gap acidosis. Second, alkalemia increases the anion gap, by causing lactate generation and by titrating plasma buffers, most notably albumin.[8] (Thus in respiratory alkalosis, the bicarbonate concentration will be low in compensation, and the anion gap may be elevated, giving a false impression of a high anion gap metabolic acidosis by inspection of the electrolytes alone.)

If bicarbonate is lost (e.g., through diarrhea) or hydrochloric acid is gained (e.g., renal tubular acidosis or administration of unbuffered amino acid solutions[9]), the bicarbonate concentration falls with a commensurate increase in the plasma chloride concentration; thus the anion gap is unchanged. If, on the other hand, bicarbonate is lost in buffering an organic acid such as lactic acid or a ketoacid, the decrement in the bicarbonate concentration is more or less matched by an increase in the anion gap. These processes are illustrated in Fig. 54.1.

Box 54.1 lists the causes of hyperchloremic metabolic acidosis. Two diagnoses are of particular interest in the critical care arena. First is the posthypocapnic metabolic acidosis, in which bicarbonate falls in compensation for a chronic respiratory alkalosis. When "normal" ventilation is restored, the pH falls until bicarbonate can be retained, giving the appearance of a hyperchloremic metabolic acidosis. This emphasizes the importance of observation over time in the analysis of acid-base status. The second entity of interest is a so-called dilutional hyperchloremic acidosis. This is seen in patients who are rapidly resuscitated with large volumes of isotonic saline solution. The acidosis traditionally has been attributed to dilution of blood bicarbonate. Analysis based on physical-chemistry principles, however, may better explain the phenomenon (see later text).[10]

The differential diagnosis of high anion gap metabolic acidosis is limited (Box 54.2). The most common cause in critically ill patients is a lactic acidosis. The causes of lactic acidosis are numerous. As shown in Box 54.3, they are divided into type A (imbalance between tissue oxygen demand and supply) and type B (all others).[5] Diabetic ketoacidosis (see Chapter 55) and intoxications (see Chapter 65) are discussed elsewhere. Two causes of high anion gap acidosis recently added to the differential diagnosis, and of particular relevance to intensivists, are pyroglutamic acidosis and intoxication with propylene glycol.

• BOX 54.1 Causes of Hyperchloremic Metabolic Acidosis

Extrarenal Loss of Base
Diarrhea
Pancreatic fistula
Ureteral diversion

Extrarenal Gain of Acid
Ammonium chloride
Hydrochloric acid
Sodium chloride
Toluene inhalation (glue sniffing)

Renal Loss of Base
Type II renal tubular acidosis
Posthypocapnic state
Excretion of organic anions (bicarbonate precursors)

Renal Acid Excretory Defect
Type IV renal tubular acidosis
- Chronic kidney disease
- Hypoaldosteronism
- Urinary tract obstruction

Type I renal tubular acidosis
- Sickle cell nephropathy
- Lupus nephritis
- Renal transplant

• BOX 54.2 Causes of High Anion-Gap Metabolic Acidosis

Ketoacidoses
- Diabetic
- Alcoholic
- Starvation

Intoxications
- Methanol
- Ethylene glycol
- Propylene glycol
- Salicylate

Pyroglutamic acidosis
- Congenital
- Acquired

Lactic acidosis (see Box 54.3)

Uremic acidosis

• BOX 54.3 Causes of Lactic Acidosis

Type A (Tissue Oxygen Supply: Demand Mismatch)

Decreased tissue oxygen delivery
- Shock
- Hypoxemia
- Severe anemia
- Carbon monoxide poisoning

Increased tissue oxygen demand
- Grand mal seizure
- Extreme exercise

Type B

Impaired oxygen utilization
- Cyanide poisoning
- Linezolid
- Metformin
- Antiretroviral agents (nucleosides and nucleoside reverse transcriptase inhibitors [NRTIs])
- Acetaminophen

Excessive lactate production
- Sepsis
- HIV infection
- Alcohols (EtOH, MeOH, ethylene glycol, propylene glycol, sorbitol)
- Propofol
- Diabetes mellitus
- Alkalemia
- Malignancy
- Pheochromocytoma
- Sorbitol/fructose
- Thiamine deficiency
- Congenital enzyme defects (tricarboxylic acid cycle, pyruvate transport)

Decreased lactate metabolism
- Liver failure

D-lactic acidosis

EtOH, *Ethanol;* MeOH, *methanol;* HIV, *human immunodeficiency virus.*

Pyroglutamic acid is a metabolic intermediate in the γ-glutamyl cycle, one product of which is glutathione. Pyroglutamic acidosis may be congenital (caused by one of several enzyme deficiencies) or acquired.[8] The acquired syndrome may be caused by acetaminophen (which depletes glutathione, leading to uninhibited pyroglutamic acid synthesis), certain antibiotics, or glycine deficiency. The acidosis may be profound and the anion gap greater than 30 mmol/L.[11] Definitive diagnosis is made by urinary screening for organic acids. In practice, however, circumstantial evidence suggests the acquired syndrome and the diagnosis are supported by a favorable response to appropriate intervention.

Propylene glycol is a solvent for medications, many of which (such as lorazepam, nitroglycerine, etomidate, and phenytoin) are commonly infused intravenously in critically ill patients. Propylene glycol is metabolized by alcohol dehydrogenase to lactic acid. High anion gap acidosis has been associated with high- and even low-dose infusions, particularly of lorazepam.[7,12] Thus development of a high anion gap acidosis in a critically ill patient should prompt a search for a source of propylene glycol because withdrawal of the agent will promptly alleviate the acidosis.

Consequences of Acidemia

It has been generally accepted that severe acidemia (pH < 7.20) is associated with a variety of deleterious effects. Of particular concern are the cardiovascular effects, including pressure-resistant arterial vasodilation, venoconstriction, diminished myocardial contractility, and impaired hepatic and renal perfusion.[13] (Some controversy exists as to which of these effects are directly caused by acidemia.[4]) A predisposition to malignant arrhythmias has been reported in vitro and in animal models. Finally, numerous metabolic derangements have been attributed to the effect of acidemia on key enzymes in metabolic pathways, resulting in sympathetic hyperactivity with diminished catecholamine responsiveness; insulin resistance and suppressed glycolysis; and reduced hepatic lactic acid uptake and metabolism.[14]

Diagnosis of Acid-Base Disorders

Acid-base disorders are revealed most commonly through the basic metabolic chemistry panel, when the plasma bicarbonate concentration is noted to be outside the normal range. If the bicarbonate is low, and if the anion gap is clearly elevated on that sample, a diagnosis of high anion gap metabolic acidosis can be made with some confidence, keeping in mind the pitfalls in the interpretation of the anion gap mentioned previously.[7]

If the bicarbonate is low and the anion gap normal, two possibilities exist: either a hyperchloremic metabolic acidosis or a respiratory alkalosis with metabolic compensation. These two entities can be distinguished by examination of the blood pH and blood gases; a low pH is diagnostic of the former.

If the bicarbonate concentration is high, again there are two alternative diagnoses requiring blood pH measurement for their differentiation: either a metabolic alkalosis or metabolic compensation for a respiratory acidosis.

Once the primary disturbance has been identified, the astute clinician, recognizing the possibility of a mixed disturbance, is obligated to ask, "Is that all there is?" This question can be answered only by an understanding of the rules of normal compensation for simple acid-base disorders (see Table 54.1).[2] Knowing at least the expected direction of compensation allows the clinician to diagnose the most obvious mixed disturbances. For example, if the pH is low, the bicarbonate is low, and the Pco_2 is above 40 torr, there is clearly a mixed metabolic and respiratory acidosis. Similarly, if the pH is high, the bicarbonate is high and the Pco_2 is below 40 torr, the diagnosis is a mixed respiratory and metabolic alkalosis. More subtle mixed disorders can be diagnosed only by understanding not only the expected direction, but the expected magnitude of compensation. This allows one to conclude, for example, whether the hyperventilation in a patient with metabolic

acidosis is appropriate (expected compensation), inadequate (a separate respiratory acidosis), or excessive (a separate respiratory alkalosis).

The preceding method permits the diagnosis of simple and dual acid-base disorders. Triple acid-base disorders can be diagnosed only by comparing the change in the anion gap with the change in the plasma bicarbonate concentration. Most simply conceived, the fall in the bicarbonate should roughly equal the rise in the anion gap (see Fig. 54.1). If the rise in the anion gap exceeds the fall in the bicarbonate, a metabolic alkalosis is said to be present in addition to the high anion gap acidosis. Conversely, if the fall in the bicarbonate exceeds the rise in the anion gap, mixed hyperchloremic and high anion gap acidoses are said to coexist. Although this analysis is useful in the case of large discrepancies, in more subtle cases it is confounded by theoretical and practical considerations.[5,15]

Note that the plasma bicarbonate concentration may be completely normal in the setting of complex countervailing acid-base disturbances—for example, the high anion gap acidosis and a metabolic alkalosis seen in a patient with diabetic ketoacidosis (DKA) and vomiting. Thus important acid-base disturbances may be overlooked unless clinicians routinely calculate the anion gap when caring for critically ill patients.

The classical approach to acid-base disorders previously described has been challenged recently by proponents of a physical-chemistry approach described originally by Stewart.[16] According to this method, the pH of the blood depends on the ionization of water by the difference in the concentration of so-called strong ions (the strong ion difference [SID]). The SID offers a quantitative approach to measuring the degree of acidosis in hyperchloremic metabolic acidosis. Although there is evidence that this approach may have prognostic capabilities in patients with severe sepsis and septic shock with hyperchloremic metabolic acidosis, the complexity of the equations for calculating the SID makes this method cumbersome in clinical settings.[17] The main utility of this construct in the critical care setting seems to be its explanation of a hyperchloremic metabolic acidosis in patients who receive large volumes of isotonic saline solution.

Treatment of Metabolic Acidosis

Although severe acidemia has not been definitively determined to be deleterious to patients, blood pH < 7.10 leaves little room for additional acid burden without a precipitous fall in pH. Therefore most clinicians favor treating metabolic acidosis with blood pH ≤ 7.10. Any respiratory contribution to the acidemia must be corrected before administering alkali.

Treatment of hyperchloremic metabolic acidosis is straightforward. In cases of acute metabolic acidosis, treatment depends on successful therapy of the underlying cause (e.g., diarrhea) and reduction of the bicarbonate deficit.

Sodium bicarbonate is the alkalinizing agent of choice for most patients with severe acidemia. Alternative alkalinizing agents such as salts of citrate, acetate, and lactate, which under normal circumstances are oxidized in the liver to bicarbonate, should not be used to treat acidemia in patients with suspected or confirmed hepatic impairment or circulatory compromise. Bicarbonate dosing must be empirical because the bicarbonate deficit is not calculable in practice.[18] Rapid infusion of undiluted ampoules of sodium bicarbonate (1000 mmol/L) is recommended for patients with severe acidemia. The goal is to raise the blood pH no higher than 7.20. Excessive bicarbonate administration, or bicarbonate administration to patients with high circulating concentration of metabolizable conjugate bases such as ketones or lactate, runs the risk of overshoot alkalemia. Administration of undiluted ampules will tend to cause hyperosmolality, the risk of which may be mitigated by administration of sodium bicarbonate as an isotonic solution (e.g., 150 mmol sodium bicarbonate in 1 L of water). Large volumes of any bicarbonate solution can lead to volume overload, a reduction in the ionized calcium concentration (see "Hypocalcemia") and increased generation of CO_2. This last effect causes a respiratory acidosis in patients whose ventilation cannot increase. Plasma electrolytes and blood gases must be monitored frequently to guide adjustments in the composition of the solution and its rate of infusion.

Tris-hydroxymethyl aminomethane, or THAM, is an amino alcohol that buffers without generating CO_2. It has the advantage, therefore, of avoiding a superimposed respiratory acidosis. It has been used successfully in animals and humans with various metabolic acidoses.[13,19] It is eliminated by the kidney, and thus should be used with caution in the setting of renal insufficiency. Risks include hyperkalemia, hypoglycemia, and hepatic necrosis (in neonates).[7]

The treatment of choice for lactic acidosis is reversal of the underlying cause of the acidosis (see Box 54.3). Pending resolution of the underlying disorder, however, the intensivist is often confronted with an unstable patient who is profoundly acidemic. Treatment at this stage is controversial.[20] The debate has focused on the potentially deleterious effects of bicarbonate administration in lactic acidosis.[13,21] In addition to the effects already mentioned, bicarbonate in animal models of lactic acidosis has been associated with increased lactate generation, reduction in intracellular pH, increased venous Pco_2, and reduction in cardiac output. (This last effect correlates well with the reduction in ionized calcium concentration.[13]) Studies in humans, though few, likewise show no improvement in cardiac output, morbidity or mortality with bicarbonate.[22] Continuous hemodialysis (e.g., continuous venovenous hemodialysis) may be a promising tool for treating lactic acidosis, because it provides large amounts of bicarbonate without the risks of volume overload or hypocalcemia. Metformin-associated lactic acidosis is particularly amenable to treatment with renal replacement therapy because it removes the culprit toxin.[23] Treatment of DKA and the acidoses associated with other intoxications are discussed in Chapters 55 and 65, respectively.

Metabolic Alkalosis

Definition and Classification

Metabolic alkalosis is a process leading to accumulation of extracellular bicarbonate which, if unopposed, will result in an increase in the plasma pH (alkalemia). In its pure form, it is accompanied by compensatory hypoventilation (CO_2 retention).[2]

From a pathophysiologic perspective, metabolic alkalosis is divided into those factors that generate the alkalosis and those factors that maintain or perpetuate it.[24,25] Metabolic alkalosis is generated by addition of bicarbonate to the blood. This can occur either by loss of acid from the body or by addition of exogenous alkali. Loss of acid may be from the stomach (e.g., vomiting or gastric suction) or kidney. Renal acid loss is enhanced by a high rate of sodium delivery to the distal nephron, high circulating mineralocorticoid levels, potassium depletion, and high rates of renal ammoniagenesis.

Because of the kidney's prodigious ability to excrete bicarbonate, however, addition of bicarbonate to the blood is not sufficient to cause a sustained metabolic alkalosis. Some mechanism(s) to

maintain the alkalosis must prevail. The most common mechanism contributing to the maintenance of metabolic alkalosis is volume depletion, either absolute or relative (e.g., congestive heart failure), which (1) reduces glomerular filtration, (2) enhances tubular bicarbonate reabsorption, and (3) causes secondary hyperaldosteronism, further enhancing urinary acidification. Another common perpetuating factor is potassium depletion, which stimulates proton secretion at several sites along the nephron.

Patients with metabolic alkalosis and signs of volume expansion—especially hypertension—usually have excess mineralocorticoid as the explanation for the metabolic alkalosis. Aldosterone and glucocorticoids (other than dexamethasone) stimulate renal loss of acid and K, and thereby generate and maintain the alkalosis.

Given the pathophysiology described, it is useful to approach the patient with metabolic alkalosis with special attention to the ECF volume status, centering on the history and physical examination, followed by sequential analysis of blood chemistries.[26] Causes of metabolic alkalosis are shown in Box 54.4. One entity unique to critically ill patients is the posthypercapnic metabolic alkalosis. This syndrome is caused by abrupt treatment (usually with tracheal intubation and mechanical ventilation) of a patient with chronic respiratory acidosis. The renal bicarbonate retention that compensated for the chronic respiratory acidosis persists (because of volume depletion) after restoration of a normal Pco_2, resulting in the high pH and high plasma bicarbonate characteristic of metabolic alkalosis. The key to the diagnosis is the history and sequential analysis of blood chemistries.[24]

• BOX 54.4 Causes of Metabolic Alkalosis

Intravascular Volume Depletion, Absolute or "Effective"

Gastrointestinal acid loss
- Vomiting or nasogastric suction
- Villous adenoma
- Chloride diarrhea

Renal acid loss
- Diuretics (loop, thiazide)
- Bartter syndrome
- Gitelman syndrome
- Magnesium depletion
- Posthypercapnic state
- Congestive heart failure
- Hepatic cirrhosis/ascites

Intravascular Volume Expansion

High renin, high aldosterone
- Renal artery stenosis
- Accelerated hypertension
- Renin-secreting tumor

Low renin, high aldosterone
- Primary aldosteronism

Low renin, low aldosterone
- Cushing syndrome or disease
- Exogenous mineralocorticoid
- Apparent mineralocorticoid excess syndrome
- Liddle syndrome

Renal insufficiency
- Exogenous alkali load
- Milk-alkali syndrome

Modified from Gennari FJ. Pathophysiology of metabolic alkalosis: a new classification based on the centrality of stimulated collecting duct ion transport. Am J Kidney Dis. *2011;58:626–636.*

Clinical Consequences

Alkalemia in critically ill patients is associated with increased mortality.[27] Patients with combined metabolic and respiratory alkalosis have a higher mortality than those with respiratory alkalosis alone, and mortality in alkalemia is roughly proportional to the pH.[27] Although no causal relationship between alkalemia and mortality has been established, the pathophysiology of alkalemia is far from benign.[25] First, metabolic alkalosis suppresses ventilation, causing CO_2 retention and relative hypoxemia.[28] Second, alkalemia acutely increases hemoglobin's oxygen affinity (Bohr effect). Third, alkalemia causes vasoconstriction, particularly in the cerebral circulation.[25] All these processes tend to decrease tissue oxygen delivery.[29] (Note that chronic alkalemia inhibits 2,3-diphosphoglycerate synthesis, allowing normalization of the oxyhemoglobin desaturation curve, mitigating tissue hypoxia to some extent.) These alterations in tissue oxygen delivery could be responsible at least in part for some of the clinical manifestations of metabolic alkalosis.

Because alkalemia causes a decrease in ionized calcium concentration (see "Calcium"), many of the neuromuscular manifestations of metabolic alkalosis overlap with those of hypocalcemia, including paresthesias, tetany, and a predisposition to seizures.[1] The acutely diminished tissue oxygen delivery to the brain may contribute to the initial confusion and obtundation seen with metabolic alkalosis.

Metabolic alkalosis often is accompanied by hypokalemia and hypomagnesemia. Thus there is an association between alkalosis and arrhythmias,[24] but an independent effect of the alkalosis on cardiac arrhythmogenesis has not been established.

Increases in blood lactate concentration may occur in patients with metabolic alkalosis owing to upregulation of phosphofructokinase and thus glycolysis, and because of tissue hypoxia (see earlier text).[8] With severe metabolic alkalosis (arterial pH >7.55), the tissue hypoxia may be so marked that compensatory hypoventilation will be overridden by hypoxic drive, resulting in a normal to low arterial Pco_2 and elevated blood lactate levels (so-called lactic alkalosis).[30]

Treatment

Treatment of metabolic alkalosis entails correcting the factor(s) responsible for its maintenance, and, if possible, correcting the factor that generated the alkalosis. Once the underlying diagnosis is clear (see Box 54.4), therapy is usually straightforward. If the metabolic alkalosis is maintained by chloride depletion and ECF volume contraction, the intravascular volume should be restored to normal, usually with intravenous isotonic saline solution.[24,25] Potassium should be given, as potassium chloride (KCl), to replace any deficits (see "Disorders of Potassium Homeostatis") because potassium depletion perpetuates the metabolic alkalosis. If gastric suction cannot be stopped, acid loss can be reduced by the use of histamine H_2 blockers and proton pump inhibitors.

Treating patients with metabolic alkalosis in the setting of volume overload and diminished effective circulating volume (e.g., congestive heart failure, hepatic cirrhosis) is more challenging, because infusion of saline solution is contraindicated. Unless hyperkalemia is present, chloride should be replenished with KCl supplementation. In rare cases of concurrent hyperkalemia and metabolic alkalosis, acetazolamide (a carbonic anhydrase inhibitor) may be of benefit as it produces a bicarbonate diuresis. Acetazolamide should be avoided in patients with hypokalemia, because the alkaline diuresis will cause renal potassium wasting and worsen the hypokalemia.[24] Another potential complication of acetazolamide administration,

particularly in patients with impending ventilatory failure, is worsening of hypercapnia due to inhibition of red blood cell carbonic anhydrase and impaired CO_2 transport.[25] Hydrochloric acid infusion, as a 0.1- to 0.25-N solution, has been used with success in patients with severe metabolic alkalosis (pH > 7.55 and systemic instability such as encephalopathy or cardiac arrhythmia[24]) refractory to conventional measures.[25,31] Correction of the metabolic disturbances has been reported with infusion of 0.25-N HCl at 100 mL/h over about 12 hours.[31] Extreme care must be taken to ensure that the infusion catheter is properly positioned within the vena cava because the solution is highly caustic. Plasma chemistries must be monitored frequently to avoid over-correction. If renal function is severely impaired or medical therapy is not possible, hemodialysis against a low-bicarbonate bath may be used.[24]

In states of primary mineralocorticoid excess, an aldosterone antagonist such as spironolactone should be used until the underlying abnormality can be corrected. Other potassium-sparing diuretics, such as amiloride and triamterene, are useful as well and are essential in managing the rare patient with Liddle syndrome.

Disorders of Potassium Homeostasis

Normal Potassium Physiology

Disorders of potassium homeostasis are common in hospitalized patients and may be associated with severe adverse clinical outcomes, including death.[32,33] Prevention and proper treatment of hyperkalemia and hypokalemia depend on an understanding of the underlying physiology.

The total body potassium content of a 70-kg adult is about 3500 mmol, of which only 2% (about 70 mmol) is extracellular.[34] This uneven distribution reflects the large gradient between the intracellular potassium concentration (K_i ~ 140 mmol/L) and the extracellular potassium concentration (K_e ~ 4.5 mmol/L), a gradient that is maintained by the intrinsic ion permeability of cell membranes and by Na-K ATPase, the sodium-potassium pump.[35] The K_e:K_i ratio largely determines the resting membrane potential of cells and thus is crucial for proper function of excitable tissues (muscle and nerve).[35] Small absolute changes in K_e will perturb the ratio significantly. Therefore disturbances of K_e (measured as changes in plasma potassium concentration, or P_K) may have serious, even lethal, consequences mainly in the form of excitable tissue dysfunction.

It is not surprising, therefore, that the extracellular potassium concentration is tightly regulated. In fact, two separate and cooperative systems participate in potassium homeostasis. One system regulates external potassium balance: the total-body parity of potassium elimination with potassium intake. The other system regulates internal potassium balance: the distribution of potassium between the intracellular and ECF compartments. This latter system provides a short-term defense against changes in the P_K that might otherwise result from total-body potassium losses or gains.

Regulation of Internal Potassium Balance

Internal potassium balance protects against changes in K_e; potassium tends to move out of cells during potassium depletion and into cells following potassium intake. This process tends to mitigate short-term fluctuations in K_e:K_i.[36,37] The factors that influence internal potassium balance include hormones, acid-base status, plasma tonicity, exercise, and cell integrity (Box 54.5).

The direction and magnitude of an acid-base–related change in P_K depend on the nature and the duration of the disturbance.[38]

• BOX 54.5 Factors Affecting Internal Potassium Balance

Factors Causing Cellular Potassium Influx

Insulin
β_2-Adrenoceptor agonist
(Metabolic alkalosis)[a]

Factors Causing Cellular Potassium Efflux

Cell ischemia/lysis
Exercise
Plasma hypertonicity
α-Adrenoceptor agonist
(Metabolic acidosis)[a]

[a]*Factors shown in parentheses have a minor or variable effect. See text.*

The most consistent and pronounced relationship between changes in pH and P_K occurs in acute mineral (hyperchloremic) acidosis, in which there is a strong inverse relationship between these two variables.[39,40] Interestingly, hypokalemia is seen with prolonged mineral acidosis in patients with normal renal function and reflects increased renal potassium excretion.[40] Unlike mineral acidoses, however, even severe acute organic (high anion gap) acidoses are not usually associated with hyperkalemia.[41–44] Nonetheless, factors coincident with the acidosis may alter P_K. For example, mesenteric ischemia may result in both lactic acidosis (from anaerobic metabolism) and hyperkalemia owing to potassium efflux from ischemic tissue. Even the hyperkalemia so commonly seen in patients with DKA does not result from the acidemia; rather, it appears to be a consequence of the characteristic insulin deficiency and hyperglycemia (see the next paragraph on hypertonicity).[44] Respiratory disturbances typically alter P_K less than metabolic disturbances. Alkaloses, respiratory or metabolic, have less effect on P_K than their corresponding acidosis.[39] Bicarbonate administration, which was once thought to reduce the P_K by stimulating cellular potassium uptake,[45] is now known to have very little if any immediate effect on internal potassium balance,[46,47] except perhaps in patients with preexisting severe metabolic acidosis.[41] It is clear, however, that long-standing alkalemia causes urinary potassium losses that may, over time, result in profound potassium depletion.[48]

Hypertonicity, as seen with hypertonic fluid administration[49] or diabetic hyperglycemic states,[50] leads to hyperkalemia, probably as a result of convective potassium efflux from cells by way of solvent drag. Lethal hyperkalemia has been attributed to this phenomenon in diabetic patients with end-stage renal disease.[51]

Exercise causes a transient shift of potassium out of cells. Clinically significant hyperkalemia may result from exercise[52,53] (and clinically misleading local venous hyperkalemia results from fist clenching during phlebotomy[54]).

Regulation of External Potassium Balance

In contrast to the prodigious capacity of the kidney to excrete potassium,[55] renal potassium conservation is imperfect and explains why significant potassium depletion and hypokalemia may result from dietary potassium deficiency alone.[56]

Normally, 90% to 95% of dietary potassium is eliminated through the kidney, and only about 5% to 10% through the intestine. It is the kidney that is almost entirely responsible for matching potassium output to potassium intake to maintain total

body potassium constant.[57] The majority of potassium excreted by the kidney derives from potassium secretion in the distal nephron (late distal tubule and collecting duct).[57] Virtually all regulation of potassium excretion takes place at this site in the nephron, under the influence of two principal factors: the rate of flow and sodium delivery through that part of the nephron, and the effect of aldosterone.[57] Potassium secretion is directly proportional to flow rate and sodium delivery through the distal nephron, explaining in part why diuretic use often is accompanied by hypokalemia.

Metabolic acidosis with acidemia results in inhibition of renal potassium secretion.[41] In contrast, metabolic alkalosis and bicarbonate delivery to the distal nephron stimulate kaliuresis by increasing the electrochemical driving force for potassium secretion.[57] Other anions that are poorly reabsorbed in the distal nephron (e.g., synthetic penicillins) have a similar effect to stimulate potassium secretion.[58]

It is well established that aldosterone participates in a homeostatic feedback loop with P_K such that increases in P_K stimulate adrenal aldosterone production, which in turn reduces P_K primarily by stimulating renal potassium excretion.[57] Hypokalemia is a prominent feature of primary aldosteronism (Conn syndrome) because the high circulating aldosterone levels are accompanied by volume expansion and thus a high rate of sodium delivery to the distal nephron. When circulating aldosterone levels are high owing to volume depletion (secondary aldosteronism), the increase in distal potassium secretion is offset by a decrease in distal nephron flow, thus mitigating renal potassium loss. Indeed, it is usually when patients with secondary hyperaldosteronism (e.g., in congestive heart failure or hepatic cirrhosis) are treated with diuretic drugs that distal nephron flow is increased and hypokalemia may ensue.

The effect of dexamethasone (a pure glucocorticoid) to enhance renal potassium excretion appears to result entirely from hemodynamic changes that cause an increase in glomerular filtration rate and distal flow rate. All other glucocorticoids tend to further stimulate potassium secretion in proportion to their mineralocorticoid activity.[57]

Magnesium deficiency is associated with renal potassium wasting and may result in severe potassium depletion.[59] Because magnesium, like calcium, acts to stabilize excitable membranes, the deleterious effects of hypokalemia on the myocardium are magnified by concurrent hypomagnesemia (see later "Clinical Manifestations of Potassium Imbalance").[60]

Disorders of Potassium Homeostasis

Disorders of potassium homeostasis may be conveniently divided according to the duration of the disturbance: acute (<48 hours' duration) or chronic. Such a distinction is particularly applicable to the medical intensive care setting where blood chemistries are sampled frequently and a patient's condition and therapy may change radically over a short time. In addition, the approach to treatment varies according to the acuity of the disturbance. The treatment of acute disturbances is largely independent of their cause, whereas the rational treatment of chronic disturbances depends on understanding their pathogenesis.

Acute Hyperkalemia (Box 54.6)

Excessive Potassium Intake

Given an acute potassium load, a normal individual will excrete about 50% in the urine and transport about 90% of the remainder into cells over 4 to 6 hours.[61] It is possible to overwhelm the adaptive mechanisms such that if too much potassium is taken in too quickly, significant hyperkalemia will result. Such events are almost always iatrogenic (i.e., overly aggressive potassium replacement therapy).[62] One's ability to tolerate a potassium load declines with disordered internal balance (see later text) and impaired renal potassium excretory capacity.[63] In such circumstances, an otherwise tolerable increase in potassium intake may cause clinically significant hyperkalemia. Doses of oral potassium supplements as small as 30 to 45 mmol have resulted in severe hyperkalemia in patients with impaired external or internal potassium homeostasis.[64]

KCl, used as a supplement, is the drug most commonly implicated in acute hyperkalemia.[63,65] Banked blood represents a trivial potassium load under most circumstances, because a unit of fresh banked blood—either whole or packed cells—contains only about 7 mmol of K.[66] (The potassium concentration in banked blood does increase substantially as the blood ages, however, as a result of potassium egress from older erythrocytes.[67]) Thus severe hyperkalemia would result only from massive transfusion of compatible blood.[67,68] Infants[69] or patients with impaired renal potassium excretory capacity may develop hyperkalemia from an otherwise tolerable transfusion.

Patients undergoing open heart surgery are exposed to cardioplegic solutions containing KC1, typically at about 16 mmol/L,[70] which may lead to clinically significant hyperkalemia in the postoperative period, especially in patients with diabetes mellitus with or without renal failure.[71]

Abnormal Potassium Distribution

Acute hyperkalemia may result from sudden redistribution of intracellular potassium to the extracellular space. If only 2% of intracellular potassium were to leak unopposed from cells, P_K would immediately double. Fortunately, such dramatic circumstances are rarely encountered. Nevertheless, smaller degrees of potassium redistribution commonly result in clinically significant hyperkalemia.

• BOX 54.6 Causes of Acute Hyperkalemia

Excessive Potassium Intake

Oral
Intravenous
Blood transfusion
Cardioplegic solutions

Transcellular Potassium Shift

With acute renal failure
  Rhabdomyolysis
  Tumor lysis syndrome
Tissue infarction
  Mesenteric
  Limb
Hypertonicity
  Hyperglycemia
Metabolic acidosis
Drug-induced
  Digitalis intoxication
  Succinylcholine
Hyperkalemic periodic paralysis
Pseudohyperkalemia
  Thrombocytosis
  Leukocytosis
  In vitro hemolysis
  Fist clenching with phlebotomy

Among the most impressive syndromes associated with acute hyperkalemia are those involving rapid cell lysis. The tumor lysis syndrome results from treatment of chemosensitive bulky tumors with release of intracellular contents, including potassium, into the ECF.[72] Extreme hyperkalemia even causing sudden death[73] has featured prominently in some series of patients. Most such patients were in renal failure from acute uric acid nephropathy, thus impairing their ability to excrete the potassium load.[73] Rhabdomyolysis, either traumatic or nontraumatic, may result in sudden massive influx of potassium to the extracellular space.[74] Hyperkalemia is present in about 40% of patients upon presentation with rhabdomyolysis[75] and is more common among patients whose course is complicated by oliguric acute renal failure.[76] Alcohol[75] and cocaine[77] are commonly implicated in the development of rhabdomyolysis. Extreme hyperkalemia in this latter context has been reported.[78] Statin drugs are frequently associated with rhabdomyolysis,[79] rarely causing extreme hyperkalemia.[80] Other circumstances that may result in redistributive hyperkalemia include severe extensive burns, hemolytic transfusion reactions, and mesenteric ischemia or infarction.

Pharmacologic Agents

Several drugs may rarely cause acute hyperkalemia by redistribution: digitalis glycosides and succinylcholine. Massive digitalis overdose has been associated with extreme hyperkalemia.[81,82] Succinylcholine depolarizes the motor end plate and in normal individuals causes a trivial amount of potassium leak from muscle, resulting in an increase in P_K by about 0.5 mmol/L.[83] In patients with neuromuscular disorders, muscle damage, or prolonged immobilization, however, muscle depolarization may be more widespread, causing severe hyperkalemia.[84] Prolonged use of nondepolarizing neuromuscular blockers in critically ill patients may predispose to succinylcholine-induced hyperkalemia.[85] Owing to a reduction in circulating insulin levels, somatostatin and octreotide may impair normal cellular potassium uptake, particularly in the end-stage renal disease population.[86,87]

Hyperkalemic Periodic Paralysis

This rare syndrome of episodic hyperkalemia and paralysis is caused by a mutation of the skeletal muscle sodium channel, inherited in an autosomal dominant pattern.[88] Attacks may be precipitated by exercise, fasting, exposure to cold, and potassium administration and prevented by frequent carbohydrate snacks. Attacks are usually brief and treatment consists of carbohydrate ingestion. Severe attacks may require intravenous glucose infusions.[89]

Acute Renal Failure

Hyperkalemia accompanies acute renal failure in 30% to 50% of cases. It is seen most commonly in oliguric renal failure. Contributing factors include tissue destruction (e.g., tumor lysis syndrome, rhabdomyolysis) and increased catabolism.[90]

Pseudohyperkalemia

Pseudohyperkalemia refers to a measured potassium that is higher than that circulating in the patient's blood. It has a number of possible causes. First, it may be caused by efflux of potassium out of blood cells in the test tube after phlebotomy. This may be seen in a serum specimen in cases of thrombocytosis[91] or leukocytosis,[92] when the clot causes cell lysis in vitro. These days, many clinical laboratories measure electrolytes in plasma (unclotted) specimens. Even under these conditions, extreme leukocytosis may cause pseudohyperkalemia if the specimen is chilled for a long time before the plasma is separated, leading to passive potassium leak from cells.[93] In chronic lymphocytic leukemia, centrifugation of the blood can cause disruption of the fragile leukemia cells, leading to liberation of intracellular potassium. This can be mitigated by clotting of the specimen before centrifugation as the clot will protect the leukemia cells from damage.[94] Hemolysis during specimen collection will spuriously raise P_K by liberating intraerythrocyte potassium. Second, if the patient's arm is exercised by fist clenching with a tourniquet in place before the specimen is drawn, the sampled blood potassium concentration will rise significantly as a result of local muscle release of intracellular potassium.[54]

• BOX 54.7 Causes of Acute Hypokalemia

Treatment of diabetic ketoacidosis
Refeeding syndrome
Rapid cell production
  Vitamin B_{12} treatment of pernicious anemia
  GM-CSF treatment of leukopenia
Pharmacologic agents
  β_2-Adrenoceptor agonists
  Epinephrine
  Soluble barium salts
Hypokalemic periodic paralysis
  Familial
  Sporadic
  Thyrotoxic
Pseudohypokalemia

GM-CSF, *Granulocyte-macrophage colony-stimulating factor.*

Acute Hypokalemia

Hypokalemia that develops over hours is virtually always the result of redistribution of potassium from the extracellular to the intracellular space. The causes of acute hypokalemia are summarized in Box 54.7. A few causes, commonly seen in the critical care context, merit elaboration.

Treatment of Diabetic Ketoacidosis

It is well recognized that patients presenting in DKA are always severely total body potassium depleted, as a result of the glucose-driven osmotic diuresis (and hence, kaliuresis), poor nutrition, and vomiting during the development of DKA.[44] Paradoxically, most patients in DKA have a normal P_K upon admission.[95] Insulin deficiency and hyperglycemia appear to account for the preservation of a normal P_K despite severe total body potassium depletion.[44] Once therapy for DKA is instituted, however, P_K typically plummets as potassium is rapidly taken up by cells under the influence of insulin. Hypokalemia in this setting may lead to respiratory arrest.[96] Potassium replacement at rates up to 120 mmol/h has been reported, with total potassium supplementation of 600 to 800 mmol within the first 24 hours of treatment.[97]

Refeeding

A situation analogous to DKA arises during aggressive refeeding after prolonged starvation or with aggressive "hyperalimentation" of chronically ill patients. The glucose-stimulated hyperinsulinemia and tissue anabolism shift potassium into cells, rapidly depleting extracellular potassium.[98] Death in the setting of refeeding has been reported and may be partly due to rapid cellular uptake of other ions (e.g., phosphorus, magnesium).[99]

Pharmacologic Agents

Specific β_2-adrenoceptor agonists (e.g., albuterol) may cause electrophysiologically significant hypokalemia, especially when given to patients who are potassium depleted from the use of diuretic drugs.[100] Epinephrine, given intravenously (IV) in a dose about 5% of that recommended for cardiac resuscitation, causes a fall in P_K by about 1 mmol/L.[101] Such a dose achieves plasma levels of epinephrine comparable to those seen after acute myocardial infarction and may explain the transient hypokalemia following resuscitation from cardiac arrest even without the use of exogenous epinephrine (postresuscitation hypokalemia).[102,103] A rare cause of severe hypokalemia is poisoning with soluble barium salts, such as the chloride, carbonate, hydroxide and sulfide. Soluble barium salts are used in pesticides and some depilatories, which may be ingested accidentally or intentionally.[104] Thiopentone, a barbiturate used to induce coma for refractory intracranial hypertension, is associated with redistributive hypokalemia in the majority of treated patients within 12 hours of initiating therapy.[105]

Therapeutic Hypothermia

Therapeutic hypothermia is used to improve survival and neurologic outcomes in patients with cardiac arrest and ventricular fibrillation. Hypokalemia has been reported during the cooling phase of this therapy[106] and may be a predictor of polymorphic ventricular tachycardia in these patients.[107] The hypokalemia is generally mild, and there is uncertainty as to whether to treat mild hypokalemia owing to the potential risk of severe rebound hyperkalemia during the rewarming phase.[108,109]

Hypokalemic Periodic Paralysis

Three forms of this rare syndrome have been described: familial, sporadic. and thyrotoxic.[110,111] All have in common attacks of muscle weakness accompanied by acute hypokalemia caused by cellular potassium uptake. Death may occur due to ventilatory failure or cardiac dysrhythmias. The familial variety—resulting from a skeletal muscle calcium channelopathy[88]—is inherited in an autosomal dominant pattern, with onset of clinical manifestations typically in the second decade of life. Attacks may occur after carbohydrate or salt ingestion, or exercise. Administration of potassium orally or IV will abort an acute attack but is ineffective in preventing attacks.[110] The sporadic variety of hypokalemic periodic paralysis is identical to the familial form except for the absence of a hereditary pattern. Thyrotoxic periodic paralysis was first described in Asians but is now recognized to be nearly ubiquitous.[111] The usual onset of symptoms is in the third decade. Severe hypophosphatemia may accompany the hypokalemia.[112] Treatment of the disorder is same as treatment of hyperthyroidism.

Pseudohypokalemia

Severe leukocytosis may cause spuriously low plasma potassium concentrations if blood cells are left in contact with the plasma for a long time at room temperature or higher. This phenomenon results from ongoing cell metabolism in vitro with glucose and potassium uptake.[59] Unexpected hypokalemia and hypoglycemia in the setting of leukocytosis should alert the clinician to this phenomenon.

Chronic Hyperkalemia

Renal Failure

Patients with chronic kidney disease tend to maintain a normal P_K until renal function declines to about 10% of normal.[113] Aldosterone and insulin both appear to play a role in the extrarenal potassium adaptation in chronic kidney disease.[114] This explains why patients with chronic kidney disease who are mineralocorticoid and/or insulin deficient have a particular predisposition to hyperkalemia.[115]

Mineralocorticoid Deficiency

Mineralocorticoid deficiency may result from global adrenal insufficiency (Addison disease) or from selective defects in the renin-angiotensin-aldosterone axis (see Chapter 56). Hyperkalemia in the setting of unexplained hypotension should immediately raise suspicion for adrenal insufficiency. A common setting for isolated mineralocorticoid deficiency is the syndrome of hyporeninemic hypoaldosteronism.[115] This syndrome is most often seen in elderly patients with diabetes mellitus and moderate renal insufficiency. Hyperkalemia is a universal finding. An associated hyperchloremic metabolic acidosis (type IV renal tubular acidosis) is characteristic.[115] In addition to diabetes mellitus, two other systemic diseases are associated with this syndrome: the AIDS[116,117] and systemic lupus erythematosus.[118]

Aldosterone deficiency may be induced by a variety of pharmacologic agents acting at different sites in the renin-angiotensin-aldosterone axis. β-Adrenoceptor blockers and, to a greater extent, cyclooxygenase inhibitors (COX-1 and COX-2), predispose patients to hyperkalemia by suppressing renin release.[119] As a general rule, COX inhibitors should be avoided in patients with renal insufficiency or those who are otherwise prone to hyperkalemia either because of diabetes or the use of other implicated drugs. Converting enzyme inhibitors and angiotensin receptor blockers decrease aldosterone biosynthesis. These drugs are reported to be implicated in 10% to 38% of hyperkalemia in hospitalized patients.[120] Volume depletion and/or hypotension increase the risk of hyperkalemia with all these agents.

High- and low-dose heparin therapy decreases circulating aldosterone levels by selectively inhibiting aldosterone biosynthesis.[121] Hyperkalemia is seen with the use of low–molecular-weight heparins as well, particularly in patients with diabetes mellitus.[122]

Renal Potassium Secretory Defect

An isolated defect in renal potassium secretion (often with a renal tubular acidosis) is associated with sickle cell disease or trait,[123] systemic lupus erythematosus,[118] and after renal transplantation.[124] In this last circumstance, the hyperkalemia is exacerbated by the use of cyclosporine and tacrolimus for immunosuppression.[125,126] A syndrome of hyperkalemic (type IV) distal renal tubular acidosis is seen in patients with urinary tract obstruction.[127]

The so-called potassium-sparing diuretics (spironolactone, eplerenone, amiloride, and triamterene) impair renal potassium excretion by blocking sodium reabsorption in the distal nephron. Two antibiotics, pentamidine[128] and trimethoprim,[129,130] cause hyperkalemia, occasionally severe, by blocking sodium reabsorption in the distal nephron.

Chronic Hypokalemia

Chronic hypokalemia is virtually always the result of altered external balance: insufficient potassium intake, excessive potassium losses, or a combination of the two. Losses most often are either GI or renal.

Inadequate Potassium Intake

Because renal potassium conservation is not perfect, severe dietary potassium restriction causes hypokalemia in 3 to 7 days in normal humans.[56] In one series of hypokalemic hospitalized patients,

inadequate potassium supplementation during IV therapy contributed to the development of severe hypokalemia in 45% of cases and was the sole cause in 6%.[131] Other disorders associated with nutritional hypokalemia include anorexia nervosa, alcoholism, and malignancy.

Excessive Potassium Losses

Hypokalemia may develop as a result of both upper and lower GI fluid losses, but the pathogenesis is quite different in the two situations. With diarrhea, the potassium is lost from the gut.[132] Gastric fluid losses (e.g., vomiting or gastric suction) are associated with hypokalemia. Paradoxically, however, most of the potassium losses are renal, not gastric. Gastric fluid potassium concentration is only 5 to 10 mmol/L. Thus only massive gastric fluid losses would, alone, significantly deplete total body potassium stores. The gastric fluid losses, however, stimulate renal potassium secretion in several ways. First, by generating a metabolic alkalosis and increasing bicarbonate delivery to the distal nephron, potassium secretion is stimulated. The metabolic alkalosis also leads to cellular proton loss and potassium uptake, which in renal epithelial cells, enhances potassium secretion. Finally, the volume contraction which usually accompanies GI fluid losses causes secondary aldosteronism, which further augments urinary potassium losses. Thus in this situation, urinary potassium concentration is typically high while urinary chloride concentration is low owing to volume contraction. (Urinary sodium losses may be high owing to natriuresis obligated by the bicarbonaturia.)

All diuretics work by inhibiting sodium and chloride reabsorption by the nephron. Those drugs that act proximal to the potassium secretory site in the nephron promote a kaliuresis by increasing delivery of fluid distally and causing secondary aldosteronism. Thus hypokalemia frequently accompanies the use of the two most common classes of diuretics: thiazides and loop diuretics.[133] Carbonic anhydrase inhibitors exert an additional kaliuretic effect by shunting bicarbonate-rich, chloride-poor fluid to the distal nephron.[134] Combining two potassium-wasting diuretics for added diuretic effect (e.g., furosemide plus metolazone) can result in severe hypokalemia. In such cases, P_K has been found to fall below 3.5 mmol/L in more than 80% of patients and below 3.0 mmol/L in more than half.[133]

Various antibiotic agents may cause renal potassium wasting and thereby hypokalemia; 90% of patients receiving amphotericin B require potassium supplementation.[135] Penicillin antibiotics, particularly polyanionic derivatives such as carbenicillin and ticarcillin, have been associated with hypokalemia.[136]

Mineralocorticoids predispose to hypokalemia by stimulating renal potassium excretion. Mineralocorticoid excess may be primary[137] (Conn syndrome) or secondary to diminished real or "effective" circulating volume. All glucocorticoid drugs except dexamethasone possess some mineralocorticoid activity. Therefore prolonged administration of these agents can cause severe hypokalemia. In edematous patients with secondary aldosteronism (e.g., congestive heart failure, hepatic cirrhosis) hypokalemia commonly ensues only when diuretic therapy enhances distal nephron flow rate.

Magnesium deficiency is associated with renal potassium wasting and may result in severe potassium depletion (see later text). Because magnesium, like calcium, acts to stabilize excitable membranes, the deleterious effects of hypokalemia on the myocardium are magnified by concurrent hypomagnesemia.[138] The intensive care setting is fraught with potential causes of hypomagnesemia (see "Disorders of Magnesium Homeostasis").

Hypercalcemia causes a salt and water diuresis and is therefore commonly associated with renal hypokalemia (see "Calcium").[139] In one series, one-third of hypercalcemic patients were hypokalemic with no other predisposing factors; the prevalence was 52% in patients with hypercalcemia of malignancy. P_K was inversely proportional to the plasma calcium concentration.[140]

Several inborn tubular transport abnormalities are associated with chronic hypokalemia (and metabolic alkalosis). Bartter and Gitelman syndromes are associated with volume contraction and normal blood pressure, and Liddle syndrome with hypertension.[141]

Clinical Manifestations of Potassium Imbalance

Alterations in P_K have a variety of adverse clinical consequences, the expression of which may be magnified in the critically ill patient. The most serious of these manifestations are those involving excitable tissues.

Clinical Manifestations of Hyperkalemia

Cardiac Effects

Hyperkalemia depolarizes the cell membrane, slows ventricular conduction, and decreases the duration of the action potential. These changes produce the classic electrocardiographic (ECG) manifestations of hyperkalemia, including (in order of their usual appearance) peaked T waves, prolongation of the PR interval, widening of the QRS complex, loss of the P wave, "sine wave" configuration, or ventricular fibrillation and asystole.[142,143] These ECG changes may be modified by a multitude of factors such as ECF pH, calcium concentration, sodium concentration, and the rate of rise of P_K.[142]

ECG changes may not accompany changes in P_K. If present, these ECG changes certainly suggest hyperkalemia. However, in the absence of the classic ECG changes, the clinician should not be lulled into a false sense of security when evaluating a hyperkalemic patient. Normal electrocardiograms occur despite extreme hyperkalemia[144] and the first cardiac manifestation of hyperkalemia may be ventricular fibrillation.[145] Consequently, P_K greater than 6.5 mmol/L, even with a normal ECG, should be treated as an emergency (see "Treatment of Potassium Imbalance").

Neuromuscular Effects

Hyperkalemia may result in paresthesias and weakness progressing to a flaccid paralysis, which typically spares the diaphragm. Reflexes are depressed or absent. Cranial nerves are rarely involved and sensory changes are minimal.[146]

Metabolic Effects

Hyperkalemia decreases renal ammoniagenesis, which by itself may produce a mild hyperchloremic metabolic acidosis,[147] and limits the kidney's ability to excrete an acid load and thus prevent correction of a metabolic acidosis.[148]

Clinical Manifestations of Hypokalemia

Although less immediately life-threatening than hyperkalemia, hypokalemia has many detrimental effects in critically ill patients. Along with cardiac and neuromuscular manifestations are many more subtle effects.

Cardiac Effects

Hypokalemia hyperpolarizes the cell membrane and prolongs the cardiac action potential.[149] These changes are associated with the following ECG manifestations: ST-segment depression,

a decrease in T-wave amplitude, and an increase in U-wave amplitude.[142,143] However, because all of these are nonspecific, the ECG is an even less reliable index of hypokalemia than it is of hyperkalemia.

Hypokalemia may be associated with an increased incidence of arrhythmias and conduction defects. It is well established that potassium depletion increases the cardiac toxicity of digitalis glycosides.[150] However, controversy exists as to whether hypokalemia per se induces ventricular arrhythmias in patients not taking digitalis. There is an increase in benign ventricular ectopy in hypokalemic patients without acute myocardial ischemia.[151] The clinical importance of this observation is unclear. In individuals hospitalized with acute myocardial infarction, however, a correlation between hypokalemia and ventricular tachycardia and fibrillation was observed.[152] Because potassium repletion did not reduce the occurrence of these arrhythmias, it is unlikely that hypokalemia was the sole arrhythmogenic factor.[152] It has been demonstrated that patients presenting with acute myocardial infarction show a U-shaped relationship between mean in-hospital P_K and mortality, such that P_K values less than 3.5 mmol/L or greater than 4.5 mmol/L were each associated with higher in-hospital mortality. The lowest mortality was seen in patients with P_K 3.5 to 4.0 mmol/L, implying that potassium supplementation to achieve higher concentrations was not justifiable.[153]

Neuromuscular Effects

Modest hypokalemia generally presents as weakness, myalgias, muscle fatigue, and "restless" legs. With more severe hypokalemia (<2 mmol/L), paralysis may supervene. This usually involves the extremities but may progress to include the trunk and muscles of ventilation. As with hyperkalemia, cranial nerves typically are spared and sensory function usually remains intact.[59] It is important to note that these manifestations may be masked by concomitant hypocalcemia and may only appear when calcium is replenished. Conversely, in patients with hypokalemia and hypocalcemia, tetany may develop only after potassium replacement.[59] Smooth muscle dysfunction (ileus, gastroparesis) is more commonly seen with hypokalemia than with hyperkalemia.

In addition to the effects of potassium depletion on the electrical properties of the neuromuscular system, profound hypokalemia may result in muscle injury and frank rhabdomyolysis, even in bedbound patients.[154]

Miscellaneous Effects

Hypokalemia and potassium depletion are associated with glucose intolerance,[155] increased protein catabolism, polydipsia and polyuria,[59] and metabolic alkalosis.[156]

Evaluation of Disorders of Potassium Homeostasis

The diagnostic approach to disorders of potassium homeostasis may be focused by dividing them according to their duration: acute (or of unknown duration) versus chronic.

Evaluation of Acute Hyperkalemia

When P_K rises abruptly or if P_K is high (>6.5 mmol/L) on initial presentation of the patient, the first step is to obtain an ECG to look for electrophysiologic evidence of hyperkalemia. In the presence of such signs, treatment for hyperkalemia should begin urgently (see "Treatment of Potassium Imbalance"). At the same time, an unclotted blood sample should be obtained, using meticulous phlebotomy technique, for another set of electrolytes, glucose, blood urea nitrogen and creatinine, and complete blood cell count. Urine should be tested for heme pigments to exclude acute rhabdomyolysis or hemolysis. The patient's list of medications and diet should be reviewed promptly, looking for exogenous sources of potassium and drugs that may impair potassium tolerance (see Box 54.6).

Evaluation of Chronic (Sustained) Hyperkalemia

Fig. 54.2 outlines an approach to the patient with sustained hyperkalemia lasting for days. Failure to stimulate cortisol release with a cosyntropin stimulation test (see Chapter 56) supports a diagnosis of Addison's disease. In the absence of that diagnosis, the patient is likely to have either selective aldosterone deficiency and/or tubular unresponsiveness to aldosterone. Assessment of the renin-angiotensin-aldosterone axis is most simply done by measuring plasma renin activity (PRA) and aldosterone levels in the basal and diuretic/posture-stimulated state.[115] Diabetic nephropathy and chronic tubule-interstitial disease can result in hyporeninemic hypoaldosteronism where both the PRA and aldosterone levels are low. Primary adrenal insufficiency or selective aldosterone insufficiency is associated with low aldosterone levels but a high PRA. Aldosterone resistance, as can be seen with the use of potassium-sparing diuretics, distal renal tubular acidosis, or pseudohypoaldosteronism type I (epithelial sodium channelopathy or loss-of-function mutation of the mineralocorticoid receptor) can result in both high PRA and aldosterone levels.[157] Historically, the trans-tubular potassium gradient (TTKG) had been used to help assess the distal tubular responsiveness to aldosterone; however, owing to incorrect assumptions regarding tubular urea recycling that are beyond the scope of this chapter, the TTKG is now considered an invalid tool in the assessment of sustained hyperkalemia.[158]

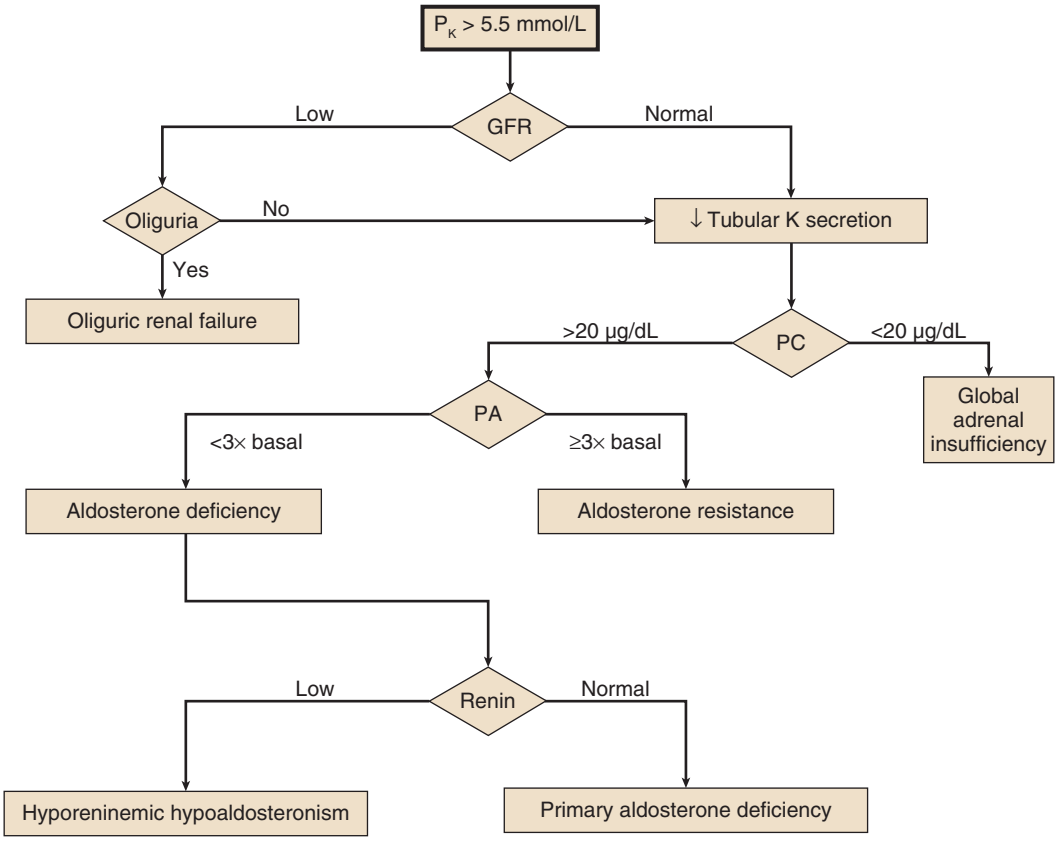
Evaluation of Acute Hypokalemia

Hypokalemia accompanied by serious cardiac or neuromuscular manifestations is an emergency. Likewise, urgent therapy is indicated for profound hypokalemia (P_K < 2.0 mmol/L) even in the absence of clinical complications. In addition, moderate hypokalemia (P_K < 3.0 mmol/L) in patients taking digitalis,[150] and perhaps with acute myocardial ischemia,[152] should be treated urgently because of the risk of ventricular arrhythmias. In all these situations, it is imperative that the blood specimen be obtained and handled properly, especially in patients with leukocytosis, since rapid administration of potassium to a patient with pseudohypokalemia may cause severe hyperkalemia.

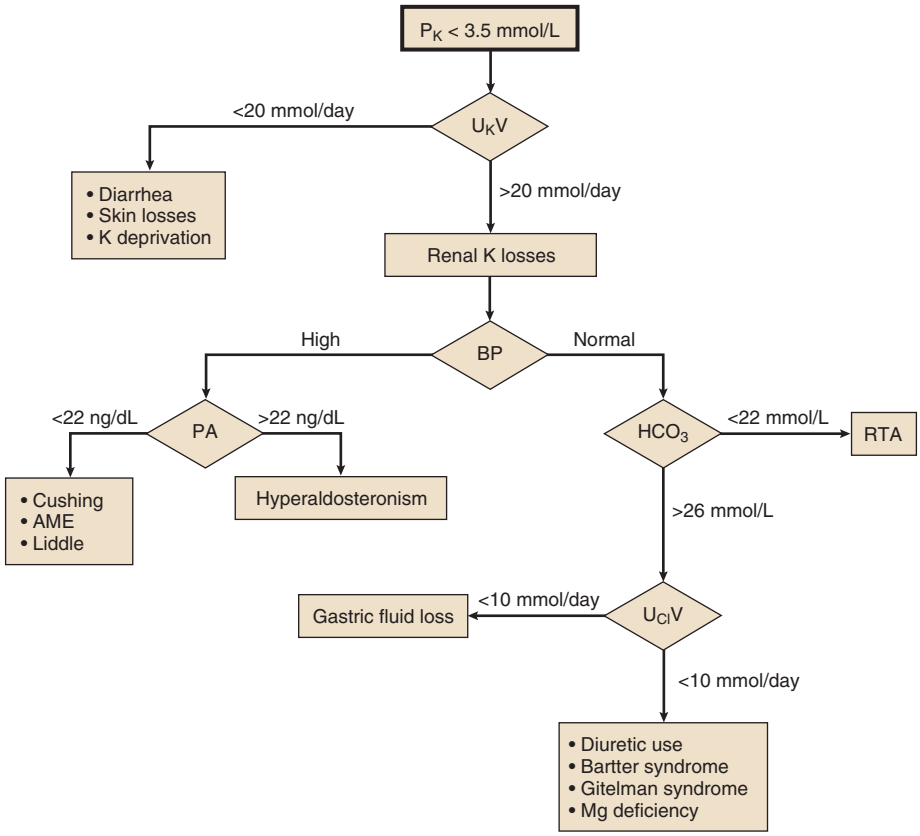
The remainder of the evaluation of acute hypokalemia derives mainly from the patient's history with an emphasis on interventions causing cellular potassium uptake (e.g., insulin, β-adrenergic agonists) or a rapid increase in tissue anabolism (e.g., total parenteral nutrition), and a history of periodic paralysis. Patients with hypokalemia upon presentation should be evaluated as though their hypokalemia were acute.

Evaluation of Chronic Hypokalemia

Once acute hypokalemia and transient potassium redistribution have been excluded, one should next determine whether the kidney is responding appropriately to the potassium deficit or whether it is contributing to the problem. This is best done by measuring the 24-hour urinary excretion of potassium during potassium repletion (Fig. 54.3). Potassium excretion less than 20 mmol/day suggests appropriate renal potassium conservation and points to extrarenal



• **Fig. 54.2** Diagnostic evaluation of chronic hyperkalemia. *GFR,* Glomerular filtration rate; *PA,* stimulated plasma aldosterone (see text); *PC,* stimulated plasma cortisol (see Chapter 56).



• **Fig. 54.3** Diagnostic evaluation of chronic hypokalemia. *AME,* Syndrome of apparent mineralocorticoid excess; *BP,* blood pressure; HCO_3^-, bicarbonate; *PA,* stimulated plasma aldosterone (see text); *RTA,* renal tubular acidosis; $U_{Cl}V$, urinary chloride excretion; U_KV, urinary potassium excretion.

(lower GI or skin) potassium losses, recovery from diuretic-induced hypokalemia, or chronically potassium-deficient diet. Excretion of greater than 20 mmol/day is evidence of inadequate renal potassium conservation, indicating a renal cause of the hypokalemia. Renal potassium losses associated with normal systemic blood pressure are most commonly seen with the use of thiazide or loop diuretics and are accompanied by a metabolic alkalosis. Other causes of hypokalemia with metabolic alkalosis in a normotensive patient include gastric fluid loss and Bartter and Gitelman syndromes. These are separable most often by history, but if not, the urinary chloride measurement will be helpful, being low with gastric fluid losses. Renal hypokalemia may accompany a renal tubular acidosis, in which case the plasma bicarbonate will be low.

Mineralocorticoid excess may be the cause if the renal potassium loss is associated with systemic hypertension, and the renin-aldosterone axis should be studied with basal and saline solution–suppressed blood hormone measurements. High PRA and aldosterone levels suggest renal artery stenosis, malignant hypertension, or rarely a renin-secreting tumor. Low PRA and high aldosterone levels indicate primary aldosteronism. When both PRA and aldosterone levels are low, one should suspect the syndrome of apparent mineralocorticoid excess, Cushing syndrome, or rarely Liddle syndrome. Note that Cushing syndrome owing to ectopic adrenocorticotropic hormone secretion often is not accompanied by typical cushingoid features.[159]

Treatment of Potassium Imbalance

In general, the initial treatment of acute severe potassium imbalance is independent of the cause of the disturbance, whereas the rational therapy of chronic hyperkalemia or hypokalemia depends on an understanding of its pathogenesis.

Acute Hyperkalemia

In considering when hyperkalemia constitutes an emergency, two points should be kept in mind. First, the electrophysiologic effects of hyperkalemia are directly proportional to both the absolute P_K and its rate of rise.[142] Second, whereas the ECG manifestations of hyperkalemia are generally progressive and proportional to the P_K, ventricular fibrillation may be the first ECG disturbance of hyperkalemia[145]; conversely, a normal ECG may be seen with extreme hyperkalemia.[144] Thus it is apparent that neither the ECG nor the P_K alone is an adequate index of the urgency of hyperkalemia, and that the clinical context must be considered when assessing a hyperkalemic patient. Because most patients manifest hyperkalemic ECG changes at P_K greater than 6.7 mmol/L,[143] hyperkalemia should be treated emergently for (1) P_K greater than 6.5 mmol/L or (2) ECG manifestations of hyperkalemia regardless of the P_K.[160]

Therapy of acute or severe hyperkalemia is directed at preventing or ameliorating its untoward electrophysiologic effects on the myocardium. The goals of therapy, in chronologic order, are as follows (Table 54.2):

1. Antagonize the effect of hyperkalemia on excitable cell membranes.
2. Redistribute extracellular potassium into cells.
3. Enhance elimination of potassium from the body.

Membrane Antagonism

Calcium. Calcium directly antagonizes the myocardial effects of hyperkalemia without lowering P_K.[161] During treatment with

TABLE 54.2 Emergency Treatment of Hyperkalemia

Agent	Dose	Onset	Duration	Complications
Membrane Stabilization				
Calcium gluconate (10%)	10 mL IV over 10 min	Immediate	30–60 min	Hypercalcemia
Hypertonic (3%) sodium chloride	50 mL IV push	Immediate	Unknown	Volume overload Hypertonicity
Redistribution				
Insulin (short-acting)	10 units IV push, with 25–40 g dextrose (50% solution)	20 min	4–6 h	Hypoglycemia
Albuterol	20 mg in 4 mL normal saline solution, nebulized over 10 min	30 min	2 h	Tachycardia Inconsistent response
Elimination				
Loop diuretics				
Furosemide	40–80 mg IV	15 min	2–3 h	Volume depletion
Bumetanide	2–4 mg IV			
Sodium bicarbonate	150 mmol/L IV at variable rate	Hours	Duration of infusion	Metabolic alkalosis Volume overload
Sodium polystyrene sulfonate (Kayexalate, Kionex)	15–30 g in 15–30 mL 70% sorbitol orally)	> 2 h	4–6 h	Variable effect Intestinal necrosis
Hemodialysis		Immediate	3 h	Arrhythmias

calcium, the ECG should be monitored continuously. The dose may be repeated in 5 minutes if there is no improvement in the ECG, or if the ECG deteriorates after an initial improvement.[162] There are several case reports of sudden death in patients given intravenous calcium while also receiving digitalis glycosides.[163] Although these observations do not provide clear guidance, it may be wise to administer intravenous calcium with great caution to patients known or strongly suspected to have toxic levels of digitalis glycosides.

Hypertonic Saline Solution. Intravenous hypertonic sodium chloride has been shown to reverse the ECG changes of hyperkalemia in patients with concurrent hyponatremia.[164] Whether hypertonic saline solution is effective in the treatment of eunatremic patients has not been established. Moreover, the extracellular volume load imposed by hypertonic saline solution argues against its use.

Redistribution of Potassium Into Cells

Insulin. Insulin reliably lowers P_K in a dose-dependent manner. An intravenous dose of 10 units of regular insulin given as a bolus along with an intravenous bolus of dextrose (50 g as a 50% solution) to adult patients lowers the P_K by about 0.8 mmol/L after an hour.[165] After the initial bolus, a dextrose infusion should be started, because a single bolus of 25 g of dextrose has been shown to be inadequate to prevent hypoglycemia at 60 minutes.[166] There seems to be no advantage of a continuous insulin infusion over a bolus injection.[38] Insulin should be used without dextrose in hyperglycemic patients; indeed, the cause of the hyperkalemia in those patients may be the hyperglycemia itself.[50]

Albuterol. P_K has been shown to decline by 0.6 mmol/L after inhalation of 10 mg of albuterol, and by about 1.0 mmol/L after 20 mg in patients with end-stage renal disease.[167] The effect of insulin is additive with that of albuterol, with the combination reported to result in a decline in P_K by about 1.2 mmol/L at 60 minutes.[166] Even among patients not taking β-blockers chronically, as many as 40% appear to be resistant to the hypokalemic effect of albuterol.[166,167] For that reason, albuterol should never be used alone for the treatment of urgent hyperkalemia.

Bicarbonate. The putative benefits of a bolus injection of sodium bicarbonate in the emergency treatment of hyperkalemia pervaded the literature until recently. Ironically, this dogma was based on studies using a prolonged (4–6 hours) infusion of bicarbonate.[45] It has now been clearly demonstrated that short-term bicarbonate infusion does not reduce P_K in patients with dialysis-dependent kidney failure, implying that it does not cause potassium shift into cells.[46,47,160]

Elimination of Potassium From the Body

Enhanced Renal Elimination. Hyperkalemia occurs most often in patients with renal insufficiency. However, renal potassium excretion may be enhanced even in patients with moderate renal failure by increasing distal nephron flow. This may be accomplished with saline or sodium bicarbonate infusions and may be enhanced further by the use of loop diuretics. Diuretic-induced volume contraction must be avoided because this will lead to decreased distal nephron flow and reduced potassium excretion.[162] It must be emphasized that for obvious reasons this treatment strategy is not a consideration for the treatment of acute hyperkalemia in the anuric patient.

Exchange Resin. Sodium polystyrene sulfonate (SPS, Kayexalate, Kionex) is a cation exchange resin that exchanges sodium for secreted potassium in the colon. Each gram of resin binds approximately 0.65 mmol of potassium in vivo, although the effect is highly variable and unpredictable.[38] The resin causes constipation and hence almost always is given with a cathartic. It is more effective when given orally than by retention enema.[38]

There are two concerns with the use of SPS for the treatment of urgent hyperkalemia. The first is its slow effect. When given orally, the onset of action is at least 2 hours and the maximum effect may not be seen for 6 hours or more. One recent study in hemodialysis patients failed to show any effect on P_K after an oral dose of SPS.[168] The second concern with SPS is its possible toxicity. There are numerous case reports of patients who developed intestinal necrosis after exposure to SPS in sorbitol as an enema[169–171] and orally.[172] A retrospective study estimated the incidence of colonic necrosis to be 1.8% among postoperative patients.[172] For these reasons, some authorities consider the use of SPS to be unjustifiable.[173]

A newer cation exchange resin, patiromer sorbitex calcium (Veltassa) binds potassium in exchange for calcium in the GI lumen and is approved for the treatment of chronic hyperkalemia.[174] Because of its delayed onset of action, patiromer is of limited use in the critical care setting; the manufacturer clearly states that it is not indicated for use as an emergency treatment for life-threatening hyperkalemia.

Dialysis. Hemodialysis is the dialytic method of choice for removal of potassium from the body. P_K falls by over 1 mmol/L in the first 60 minutes of hemodialysis and a total of 2 mmol/L by 180 minutes, after which it reaches a plateau.[38] Rebound always occurs after dialysis, with 35% of the reduction abolished after an hour and nearly 70% after 6 hours.[38] There is controversy as to whether dialysis for severe hyperkalemia precipitates serious ventricular arrhythmias; however, in the hemodialysis population, hyperkalemia independently has been associated with adverse outcomes.[175] Because of the possibility of serious ventricular ectopy, patients undergoing dialysis for severe hyperkalemia should have continuous ECG monitoring.[38] The rate of potassium removal with peritoneal dialysis is much slower than with hemodialysis.[38]

Chronic Hyperkalemia

As established previously, chronic hyperkalemia always implies deficient renal potassium excretion. It follows that the therapy of chronic hyperkalemia is primarily directed toward stimulating renal potassium excretion while limiting potassium intake. For all adults with chronic hyperkalemia, daily potassium intake should be restricted to 60 mmol. All drugs known to impair either internal or external potassium balance should be eliminated if possible. Finally, all patients with chronic hyperkalemia should be evaluated for occult urinary tract obstruction.

Further therapy of the persistently hyperkalemic patient should be guided by the diagnostic evaluation outlined in Fig. 54.2. In cases of mineralocorticoid unresponsiveness or when mineralocorticoid treatment is complicated by fluid overload, a thiazide or loop diuretic can be added to the regimen. This will restore normal volume status and enhance renal tubular potassium secretion in many mineralocorticoid-resistant patients. It is crucial to avoid diuretic-induced volume depletion, however, since this will exacerbate the renal potassium secretory defect.

Patients who fail to respond to the previous measures may be given sodium bicarbonate, which will stimulate renal potassium secretion. This is especially appropriate for patients whose chronic hyperkalemia is accompanied by a renal tubular acidosis (type IV renal tubular acidosis). The usual dose is 1 to 2 mmol bicarbonate/kg body weight per day in 3 or 4 divided doses.[162] Lastly, patiromer sorbitex calcium is indicated for use in controlling chronic hyperkalemia.[174]

Acute Hypokalemia

A low P_K almost always indicates a large total body potassium deficit. In fact, P_K decreases by approximately 0.3 mmol/L for each decrement of 100 mmol total body potassium.[176] But if potassium is replenished too quickly, the homeostatic mechanisms that defend P_K will be overwhelmed and P_K will rise abruptly. The rate of rise of P_K with potassium administration can be greatly altered by factors that affect internal potassium balance. For example, during treatment of DKA with insulin, cellular uptake of potassium may be massive, obligating enormous replacement doses of potassium. Conversely, insulin deficiency markedly impairs tolerance to a potassium load.[61]

See "Evaluation of Acute Hypokalemia" for definitions of urgent hypokalemia. Limited information exists on which to base a rational prescription of KCl in an emergency.[61,177,178]

Based on the available literature, we can estimate that nondiabetic patients with normal renal function should respond well to a 1- to 2-hour infusion of KCl at 0.6 mmol/kg per hour given IV in saline solution. In patients with kidney function reduction of any degree, the infusion rate should be halved (0.3 mmol/kg per hour). Patients with diabetes mellitus not being treated for DKA or hyperglycemia should receive no more than 0.2 mmol/kg per hour, or about 0.1 mmol/kg per hour in the setting of renal failure. For severe hypokalemia, the ECG should be monitored continuously and the infusion stopped immediately if signs of hyperkalemia develop. The maximum increase in P_K is seen at the end of the infusion, and about 50% of the increase is lost over the next 2 to 3 hours when a new steady state is achieved. Thus P_K should be measured at the end of the infusion. If the patient is still dangerously hypokalemic at this point, additional potassium may be given. If at the end of the infusion P_K is in an acceptable range, the measurement should be repeated 2 to 3 hours later when disposal of potassium load is complete to determine the need for further treatment.[162]

Hypokalemia in the setting of aggressive "refeeding," and especially in the treatment of severe DKA, should be treated initially as described previously. Frequent monitoring of P_K with rapid laboratory turnaround time is critical for proper management.

Hypokalemia that is not life-threatening is best treated with oral potassium replacement. It is important to recognize that GI absorption of an oral dose of KC1 elixir is essentially complete. Dangerous hyperkalemia can occur in entirely normal individuals following KCl ingestion.[179] The maximum increase in P_K is seen 1.5 to 2 hours after an oral potassium load. Thus a sensible oral dose of KCl in moderate hypokalemia should probably not exceed the hourly IV doses proposed earlier. There is no reason to give a simultaneous oral and IV potassium dose; serious hyperkalemia may ensue.

Chronic Hypokalemia

The treatment of chronic hypokalemia depends entirely on identifying and, if possible, remediating the cause (Fig. 54.3). When the cause of the excessive potassium loss cannot be treated specifically, maintenance potassium supplementation is needed.

Disorders of Water Homeostasis

Hyponatremia and hypernatremia reflect disorders of water homeostasis. They are common disorders in critically ill patients and are associated with increased morbidity and mortality.[180,181]

Physiology of Water Homeostasis

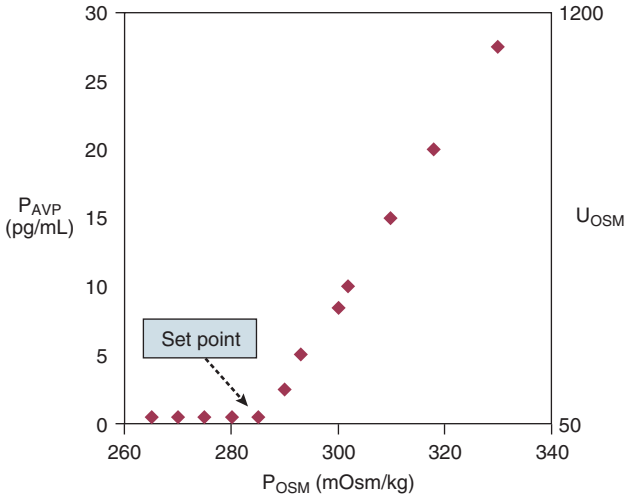
Normal plasma sodium concentration varies very little—even less than the "normal" range of clinical laboratories (135–145 mmol/L). This tight regulation depends on the following elements: (1) pituitary secretion of arginine vasopressin (AVP; also known as antidiuretic hormone, or ADH) that varies over a wide range in response to physiologic stimuli; (2) kidneys that are capable of responding to circulating vasopressin by varying the urine concentration; (3) intact thirst; and (4) access to water.

Tonicity or effective osmolality describes the capacity of particles in solution to effect water movement across a semi-permeable membrane like the cell membrane. The normal response to water ingestion (of sufficient magnitude to lower the plasma osmolality even slightly) is the excretion of maximally dilute urine (urine osmolality <100 mOsm/kg). The underlying physiologic sequence is as follows: the plasma hypotonicity is sensed by the cells comprising the hypothalamic osmostat. These hypothalamic nuclei then proportionately reduce their synthesis of AVP, also known as ADH, leading to diminished AVP release into the circulation by the posterior pituitary. The lower circulating AVP concentration, in turn, results in the insertion of proportionately fewer water channels into the collecting duct of the kidney. This, in turn, creates a more water-impermeable conduit, preventing water reabsorption and allowing excretion of the dilute urine elaborated by the more proximal segments of the nephron.[182]

Conversely, plasma hypertonicity leads to higher circulating AVP concentration and proportionately higher water permeability of the collecting duct, and the excretion of a concentrated urine.[182]

Fig. 54.4 shows the relationship among plasma osmolality, plasma AVP concentration, and urine osmolality. The normal "set point" is a plasma osmolality about 285 mOsm/kg. Notice that the minimum urine osmolality is about 50 mOsm/kg, and the maximum is about 1200 mOsm/kg.[183]

When plasma osmolality rises beyond 290 to 295 mOsm/kg, the thirst center of the hypothalamus is stimulated. At that point, neurologically intact individuals with access to water will drink until the plasma osmolality returns to normal.[183]



• **Fig. 54.4** Typical example of the physiologic relationship between plasma osmolality *(P_{osm})*, plasma vasopressin concentration *(P_{AVP})*, and urine osmolality *(U_{osm})*. P_{AVP} and U_{osm} vary around the *set point* to maintain P_{osm} within the range of normal.

Nonosmotic Vasopressin Release

It is important to recognize that plasma osmolality is not the only determinant of AVP synthesis and release. Low arterial blood pressure and low effective arterial volume powerfully stimulate AVP release.[183] This baroreceptor-mediated AVP release is teleologic, because water retention is an important component in the defense against hypovolemia. So primal is this circulatory defense that the baroreceptor stimulation predominates over any osmolal effect on AVP release.[183] Thus a volume-contracted or hypotensive individual will have high circulating AVP levels even if his plasma osmolality is low. In addition, circulating AVP levels rise with pain, stress, nausea, hypoxia, hypercapnia, and a variety of medications, most notably epinephrine and high doses of narcotic analgesics.[183]

Hyponatremia

Epidemiology and Clinical Manifestations

Hyponatremia (plasma sodium concentration <135 mmol/L) is one of the most common electrolyte disorders, found in approximately 3% of hospitalized patients and as many as 30% of patients in ICUs.[180]

The clinical manifestations of hyponatremia are largely attributed to intracellular volume expansion (cellular edema), which occurs only when hyponatremia is associated with hypotonicity. Intracellular volume expansion is of greatest consequence in the brain, where it is translated into increased intracranial pressure because of the rigid calvarium.[184]

The pathophysiology of hypotonic hyponatremia has important implications for its management. Most cells—especially brain cells—have adaptive mechanisms for mitigating tonicity-related volume changes.[184] Cell volume peaks 1 to 2 hours after the onset of acute hypotonicity. Thereafter solute and water are lost from cells, and cell volume returns toward normal. After several days of sustained hypotonicity, cell volume is restored to near normal.[184]

The morbidity and mortality associated with hypotonic hyponatremia are influenced by several factors, including the magnitude and rate of development of the hyponatremia, the patient's age and gender, and the nature and severity of any underlying diseases.[184] The very young and very old, females, and alcoholics appear to be at particular risk.[185] Cell-volume adaptation to hypotonicity may be deficient in premenopausal women, who have more frequent and more severe neurologic consequences than men with equivalent degrees of hypotonicity.[186]

Neurologic symptoms usually do not occur until the plasma sodium concentration falls below 125 mmol/L, at which point the patient may complain of anorexia, nausea, and malaise. Between 120 and 110 mmol/L, headache, lethargy, confusion, agitation, and obtundation may be seen. More severe symptoms (seizures, coma) may occur with levels below 110 mmol/L.[187] Focal neurologic findings are unusual but do occur, and transtentorial cerebral herniation has been described in severe cases, especially in young women following surgery.[186] In that setting, hypoxemia is common and often is associated with noncardiogenic pulmonary edema.[188] Hypoxia appears to exacerbate the cerebral damage in hyponatremia.[189]

Although symptoms generally resolve with correction of the hypotonicity, permanent neurologic deficits may occur, particularly in acute severe hypotonicity, when the brain's volume-regulatory defenses may be overwhelmed.[186] Profound hypotonicity that develops in less than 24 hours may be associated with residual neurologic deficits and has a 50% mortality rate in some populations.[186] In contrast, when hypotonicity develops more gradually, symptoms are both less common and less severe. Indeed, patients with chronic hyponatremia, even in the range of 115 to 120 mmol/L, may be completely asymptomatic.[184]

Pathophysiology and Differential Diagnosis

Hyponatremia may coexist with a normal, high, or low plasma osmolality. Thus the diagnostic algorithm for hyponatremia (Fig. 54.5) begins with an assessment of the plasma osmolality (P_{osm}). This may be estimated by the following formula:

$$\text{Estimated } P_{osm} = (2 \times P_{Na}) + \frac{P_{gluc}}{18} + \frac{BUN}{2.8}$$

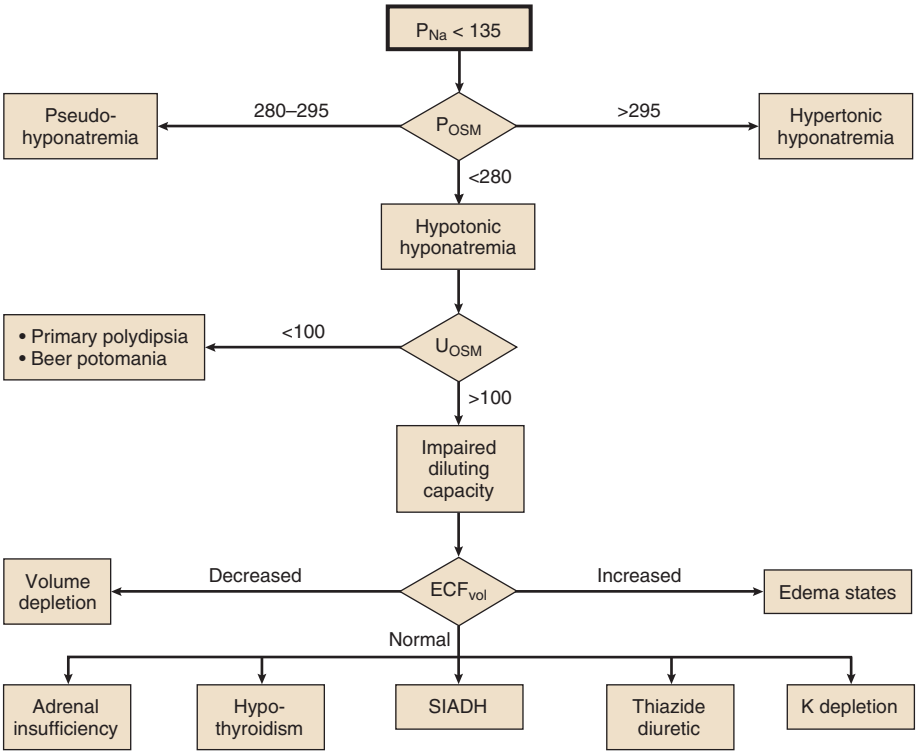
where P_{gluc} is the plasma glucose concentration and BUN is the blood urea nitrogen concentration (both in milligrams per deciliter). If there is a suspicion that an unmeasured, osmotically effective solute may be implicated (e.g., mannitol or glycerol), the P_{osm} should be measured directly.

Isotonic hyponatremia (also known as factitious or pseudohyponatremia) is a laboratory artifact seen with analytic techniques that measure the mass of sodium per unit volume of plasma sampled.[190] It is seen in the presence of marked hypertriglyceridemia or paraproteinemia, when the measurement method involves a predilution step. Direct potentiometry (which uses an ion-selective electrode in undiluted plasma) avoids this problem.[190]

Hypertonic hyponatremia results from the presence in ECF of abnormal amounts of osmotically effective solutes other than sodium (e.g., glucose, mannitol, or glycerol). The osmotic pressure exerted by the nonsodium solute leads to redistribution of water from the intracellular to the ECF compartment, resulting in cellular dehydration and hyponatremia. The hyponatremia is real (not pseudo-), but it is accompanied by hypertonicity and a decrease in cellular volume.

Hypotonic hyponatremia is caused by an inability of the kidney to excrete sufficient electrolyte-free water to match water intake. This may occur either because the normal diluting capacity of the kidney is overwhelmed by excessive water intake or because the diluting capacity of the kidney is impaired. These alternatives usually can be distinguished by measuring the urine osmolality. A urine osmolality less than 100 mOsm/kg in a patient with hypotonic hyponatremia points to excessive water intake as the cause (see Fig. 54.5). It is a prodigious feat for an individual eating a normal diet to overwhelm the normal diluting capacity of the kidney. Estimates are that one can ingest (and excrete) about 20 L of water a day without affecting the plasma osmolality appreciably.[183] Thus patients who develop hyponatremia from so-called psychogenic or primary polydipsia—usually patients with obsessive-compulsive disorder or psychosis—typically have concurrent urinary diluting defects, either in association with the underlying mental illness or perhaps as a side effect of psychotropic or anticonvulsant medications.[191]

Not all patients with hypotonic hyponatremia and dilute urine have primary polydipsia. The patient may be ingesting a diet so deficient in protein and salt that he excretes very little solute in the urine. In that situation (called beer potomania for obvious reasons,[192] although the syndrome has been seen in other patients with very low daily solute intake[193]), the low daily solute excretion limits the total amount of water that can be eliminated even with a maximally dilute urine (i.e., maximum urine volume = solute excretion ÷ minimum U_{osm}). This might reduce the maximum water excretion to only 3 to 4 L/day, a quantity easily exceeded by an enthusiastic beer drinker.



• **Fig. 54.5** Diagnostic evaluation of hyponatremia. *ECF_{vol}*, Extracellular fluid volume status; *K*, potassium; *P_{Na}*, plasma sodium concentration; *P_{osm}*, plasma osmolality (mOsm/kg); *SIADH*, syndrome of inappropriate antidiuretic hormone secretion; *U_{osm}*, urine osmolality (mOsm/kg).

A urine osmolality above 100 mOsm/kg in the face of hypotonic hyponatremia signifies impaired urinary diluting capacity. The concentrated urine usually reflects a high circulating AVP level. Because circulating AVP is affected by systemic hemodynamics as well as osmolality, assessment of the patient's ECF volume status and hemodynamics is crucial at this juncture. Hypotonic hyponatremia may be associated with normal, decreased, or increased extracellular volume.

Euvolemic Hyponatremia

Patients with pure water excess appear clinically euvolemic because the excess water distributes throughout the total body water space; only one-third of total body water is extracellular (and only one-twelfth is intravascular). The only evidence of the slight intravascular volume expansion is low blood urea nitrogen and plasma uric acid concentration.[194] The paradigm of euvolemic hyponatremia with concentrated urine is the syndrome of inappropriate antidiuretic hormone (SIADH). It is characterized by elevated circulating AVP (ADH) levels that are inappropriate to vasopressin's two physiologic stimuli (i.e., osmotic or hemodynamic).[195] Hypotonic hyponatremia in patients with SIADH develops to the extent that water ingestion exceeds water eliminated by insensible, GI, and renal routes. Because the normal response to extracellular hypotonicity is the elaboration of maximally dilute urine (urine osmolality <100 mOsm/kg), the urine need only be inappropriately concentrated (i.e., >100 mOsm/kg) to be compatible with a diagnosis of SIADH.

Because hypothyroidism[196] and glucocorticoid insufficiency[197] may impair urinary dilution, patients in whom a diagnosis of SIADH is entertained should undergo appropriate tests of thyroid and adrenocortical function (see Chapter 60).

Once a diagnosis of SIADH is made, its cause must be established because the cause may have important implications in its own right and may be easily remediable. Box 54.8 lists important causes of SIADH. They fall into five major categories: intracranial abnormalities, intrathoracic abnormalities, tumors, drugs, and idiopathic. An important variant of SIADH is the reset osmostat syndrome,[198] in which vasopressin levels are regulated normally by tonicity, but around a lower set point than normal. This syndrome is seen most often in patients who are severely debilitated (e.g., malnutrition, metastatic cancer, advanced tuberculosis) and may account for up to one-third of cases of SIADH. The diagnosis of reset osmostat syndrome has important therapeutic implications, as discussed later.

Hyponatremia has recently been recognized to occur with some frequency in endurance-sports athletes. The incidence of hyponatremia, with serum sodium levels below 135 mmol/L, is approximately 15% in marathon and triathlon athletes; 0.6% of runners develop severe hyponatremia with serum sodium levels below 120 mEq/L.[199] The 3 major risk factors associated with hyponatremia in this setting include body mass index below 20, racing time exceeding 4 hours, and weight gain owing to excessive fluid intake during the race. Excessive water intake is the most important factor in the development of hyponatremia for runners.[199]

Hypovolemic Hyponatremia

The urinary diluting impairment in hypovolemia is mediated both by decreased delivery of fluid to the diluting segments of the nephron and by hemodynamically stimulated vasopressin release. Thus the volume-contracted patient cannot excrete electrolyte-free

• BOX 54.8 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Intracranial abnormalities
  - Infection
  - Stroke
  - Hemorrhage
  - Tumor
- Intrathoracic abnormalities
  - Malignancy
  - Pulmonary abscess
  - Pneumonia
  - Pleural effusion
  - Pneumothorax
  - Chest wall deformity
- Drugs
  - Antidiuretic drugs (vasopressin, DDAVP, oxytocin)
  - Antidepressant medications
  - Amiodarone
  - Major antipsychotic medications
  - Chlorpropamide and other sulfonylurea drugs
  - Carbamazepine
  - Cyclophosphamide
  - Methotrexate
  - Interferon alfa
  - Vinca alkaloids
  - Platinum compounds
  - Melphalan
  - Isofosfamide
  - MDMA (ecstasy)
- Extracranial tumors
  - Small cell lung carcinoma
  - Pancreatic cancer
  - Others
- HIV/AIDS
- Hereditary
  - Gain-of-function mutation of vasopressin-2 receptor
- Miscellaneous
  - Guillain-Barré syndrome
  - Nausea
  - Stress
  - Pain
  - Acute psychosis
  - *Legionella* infection
- Idiopathic

DDAVP, *1-deamino-8-D-arginine vasopressin;* HIV, *human immunodeficiency virus;* MDMA, *3,4-methylenedioxymethamphetamine.*

water normally, and even in the face of modest water ingestion may readily become hyponatremic.

The cause of the volume contraction usually is obvious (e.g., hemorrhage, vomiting, diarrhea, diuretics). When it is not, the urine sodium concentration can be helpful in distinguishing between renal and extrarenal solute losses. Renal losses (e.g., as a result of diuretic medications) are usually reflected by sodium wasting, and extrarenal losses are usually accompanied by sodium conservation (urine sodium concentration <10 mEq/L). Exceptions occur in the recovery phase after diuretic therapy and in metabolic alkalosis owing to vomiting. In the latter situation, the urine chloride concentration tends to be very low and is the best indicator of extracellular volume depletion.[200,201]

Cerebral salt wasting may be responsible for hypovolemic hyponatremia in patients with intracranial pathology (e.g., trauma, tumors, hemorrhage). The pathogenesis of the urinary salt wasting is incompletely understood. The mechanism of hyponatremia in this setting is similar to that of other hypovolemic states. As a hyponatremic syndrome in patients with central nervous system disease, cerebral salt wasting is often difficult to distinguish from SIADH, because urinary sodium excretion tends to be high. Particularly confusing in patients with cerebral salt wasting is the finding of hypouricemia, which is thought to reflect impaired solute reabsorption in the proximal tubule.[202] The key features that distinguish cerebral salt wasting from SIADH are volume depletion and urinary sodium excretion inappropriate to the patient's volume status.[202]

The hyponatremia associated with diuretic treatment is multifactorial in origin. Insofar as diuretics produce overt volume depletion, they can cause hyponatremia by the mechanisms discussed earlier. Thiazides have been associated with the development of acute severe, symptomatic hyponatremia, particularly in small, elderly women, in the absence of overt signs of volume depletion.[203] This often precipitous syndrome appears to be caused, at least in part, by increased water ingestion.[204]

Hypervolemic Hyponatremia

Hypervolemic hyponatremia generally is seen in patients who cannot excrete sodium normally because they have either severe renal failure or one of the pathologic edema-forming states (e.g., congestive heart failure, hepatic cirrhosis, the nephrotic syndrome). Patients with advanced chronic kidney disease are predisposed to hyponatremia.[205] Acute oliguric renal failure or end-stage (dialysis-dependent) renal failure will be accompanied by hyponatremia to the extent that water intake exceeds insensible and GI water elimination (see Chapter 52).

Hyponatremia is seen in more than 20% of patients presenting with decompensated congestive heart failure and more than 30% of patients admitted to the hospital with complications of hepatic cirrhosis.[206] The hormonal milieu of such patients is typical of intravascular volume depletion, even though the absolute intravascular volume typically is increased. Thus these disorders are said to be characterized by reduced effective circulating volume.[207] Because of the perceived intravascular volume depletion, renal diluting ability is compromised for reasons similar to those in hypovolemic hyponatremia.

Management and Complications

Hyponatremia per se requires treatment only when it is associated with hypotonicity. Hypertonic hyponatremia responds to the treatment of the underlying disorder, most commonly a hyperosmolar hyperglycemic state (see Chapter 55).

The therapy of hypotonic hyponatremia must be tailored to (1) the patient's signs and symptoms and (2) the duration of the disorder.[185] Severe hyponatremia (plasma sodium concentration <115 mmol/L) can be life-threatening, especially if it develops rapidly.[187,208] The therapy of symptomatic hyponatremia, irrespective of cause, is directed at raising ECF tonicity to shift water out of the intracellular space, thereby ameliorating cerebral edema. The rate of correction, however, must be carefully regulated. Overly rapid correction, particularly in patients with chronic hyponatremia, in whom cell volume adaptations may be complete, can produce osmotic demyelination syndrome (ODS).[209,210] The ODS is associated with a variety of sometimes irreversible neurologic deficits (e.g., dysarthria, dysphagia, behavioral disturbances, ataxia, quadriplegia, coma), which typically develop 3 to 10 days after treatment.[211] Additional

risk factors for osmotic demyelination include hypokalemia, malnutrition, alcoholism, advanced age, female sex, and the postoperative state, particularly after orthotopic liver transplantation.[212–214]

For patients with acute hyponatremia of less than 24 hours' duration (e.g., marathon runners, postoperative patients, users of "ecstasy"), severe, symptomatic hyponatremia is treated as an emergency to reduce intracranial pressure and the risk of herniation. An expert panel has recommended treating this condition with an intravenous bolus of 100 mL of 3% saline infused over 10 minutes. If signs or symptoms of increased intracranial pressure persist, the dose may be repeated twice.[215] In these limited circumstances, there is no recognized harm in allowing the plasma sodium concentration to correct to normal within hours.[215]

For patients with severe, symptomatic chronic hyponatremia (>48 hours' duration) or similar hyponatremia of unknown duration, clinicians should aim to raise the plasma sodium concentration by no more than 6 mmol/L in the first 6 hours and then stop the increase.[215] Correction of severe symptomatic hypotonic hyponatremia, regardless of cause, should be accomplished with hypertonic (3%) saline solution (sodium concentration 513 mmol/L). The volume of 3% saline solution required can be estimated by the following formula:

$$\text{Volume of 3\% saline solution (liters/24 hours)} = \text{Target change } P_{Na} \text{ (mmol/L per 24 hours)} \times \text{TBW (L)}$$

For example, in a 70-kg man with a plasma sodium concentration of 105 mmol/L and total body water of 42 L (60% of body weight), the amount of sodium needed to raise the plasma sodium concentration by 6 mmol/L is 6 mmol/L × 42L, or 252 mmol. Therefore 252 mmol ÷ 513 mmol/L or 0.5 L of 3% saline solution would be required in the first 6 hours, or 83 mL/h. Care should be taken to avoid overcorrecting the plasma sodium concentration, especially in patients at high risk of the ODS.[197,211] It is important to recognize that this calculation provides only a very rough guideline. The plasma sodium concentration must be monitored frequently during treatment to adjust the rate of correction. If the rate of correction begins to exceed the target rate, the hypertonic saline solution infusion should be stopped. It may be necessary to administer water (enteral or IV) with or without desmopressin to prevent overly rapid correction or to reverse overcorrection.[215]

Rapid extracellular volume expansion with hypertonic saline solution may precipitate pulmonary edema, particularly in patients with underlying heart disease. Thus patients receiving 3% saline solution should be assessed frequently for evidence of volume overload. One may administer a loop diuretic if necessary, recognizing that this will enhance electrolyte-free water clearance and accelerate the correction. Rarely, administration of isotonic (normal) saline solution to patients with SIADH paradoxically may lower the plasma sodium concentration if the urine osmolality remains high—a process that has been called desalination.[216]

The treatment of chronic asymptomatic hypotonicity should be directed at correcting the pathophysiologic mechanisms involved in generating the hypotonic state. Because euvolemic hyponatremia represents pure water excess, treatment depends on restricting water intake to less than the daily water output. Patients with SIADH excrete little or no electrolyte-free water in the urine. Therefore if water intake is limited to less than the amount of insensible water losses (~10 mL/kg body weight per day), the plasma sodium concentration will slowly rise. Patients with the reset osmostat variant of SIADH characteristically do not develop progressive hypotonicity and therapy is rarely required.

If the cause of SIADH cannot be corrected and if water restriction is poorly tolerated or ineffective, a specific vasopressin (V_2) receptor antagonist (VRA) can be used. Conivaptan (parenteral) and tolvaptan (oral) were the first VRAs to be approved by the U.S. Food and Drug Administration for clinical use. These agents have changed the management of patients with SIADH.[217] Tolvaptan reliably increases P_{Na}; however, hyponatremia recurs within 1 week after the medication is discontinued.[218] For patients admitted with hyponatremia related to decompensated congestive heart failure, tolvaptan along with diuretic therapy improves most signs and symptoms of heart failure within 1 week,[219] although no effect on 24-month mortality or heart failure morbidity has been demonstrated.[220] Before the introduction of VRAs, demeclocycline (a tetracycline antibiotic that increases electrolyte-free water excretion by inhibiting vasopressin-mediated water reabsorption in the collecting duct) was commonly used to treat patients with SIADH. Demeclocycline is contraindicated in patients with renal disease, hepatic cirrhosis, or congestive heart failure because drug-related kidney injury has been described in these situations.[221] Neither VRAs nor demeclocycline are indicated for the treatment of acute, severe hyponatremia.

Therapy of hypovolemic hyponatremia should be directed at restoring intravascular volume with intravenous isotonic saline solution while identifying and correcting the cause of the excessive solute loss. Volume repletion readily elicits a water diuresis by increasing the delivery of fluid to the renal diluting segments and suppressing vasopressin release. As with all categories of hypotonic hyponatremia, the rate of correction must be carefully controlled.

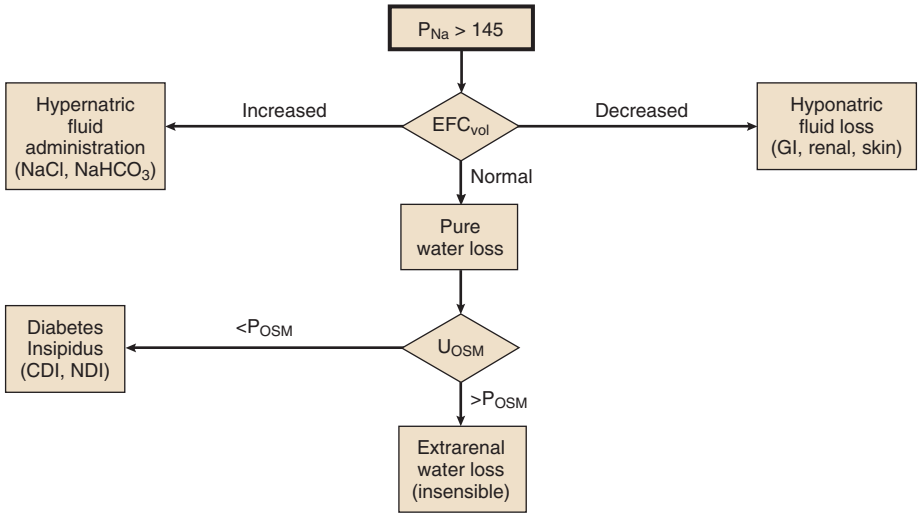
The treatment of diuretic-induced hyponatremia is straightforward: withdrawing the offending drug, liberalizing salt intake, and replenishing body potassium stores usually correct the disorder. Severe symptomatic hyponatremia in this setting should be treated with hypertonic saline solution as detailed earlier. Patients must be watched carefully after correction of the hyponatremia because relapse may occur for up to a week.[222]

Resolution of the hyponatremia associated with any of the pathologic edematous disorders ultimately depends on effective treatment of the underlying disease. Regardless of the specific therapy of the underlying disorder, the mainstay of therapy for the hyponatremic edematous patient remains salt and water restriction. Diuretics are often a double-edged sword in the hyponatremic edematous patient: they may be needed to treat pulmonary vascular congestion, peripheral edema, and ascites, but if used to excess can produce further decrements in effective arterial blood volume and exacerbate water retention. Strategies directed at increasing effective arterial blood volume (e.g., afterload reduction with angiotensin-converting enzyme inhibitors[223,224]) have had some success in increasing electrolyte-free water excretion and ameliorating hyponatremia in patients with congestive heart failure. VRAs are likely to facilitate treatment of hypervolemic hyponatremia (see earlier).[217]

Hypernatremia

Epidemiology and Clinical Manifestations

Hypernatremia is common in critically ill patients; it is present on admission in about 9% of patients and develops during the course of the ICU stay in another 6%.[225] It is associated with a significantly higher mortality than is seen in patients without hypernatremia.[225]



• **Fig. 54.6** Diagnostic evaluation of hypernatremia. *CDI,* Central diabetes insipidus; *ECF_{vol},* extracellular fluid volume status; *GI,* gastrointestinal; *NaCl,* sodium chloride; *$NaHCO_3$,* sodium bicarbonate; *NDI,* nephrogenic diabetes insipidus; *P_{Na},* plasma sodium concentration; *P_{osm},* plasma osmolality; *U_{osm},* urine osmolality.

Sustained hypernatremia develops in patients whose water output exceeds their input. Water ingestion can defend against the development of hypernatremia even when water losses are prodigious. For that reason, hypernatremia upon presentation to the hospital occurs most commonly in patients who are incapacitated: those who have impaired thirst sensation, who cannot access water or who cannot express their need for water (e.g., infants and patients with neurologic impairments). Similar predispositions prevail among critically ill patients. Thus the development of hypernatremia in hospitalized patients is considered iatrogenic, reflecting an incomplete understanding of the factors that lead to hypernatremia.[225] The increased mortality seen in patients with hypernatremia probably is due to their underlying vulnerabilities rather than an effect of the hypernatremia itself.[226]

The clinical manifestations of hypernatremia are proportional to the magnitude and rate of rise of the plasma sodium concentration and are attributable to intracellular volume contraction. To counteract cellular volume contraction, cells begin to adapt within minutes by allowing the influx of electrolytes, thus mitigating cell shrinkage. When hypernatremia lasts more than a few hours, brain cells generate new organic osmolytes. This leads to further water movement back into brain cells, restoring cell volume to near normal after about 3 days.[227] Thus chronic progressive hypernatremia is associated with fewer and milder symptoms than acute severe hypernatremia. Most often, patients with long-standing hypernatremia present with weakness, lethargy, and confusion. Seizure and coma may supervene. Acute severe hypernatremia in infants and small children is associated with intracranial bleeding,[228] presumably caused by brain shrinkage and traction on the penetrating vessels. There is some controversy, however, as to whether the hypernatremia in that situation is the cause or the effect of the intracranial hemorrhage.[229]

Differential Diagnosis

The plasma sodium concentration reflects the ratio of body sodium content to total body water. Thus hypernatremia (plasma sodium concentration >145 mmol/L) can result from loss of pure water alone, loss of hyponatric fluid, or a gain of sodium or hypernatric fluid.* It is important to distinguish among these paths to hypernatremia because they have diagnostic and therapeutic implications (Fig. 54.6).

Euvolemic Hypernatremia

Hypernatremic patients who appear euvolemic most likely have pure water loss as an explanation for their hypernatremia. This is because the water is lost from all body compartments proportionately; only one-twelfth of the water loss is intravascular. For example, a 60-kg woman with a 3-L pure water loss would experience an intravascular loss of only 250 mL (clinically imperceptible) but would develop a plasma sodium concentration of 155 mmol/L.† Pure water can be lost either through the skin and respiratory tract (so-called insensible losses) or in urine.

Insensible losses amount to about 10 mL/kg body weight per day under normal environmental conditions in an afebrile individual with a normal respiratory rate. A hot environment, fever, or rapid respiratory rate may double that rate.[183] Note that a patient supported by mechanical ventilator using humidified gas will lose no water through the respiratory tract.

The loss of large amounts of dilute, electrolyte-free water in the urine is typical of diabetes insipidus (DI). DI may be central (CDI) or nephrogenic (NDI) depending on whether the defect is in vasopressin release from the posterior pituitary or in the renal

*Hyponatric and hypernatric are used here to refer to a fluid with a sodium concentration less than (or greater than) that of plasma.

†The expected change in the serum sodium concentration is calculated as follows: [Initial total body water volume] × [Serum sodium concentration initial] ÷ [Final total body water volume]; 30 L × 140 mmol/L ÷ 27 L = 155 mmol/L.

response to circulating vasopressin, respectively. The causes of DI are shown in Box 54.9. Most cases of CDI, especially those following trauma or intracranial surgery, are self-limited, lasting 4 to 5 days. Of special interest to intensivists is a classic triphasic syndrome that may be seen following severe head trauma:

1. Initially, there is abrupt cessation of vasopressin release from the posterior pituitary, accompanied by polyuria.
2. About a week later, an antidiuretic phase ensues, characterized by urinary concentration and water retention with a tendency toward hyponatremia, lasting 5 to 6 days. This appears to result from the release of stored vasopressin from the degenerating hypothalamic neurons.
3. Persistent CDI recurs when the vasopressin stores are depleted.[230]

Regardless of the cause, patients with DI of either type usually have a plasma sodium concentration within the normal range because their water ingestion matches their urinary water output. They develop hypernatremia only with water deprivation, owing to mental or physical incapacity, and/or neglect. An awareness of the causes of DI, a careful history, and familiarity with the differential diagnosis of polyuria will prevent hypernatremia in these circumstances.

• BOX 54.9 Causes of Diabetes Insipidus

Central Diabetes Insipidus

Posthypophysectomy
Posttraumatic
Granulomatous diseases
  Histiocytosis
  Sarcoidosis
Infections
  Meningitis
  Encephalitis
Inflammatory/autoimmune:hypophysitis
Vascular
  Hypoxia
  Thrombotic or embolic stroke
  Hemorrhagic stroke
Neoplastic
  Craniopharyngioma
  Pituitary adenoma
  Lymphoma
  Meningioma
Drugs or toxins
  Ethanol
  Snake venom
Congenital/hereditary

Nephrogenic Diabetes Insipidus

Drug-induced
  Lithium
  Demeclocycline
  Cisplatin
  Ethanol
Hypokalemia
Hypercalcemia
Vascular
  Sickle cell anemia
Infiltrating lesions
  Sarcoidosis
  Multiple myeloma
  Amyloidosis
  Sjögren syndrome
Congenital
  Autosomal recessive: aquaporin-2 water channel gene mutations
  X-linked recessive: arginine vasopressin V_2 receptor gene mutations

Hypovolemic Hypernatremia

The loss of salt and water, with the water loss greater than the sodium loss, will lead to hypernatremia and volume depletion, manifested by orthostatic or persistent hypotension and tachycardia, and evidence of organ underperfusion (e.g., acute renal failure, lactic acidosis). For example, if the 60-kg woman whose plasma sodium concentration rose to 155 mmol/L (see earlier) had lost the equivalent of half-isotonic saline solution instead of pure water, her intravascular volume would have contracted by 750 mL, enough to cause at least orthostatic hypotension and tachycardia.

A common cause of hypovolemic hypernatremia is the loss of GI fluids.[231] Most GI fluids have an electrolyte concentration below that of plasma: The concentration of sodium plus potassium in stool is roughly constant at 110 to 120 mmol/L over a wide range of stool volume.[132] Gastric fluid has an even lower electrolyte concentration: about 40 to 50 mmol/L total cation concentration.[232] Diuresis, either osmotic (glucose-, mannitol- or urea-induced) or medication-induced, causes the loss of urine with an electrolyte concentration less than that of plasma, leading to volume contraction and hypernatremia. The loss of sweat, which contains some sodium, can cause hypovolemic hypernatremia in individuals who exercise vigorously in a hot environment. If the cause of the fluid loss is not apparent from the history or the physical examination, a urinary chloride concentration less than 10 mmol/L in the face of hypovolemic hypernatremia suggests that the electrolyte loss is extrarenal (cutaneous or GI).

Hypervolemic Hypernatremia

Hypervolemic hypernatremia is relatively uncommon. It results most often from the administration of hypertonic sodium salts to patients without free access to water.[231] Patients show signs of extracellular volume expansion (e.g., hypertension, edema, congestive heart failure, and pulmonary edema). In infants, this syndrome has been caused by erroneous preparation of dietary formula using salt instead of sugar; in adult outpatients, it may be caused by ingestion of a concentrated salt solution, usually for its emetic effect.[233] The risk of death is substantial and seems to be proportional to the plasma sodium concentration.[233]

In hospitalized adults, hypervolemic hypernatremia is most often iatrogenic, caused by intravenous administration of undiluted sodium bicarbonate (formulated at 1 mEq/mL or 1000 mmol/L) or sodium chloride (3% [513 mmol/L] or 23.5% [4019 mmol/L]). Not all hypervolemic hypernatremia results from the administration of hypertonic fluids. It may be seen in a volume-expanded patient who then loses hypotonic fluid.[234]

Treatment

The initial treatment of the patient with hypernatremia depends on his or her volume status. For patients with pure water losses (euvolemic), therapy has two goals: (1) reduction and/or replacement of ongoing water losses, and (2) replacement of the existing water deficit.

If the water losses are urinary (see Fig. 54.6) and due to CDI, antidiuretic hormone should be administered. Several formulations are available (Table 54.3). In the acute (postsurgical or posttraumatic) setting, l-AVP may be used either subcutaneously or intravenously, although the latter route may be associated with hypertension and coronary spasm and should therefore be used

TABLE 54.3 Pharmacologic Treatment of Central Diabetes Insipidus

Agent	Total Daily Dose	Frequency of Administration	Onset of Action (h)	Duration of Action (h)	Comments
Arginine vasopressin, 20 units/mL	5–10 units subcutaneously	q2–q4 h	1–2	2–6	Intravenous route may cause vasoconstriction and coronary spasm
Desmopressin acetate (DDAVP)					
10 μg/0.1 mL intranasal	10–40 μg intranasal	Daily or bid	1–2	8–12	
4 μg/mL injection	1–2 μg IV or subcutaneously	Daily or bid	1–2	8–12	

bid, Twice daily; *DDAVP,* 1-deamino-8-D-arginine vasopressin; *q,* every.
Modified from Singer I, Oster JR, Fishman LM. The management of diabetes insipidus in adults. *Arch Intern Med.* 1997;157:1293–1301.

with extreme caution.[235] The advantage of vasopressin in this setting is its short half-life, which allows the physician to repeatedly assess the need for continued hormone replacement, especially when the disorder may be self-limited. Desmopressin (1-deamino-8-d-arginine vasopressin [DDAVP]) is a synthetic analog of vasopressin that has no vasoconstrictor properties, thus avoiding the risks of hypertension and myocardial ischemia. The treatment of the urinary water losses associated with NDI are best treated with thiazide diuretics with or without COX inhibitors. Because most of these agents are orally administered, treatment of NDI in the critically ill patient often consists of urinary water replacement until he or she is able to take medications by mouth.

The rate of water replacement should be proportional to the rapidity with which the hypernatremia developed.[227] Thus if the hypernatremia had developed over only a few hours (such as in salt poisoning, postsurgical or posttraumatic DI), it can be corrected just as quickly. On the other hand, hypernatremia of more than a day's duration, or of unknown duration, must be correctly slowly to avoid cerebral edema. One should aim to lower the plasma sodium concentration by no more than 10 mmol/L per day.[236]

The water deficit to be corrected over 24 hours can be estimated by the following formula:

$$\text{Target positive water balance over 24 h (L)} = \text{TBW}\left(1-\frac{\text{Current } P_{Na}-10}{\text{Current } P_{Na}}\right)$$

where TBW is total body water in liters (estimated as about 0.5 × lean body weight [kg] in women and 0.6 × lean body weight in men). For example, a 60-kg woman presenting with a plasma sodium concentration of 160 mmol/L should be in positive water balance by 30 (1 – 0.94) or 1.9 L to achieve a plasma sodium concentration 150 mmol/L in 24 hours. To achieve this target, all ongoing water losses must be replaced completely and then exceeded by the calculated amount.

Water is best administered enterally as tap water. If that route is unavailable, 5% dextrose in water (D_5W) may be used, with the understanding that the capacity to metabolize glucose is limited to about 15 g/h in a critically ill adult.[237] Thus even in nondiabetic patients, the administration of more than 300 mL/h of D_5W is likely to result in hyperglycemia, which may be relatively resistant to insulin administration. Hyperglycemia will exacerbate urinary water losses by causing an osmotic diuresis. Half-normal (0.45%) saline solution may be a good alternative, as long as one recognizes that only half the administered volume is electrolyte-free water and that the sodium load may cause unwanted volume expansion.

Regardless of the degree of hypernatremia, normal (0.9%) saline solution should be given intravenously to patients who present with obvious volume depletion, manifested by hypotension, tachycardia, and evidence of impaired tissue perfusion. This is consistent with the first principles of emergency and critical care, prioritizing the adequacy of the circulation. Only after the extracellular volume deficits have been largely corrected may the physician direct his or her attention to the total body water deficit (see earlier text).

Patients with hypervolemic hypernatremia need reduction in their extracellular and intravascular volume before their water deficit can be corrected. Failure to do so will exacerbate the volume overload. For patients with adequate renal function, this may be accomplished with the use of diuretic drugs. Loop diuretics tend to cause the excretion of isotonic urine. Replacement of that urine volume with pure water will allow correction of the hypervolemia and the hypernatremia simultaneously.

Because of the imprecision of the estimation formulas and the failure of the foregoing analysis to take account of other fluids and electrolytes both administered and lost, it is crucial that the plasma electrolytes be monitored every 4 to 6 hours during the correction of severe hypernatremia, especially in view of the dire consequences of overly rapid correction.

Calcium

Calcium is required for bone mineralization, muscle contraction, nerve conduction, and blood coagulation. It is required for cell division, hormone secretion, phagocytosis, chemotaxis and activation of numerous intracellular second messengers.[238] Calcium is also responsible for activation of calcium-dependent phospholipases and proteases, generation of free radicals, cytokines release, and inhibition of adenosine triphosphate (ATP) production in the face of ischemic injury. Thus calcium plays a central role in physiologic as well as pathologic conditions.[239]

Normal Calcium Physiology

Calcium is the most abundant cation in the body. The total body calcium content of an average adult is approximately 1 kg, 99% of which is found in bones and teeth, with only 1% in plasma and soft tissues.[240] Calcium homeostasis is achieved with the cooperation of several organs, including the skeleton, the gut, and the kidney, under the influence of several hormones, mainly vitamin D, parathyroid hormone (PTH), and calcitonin.

Calcium Intake and Absorption

The daily dietary intake of calcium for an average adult in North America is 800 to 1000 mg. The main dietary source of calcium is milk and other dairy products; it is also available in the form of fortified food and calcium-containing supplements. Approximately 20% of dietary calcium is absorbed by the intestine. Intestinal absorptive capacity increases with calcium deprivation and under certain physiologic conditions such as growth spurts in children, pregnancy, and lactation.[241] Intestinal absorption occurs via both passive paracellular and active transcellular pathways. Vitamin D increases the active transport of calcium across the intestinal membranes.[240]

Renal Handling of Calcium

The filtered load of calcium (the product of glomerular filtration rate and the plasma concentration of ultrafilterable calcium) is about 10 g/day. Calcium balance is maintained when the kidneys excrete about 200 mg/day (the intestinal absorptive load). Thus the fractional excretion of calcium is only about 2%.[240,241] Of the 98% of filtered calcium reabsorbed along the nephron, 60% is reabsorbed in the proximal tubule. Approximately 15% of the filtered calcium is reabsorbed in the thick ascending limb of loop of Henle (TAL). The reabsorption of calcium in TAL is mostly passive and proportional to the lumen-positive voltage generated by the furosemide-inhibitable Na-K-2Cl transporter and luminal potassium recycling via renal outer medullary potassium channels. There is also some active transcellular transport, which is under the influence of PTH and calcitonin.[240,241] In the distal tubule, approximately 10% to 15% of filtered calcium is reabsorbed via active transcellular pathways. The apical membranes of distal convoluted tubules and connecting tubules contain highly selective epithelial calcium channels (transient receptor potential cation channel subfamily V member 5 [TRPV-5]),[240,241] which facilitates calcium entry into the cells. PTH increases the density and open probability of TRPV-5 channels.[242]

Volume expansion, hypercalcemia, acute and chronic acidosis, and loop diuretics reduce the renal calcium reabsorptive capacity and result in hypercalciuria. Conversely, hypocalcemia, alkalosis, PTH, calcitriol, and thiazide diuretics enhance renal calcium reabsorption and cause hypocalciuria.

Regulation of Plasma Calcium

Normal plasma calcium concentration is 8.8 to 10.4 mg/dL. In plasma, calcium exists in two forms: protein-bound and ultrafilterable (permeant across the glomerular filtration barrier). Approximately 40% of plasma calcium is bound to plasma proteins (predominantly albumin), cannot cross the biologic membranes, and is thus physiologically inert. The ultrafilterable portion of plasma calcium makes up the remaining 60% of plasma calcium and consists of calcium complexed with various anions such as citrate, phosphate, and lactate (about 10%), and free, ionized calcium (Ca^{2+})—the biologically active form, accounting for about 50% of plasma Ca.[243]

Plasma ionized calcium concentration is tightly regulated. Several factors play an important role in maintaining plasma Ca^{2+} concentration within a narrow range (about 4.4–5.2 mg/dL or 1.1–1.3 mmol/L). The principal regulators are PTH, vitamin D_3, and Ca^{2+} itself.

Ca^{2+} acts as a ligand for calcium-sensing receptors (CaSRs) present on the chief cells of the parathyroid glands. A rise in plasma Ca^{2+} concentration results in activation of CaSRs, which in turn inhibits PTH secretion. Conversely, a fall in Ca^{2+} concentration inhibits CaSRs, increasing PTH secretion. PTH mobilizes the calcium from bone stores, stimulates renal calcium reabsorption, and increases the conversion of $25(OH)D_3$ to 1, $25(OH)_2D_3$, the most active form of vitamin D_3. Activated vitamin D_3 increases intestinal calcium absorption. The CaSR is also present on the basolateral surface of TAL cells. Activation of the CaSRs in these cells results in a reduction in tubular calcium reabsorption. All these systems work in concert to keep the Ca^{2+} levels within physiologic levels.[238]

Plasma Calcium Measurement

Ionized calcium is the physiologically important moiety, yet total calcium is the moiety most often measured in clinical laboratories. Under normal circumstances, there is a fairly constant relationship between total and ionized calcium (see earlier text), but in critically ill patients, this relationship may be disturbed such that total calcium no longer provides a reliable index of the physiologically important calcium concentration. The two major factors affecting the ratio of ionized to total calcium are acid-base status and plasma protein concentration.

Acidemia causes displacement of calcium ions from albumin by protons and results in a relative increase in ionized calcium. Conversely, alkalemia increases calcium binding to albumin, causing a relative fall in ionized calcium levels while total plasma calcium concentration remains unchanged.[238,240]

Changes in the concentration of plasma protein, especially albumin, result in alterations in total calcium concentration. Hypoalbuminemia, common in critically ill patients, causes a reduction in total calcium concentration; hyperalbuminemia (e.g., in states of severe volume contraction) tend to cause an increase in total plasma calcium. Numerous formulas have been proposed to adjust the total calcium concentration for changes in plasma albumin concentration.[244] The most commonly used formula is based on the observation that each gram of albumin binds about 0.8 mg calcium at physiologic pH:

$$Ca_{corrected} = Ca_{observed} + (0.8 \cdot [4.0 - albumin])$$

Unfortunately, the corrected calcium correlates very poorly with physiologically active ionized calcium in various critically ill populations, typically with a very low sensitivity for diagnosis of true hypocalcemia.[244–246]

The reasons for this discrepancy are manifold, including concurrent acid-base disorders, high circulating concentrations of free fatty acids,[247] and infusions of heparin, citrate, and bicarbonate.[246] Therefore in critically ill patients, direct measurement of ionized calcium is recommended for assessing physiologic calcium concentration.

Hypocalcemia

Epidemiology

Hypocalcemia is extremely common in critically ill patients. The prevalence of ionized hypocalcemia is reported to be 60% to 85%

among medical, surgical, and trauma ICU patients.[248–251] Risk factors for the development of hypocalcemia in critically ill patients include advanced age, sepsis, acute renal failure, multiple blood transfusion, malnutrition, magnesium deficiency, severe shock, and colloid volume resuscitation.[251,252] Mortality is higher in hypocalcemic patients[249,253,254] but does not appear to be independently associated with hypocalcemia.[250,251]

Causes of Hypocalcemia

Causes of hypocalcemia are shown in Box 54.10. Hypocalcemia may be caused by disorders involving the hormonal regulators of calcium homeostasis, PTH and vitamin D; redistribution of calcium; drugs; and miscellaneous influences. We discuss causes of particular relevance to the critical care setting.

Hypoparathyroidism

Parathyroidectomy, for hyperparathyroidism or "incidentally" with thyroidectomy, may cause postoperative hypocalcemia. Risk factors for developing hypocalcemia include subtotal parathyroidectomy and simultaneous thyroidectomy. Profound, long-lasting hypocalcemia may develop, as part of the "hungry bone" syndrome, in which calcium is sequestered into the rapidly remineralizing bone.[255] Hypomagnesemia may contribute to the hypocalcemia (see "Disorders of Magnesium Homeostasis").

Vitamin D Deficiency

Vitamin D deficiency is common in elderly, institutionalized patients owing to poor dietary intake and inadequate sunlight exposure. Diseases involving liver and small intestine may result in poor absorption of vitamin D. For conversion to its most active form, vitamin D requires hydroxylation in liver and kidney. Frequently, critically ill patients have liver and kidney dysfunction, which results in impaired vitamin D synthesis and predispose to hypocalcemia.[239] Vitamin D deficiency (level < 20 ng/dL) upon admission to a medical ICU has been associated with increased mortality.[256] Whether vitamin D supplementation to critically ill patients will reduce mortality remains to be determined.

Redistribution

Citrate is useful as a preservative and anticoagulant for blood components precisely because it chelates calcium and thereby inhibits the coagulation cascade. The calcium citrate complex is then metabolized in liver, where citrate is converted into bicarbonate, and ionized calcium is released into the circulation. Massive blood transfusion may result in ionized hypocalcemia owing to chelation of calcium by citrate. However, hypocalcemia is transient in patients with normal liver function, and ionized calcium levels return to normal levels within 15 minutes of transfusion.[257] Citrate also may be used for anticoagulation of the dialysis circuit for continuous renal replacement therapy (continuous venovenous hemofiltration and variants). Under those conditions, calcium typically is infused through a central venous line to prevent hypocalcemia. Inadequate calcium replacement or concomitant liver failure may result in clinically significant hypocalcemia. In the latter case, with citrate accumulation, the total calcium may be misleadingly normal, but the ionized calcium is low.[258,259] Hypocalcemia is frequently reported with plasmapheresis where citrate is used for anticoagulation.[260] Sodium bicarbonate to treat metabolic acidosis may cause hypocalcemia from calcium binding to albumin and formation of carbonate complexes. Similarly, abrupt alkalinization from hemodialysis against a bicarbonate bath may precipitate symptomatic hypocalcemia.

Phosphate binds with calcium to form insoluble calcium phosphate complexes. Under normal physiologic conditions, calcium and phosphorus levels are tightly regulated, preventing significant complexation. Any condition that causes an acute increase in phosphate levels, however, can cause complexation and resultant ionized hypocalcemia. Examples include endogenous phosphorus overload as in the tumor lysis syndrome[72] and exogenous phosphorus overload from laxatives and cathartics.[261–264] Patients with impaired renal function are at particular risk[262] (see "Phosphorus").

Hypocalcemia in rhabdomyolysis is multifactorial and involves calcium deposition in injured muscles, formation of calcium-phosphate complex owing to hyperphosphatemia, and acute renal failure causing decreased synthesis of vitamin D.[265]

The presence of ionized hypocalcemia correlates with the development of severe acute pancreatitis[266] and is reported in up to 85% of patients with severe acute pancreatitis.[267] The cause of hypocalcemia in this setting is unclear. Calcium has been shown to accumulate in pancreas, liver, and skeletal muscle in an animal model of acute pancreatitis.[268] Low[269] and high[270,271] levels of PTH have been reported. Experimental elevation in free fatty acids, both circulating[272] (as might be seen in the hypertriglyceridemia of acute pancreatitis) and intraperitoneal,[273] have been associated

• BOX 54.10 Causes of Hypocalcemia

Hypoparathyroidism
- Acquired
  - Parathyroidectomy
  - Infiltrative or malignant disease
- Congenital
- Idiopathic

Vitamin D Deficiency
- Malnutrition
- Malabsorption
- Liver disease
- Kidney disease

Redistribution
- Tissue sequestration
  - Acute pancreatitis
  - Rhabdomyolysis
- Complexation
  - Alkali
  - Citrated blood-product transfusions
  - Citrate anticoagulation in continuous renal replacement therapy
  - Plasmapheresis
  - Bicarbonate infusion for metabolic acidosis
  - Phosphate
  - Tumor lysis syndrome
  - Fleet enemas and phosphate-containing laxatives
  - Rhabdomyolysis
- Ethylenediamine tetraacetic acid (EDTA)

Drugs
- Cis-platinum
- Bisphosphonates
- Plicamycin

Miscellaneous
- Sepsis/systemic inflammatory response syndrome
- Hypomagnesemia
- Acute renal failure

with the hypocalcemia of acute pancreatitis. Finally, high circulating endotoxin levels may have a role.[267]

Drugs

Bisphosphonates are used for the treatment of osteoporosis and hypercalcemia. They act by impairing osteoclast function and reducing osteoclast numbers. Bisphosphonate-induced hypocalcemia has been reported in patients with renal failure, hypoparathyroidism, or vitamin D deficiency.[274] Denosumab, a receptor activator of nuclear factor κ (RANK)-ligand inhibitor, is an antibody-mediated antiresorptive drug used in the treatment of postmenopausal osteoporosis, and it has been shown to cause hypocalcemia particularly in individuals with chronic kidney disease.[275] Other drugs such as colchicine, plicamycin (formerly mithramycin), and calcitonin also decrease bone release of calcium.[240] Cinacalcet, a calcimimetic, can cause hypocalcemia by stimulating the parathyroid CaSR.

Sepsis/Systemic Inflammatory Response Syndrome

Hypocalcemia is common in patients with sepsis or systemic inflammatory response syndrome.[249,253] The cause probably is multifactorial.[276] Among the proposed mechanisms are calcium sequestration,[277,278] an effect of inflammatory cytokines,[279] calcitonin precursors,[279,280] hypomagnesemia[281] with inappropriate hypoparathyroidism,[276] and probable PTH resistance.[279,282] Vitamin D deficiency, from malnutrition and inability to hydroxylate vitamin D because of coexisting liver and kidney dysfunction, also has been implicated.[276] The hypocalcemia may serve to protect vulnerable cells from the deleterious effects of calcium during sepsis. Indeed, calcium administration in this setting may be detrimental.[276]

Clinical Manifestations

Hypocalcemia affects predominantly the neuromuscular and cardiovascular systems. Neuromuscular manifestations include paresthesias (perioral and acral), hyperactive reflexes, tetany (carpopedal spasm and other muscle spasm), and seizures.[240] Laryngospasm and bronchospasm may supervene, leading to respiratory arrest.[238] Tetany may be provoked by tapping over the facial nerve and noting ipsilateral facial muscle twitching (Chvostek sign) and transiently occluding the brachial artery with a tourniquet and noting carpal spasm (Trousseau sign), although neither of these signs is specific for hypocalcemia. Prolonged hypocalcemia lasting longer than 36 hours has been associated with the development of critical illness polyneuropathy and myopathy.[283] Psychiatric manifestations include anxiety, irritability, confusion, and psychosis.[238]

Cardiovascular findings include a prolonged QT interval and, in severe hypocalcemia, bradycardia, hypotension refractory to fluids and vasopressors, heart block, heart failure, and cardiac arrest.[239]

Symptoms and signs of hypocalcemia depend on the degree of depression of ionized calcium levels and the rate of decline.[240] Mild hypocalcemia (ionized calcium >3.2 mg/dL) usually is well tolerated.

Diagnosis

When hypocalcemia is suspected in a critically ill patient, the diagnosis should be established by direct measurement of ionized calcium levels (see "Plasma Calcium Measurement"). If ionized hypocalcemia is confirmed, plasma magnesium and phosphorus should be measured. Further diagnostic evaluation derives from the differential diagnosis (see Box 54.10). Without PTH levels and vitamin D levels, the diagnosis of hypocalcemia remains obscure in the majority of critically ill patients.[249]

Treatment

Therapy of hypocalcemia depends on its severity. Hypocalcemia (ionized calcium < 3.2 mg/dL) accompanied by serious cardiovascular or neuromuscular signs should be treated urgently. Calcium gluconate (10% in 10 mL containing 90 mg elemental calcium) can be given over 5 to 10 minutes, followed by calcium gluconate infusion (500–1000 mg in 500 mL 5% dextrose over 6 hours).[240] Calcium chloride (10% in 10 mL containing 272 mg elemental calcium) contains more calcium and can rapidly increase plasma calcium levels; however, it is more irritating to the veins and must be given by a central venous catheter. Patients with renal failure, hyperphosphatemia, and serious hypocalcemia may require dialysis.

Patients receiving intravenous calcium should have frequent measurement of the ionized calcium. They should be monitored for side effects of calcium administration, including hypertension, skin flushing, nausea, vomiting, and chest pain.

Intravenous calcium should be reserved for patients who have severe symptomatic hypocalcemia or who are incapable of taking calcium orally. Administration of intravenous calcium can cause complexing with phosphorus and ectopic calcification.

Critically ill patients with mild hypocalcemia (ionized calcium >3.2 mg/dL) tend to have few if any manifestations. Patients with long-standing or chronic hypocalcemia (e.g., owing to vitamin D deficiency or hypoparathyroidism) should receive oral calcium supplementation. Calcium is available as the carbonate, citrate, phosphate, and lactate salt. Calcium requirement varies between 1 and 4 g elemental calcium daily and must be given in divided doses. Vitamin D can be added with calcium to enhance intestinal absorption.

Several points in the management of hypocalcemia should be borne in mind. First, in cases of concomitant mild hypocalcemia with hyperphosphatemia (e.g., renal failure), the hyperphosphatemia should be corrected using phosphate binders, because that alone often leads to correction of the hypocalcemia. Second, magnesium deficits should be corrected because that may restore normal calcium physiology even without calcium supplementation (see "Disorders of Magnesium Homeostasis"). Finally, concurrent severe metabolic acidosis should await correction of the hypocalcemia, because correction of the acidosis is likely to worsen the ionized hypocalcemia and precipitate tetany.

Hypercalcemia

Hypercalcemia has been reported in 15% to 30% of critically ill patients,[282,284] and thus appears to be less common than hypocalcemia. It is more common in patients with higher severity of illness and in those with concurrent renal failure.[282,284]

Causes of Hypercalcemia

Box 54.11 lists causes of hypercalcemia. About 90% of hypercalcemia in ambulatory and non-ICU patients is caused by only two entities: primary hyperparathyroidism and malignancy.[238] The spectrum is a bit broader in critically ill patients.

Primary Hyperparathyroidism

Primary hyperparathyroidism is the most common cause of hypercalcemia, accounting for more than 50% of cases in ambulatory patients. Specific causes include benign adenoma (80%–90%), hyperplasia (10%–20%), and carcinoma (1%). Biochemical abnormalities include elevated circulating intact PTH, hypercalcemia, and hypophosphatemia.[238]

• BOX 54.11 Causes of Hypercalcemia

Primary Hyperparathyroidism

Malignancy
- Parathyroid hormone–related peptide
- Ectopic parathyroid hormone
- Vitamin D–mediated
- Lytic bone lesions

Vitamin D
- Exogenous
- Endogenous

Hyperthyroidism
Adrenal insufficiency
Rhabdomyolysis, recovery
Immobilization
Drugs
- Thiazide
- Lithium
- Vitamin D/calcium supplements
- Vitamin A

Malignancies

Hypercalcemia is rarely the presenting sign of a malignancy; most malignancies are advanced at the time hypercalcemia develops. About 40% of hypercalcemia in hospitalized patients has been associated with cancer.[285] Almost 80% of malignancy-related hypercalcemia is secondary to the secretion of parathyroid hormone-related peptide (PTHrP) by the malignant cells.[285] PTHrP is not detected by clinical laboratory assays for PTH. Numerous types of malignancies are associated with PTHrP-mediated hypercalcemia, including breast,[286] renal cell, and ovarian carcinomas[238] and hematologic malignancies.[287]

Increased production of 1,25-$(OH)_2D_3$ by malignant cells is a recognized cause of hypercalcemia in patients with lymphomas.[288,289] Finally, osteolytic bone lesions from advanced cancers such as breast, lung, and multiple myeloma frequently result in hypercalcemia.[238]

Rhabdomyolysis

Rhabdomyolysis associated with acute renal failure commonly produces hypocalcemia during the initial phase (see "Hypocalcemia"). Approximately 30% of patients, mostly young men, develop hypercalcemia during resolution of the acute renal failure.[290] Release from injured muscles of previously sequestered calcium appears to be the basis for the hypercalcemia.[290,291] PTH is appropriately suppressed according to most,[292,293] but not all,[294] studies. Vitamin D levels may be elevated[292,294] or suppressed[265,293]; the contribution of vitamin D to the syndrome is unclear. Regardless of the underlying mechanism, the hypercalcemia is usually mild and self-limited.[290]

Immobilization

Immobilization is associated with hypercalcemia as the result of increased bone resorption. Risk factors include duration of bed rest, spinal cord injury, multiple skeletal fractures, and underlying disorders leading to increase bone resorption (e.g., Paget disease, malignancy).[295,296] Although hypercalcemia is usually modest and completely reversible with activity, calcitonin and bisphosphonates can be used with success if treatment is required.[295]

Medications

A small percentage (5% to 10%) of patients treated with lithium develops hypercalcemia as the result of lithium-induced hyperparathyroidism.[238] Hyperparathyroidism may or may not be reversible on discontinuation of therapy. Thiazide diuretics increase tubular reabsorption of calcium and are well known to cause modest hypercalcemia, which revert back to normal upon discontinuation of therapy. More severe hypercalcemia should prompt an evaluation for occult hyperparathyroidism. Vitamin A may increase osteoclast-mediated bone resorption and causes hypercalcemia.

Milk-Alkali Syndrome

This syndrome consists of hypercalcemia (often extreme), metabolic alkalosis, and acute renal failure. It is seen in patients who ingest large quantities of alkaline calcium salts (e.g., calcium carbonate), often with vitamin D preparations.[297] Because of the increasing use of these medications to prevent or treat osteoporosis, the incidence of this syndrome, once considered rare, appears to be increasing.[298]

Clinical Manifestations

Clinical manifestations of hypercalcemia depend on the rate of increase and absolute level of plasma calcium. The most serious manifestations are neurologic and cardiovascular. Patients may experience muscle weakness, fatigue, depression, and altered mental status. At extremely high levels, stupor and coma may ensue.[238,243] Prolonged hypercalcemia lasting longer than 36 hours has been associated with the development of critical illness polyneuropathy and myopathy.[283] Hypercalcemia causes an increased rate of cardiac repolarization and results in shortened QT interval. Conduction disturbances and malignant arrhythmias have been reported with hypercalcemia.[299,300]

Hypercalcemia may lead to acute renal failure from volume depletion and renal vasoconstriction, and polyuria and polydipsia owing to NDI.[238,243] GI symptoms include anorexia, nausea, vomiting, and constipation. Peptic ulcer disease and acute pancreatitis are exceedingly rare, especially in the acute setting.[238]

Diagnosis

The diagnosis of hypercalcemia often is apparent from the history, with an understanding of the differential diagnosis (see Box 54.11). In cases of sustained or unexplained hypercalcemia, assays for intact PTH and vitamin D metabolites are of great value. An assay for PTHrP rarely is necessary in the evaluation of hypercalcemia in a critically ill patient, because in most patients with hypercalcemia of malignancy, the cancer is advanced and the diagnosis will be obvious when the PTH and vitamin D levels are shown to be suppressed.

Treatment

The treatment strategy for hypercalcemia depends on the severity of the disturbance and on its underlying cause. Identification of the probable cause of the hypercalcemia is important both for the immediate and long-term management.

Mild hypercalcemia (total calcium ≤12 mg/dL or 3 mmol/L) is usually caused by primary hyperparathyroidism, thiazide diuretics, calcium and vitamin D supplements, lithium, and immobilization. Treatment should begin with withdrawal of the offending agent (if possible). Volume deficits should be replaced orally if possible. Early mobilization should be encouraged. Loop diuretics should be avoided in patients with mild asymptomatic hypercalcemia as they may exacerbate the volume depletion, leading to increased renal calcium reabsorption.

The immediate treatment of moderate hypercalcemia (total calcium > 12 mg/dL or 3 mmol/L, and ≤ 14 mg/dL or 3.5 mmol/L)

includes the measures discussed earlier, as well as intravenous volume expansion with isotonic saline solution. A loop diuretic will enhance renal excretion of calcium, but care must be taken to avoid volume depletion.

Severe hypercalcemia (total calcium >14 mg/dL or 3.5 mmol/L), even in the absence of signs and symptoms, should be treated as an emergency. Strategies for treatment include (1) enhanced calcium elimination, (2) reduced bone resorption, (3) decreased gut absorption of calcium, and (4) identification and treatment of the underlying cause.

Enhanced Calcium Elimination

Forced diuresis is the mainstay of treatment. Volume expansion with normal saline solution should be instituted immediately at a rate of 200 to 300 mL/h. The net fluid balance in adults should be positive approximately 2 L in 24 hours. Caution must be taken to avoid symptomatic volume overload in patients with impaired myocardial performance and/or renal insufficiency.

Once the volume deficit is adequately replaced, loop diuretics may be added to enhance renal calcium excretion. A dose of loop diuretic that at least doubles the rate of urine output can be given as often as every 8 hours.

For patients with congestive heart failure unresponsive to diuretics, or with advanced kidney failure, dialysis should be considered. Hemodialysis against a solution containing 2.0 mEq/L calcium is very effective in decreasing plasma calcium levels. Lower calcium baths are likely to cause hypotension[301] and precipitate tetany.

Reduced Bone Resorption

Several agents are available for the management of hypercalcemia. Bisphosphonates inhibit the osteoclast function and number and inhibit bone turn over. They are well tolerated, although nephrotoxicity may develop if administered too quickly.[243] Pamidronate (60–90 mg IV) reduces the plasma calcium in 48 to 72 hours and the effect may last for a month.[243] Zoledronic acid may be even more efficacious.[302] With the advent of bisphosphonates, two older agents have fallen into disfavor. Calcitonin has rapid onset of action but tachyphylaxis occurs within 48 to 72 hours. Plicamycin (formerly mithramycin) has unacceptable liver, renal, and bone marrow toxicity; thus use of this medication has fallen out of favor.

Decreased Gut Calcium Absorption

If endogenous vitamin D overproduction is implicated in the hypercalcemia (e.g., lymphoma, sarcoidosis), corticosteroids will lower the plasma calcium, at least partly by decreasing gut calcium absorption.

Disorders of Magnesium Homeostasis

Disorders of magnesium balance may be the most commonly seen electrolyte abnormalities in the ICU. Hypomagnesemia, the more common disorder, is seen in 12% of hospitalized patients and up to 65% of critically ill patients.[303–305] Because of magnesium's involvement in a host of critical physiologic functions,[306] its derangement can be expected to result in a variety of manifestations.

Normal Magnesium Physiology

The normal adult total body magnesium content is approximately 24 g or 2000 mEq, 50% to 60% of which is found in bones and 40% to 50% is in the intracellular compartment, mainly in the muscles and soft tissues. Only about 1% of total body magnesium is in the extracellular space; the normal concentration range is 1.8 to 2.3 mg/dL (1.5–1.9 mEq/L or about 0.7–1.0 mmol/L).[241] In plasma, 20% to 30% of magnesium is bound to protein, mainly albumin, with the rest (70%–80%) in a form that is filterable across the glomerulus.[241] Magnesium is taken up slowly into cells, under no known hormonal control.

Magnesium is a major constituent of chlorophyll, and therefore green vegetables are a good dietary source. Also, magnesium is found in grains, cereals, seeds, nuts, legumes, meat, and seafood.[241,307] The normal adult diet contains about 300 mg of magnesium.[308] Under normal circumstances, about one-third of that is absorbed in the small bowel; there is some obligatory secretion in that segment as well, along some minor reabsorption downstream in the colon.[303] This results in net absorption of about 100 mg/day. (Magnesium absorption is highly dependent on dietary magnesium content, however, and can increase to up to 70%–80% of dietary intake under conditions of magnesium deprivation.[241]) Unlike calcium absorption, magnesium absorption from the intestine does not seem to depend significantly on vitamin D.[241,309] The small intestinal secretion of magnesium normally amounts to a loss of only about 20 mg/day. With acute or chronic diarrhea, however, GI losses can be substantial.[241]

The filtered load of magnesium (the product of the glomerular filtration rate and the plasma concentration of ultrafilterable magnesium) is about 2500 mg/day. To maintain external magnesium balance, the renal excretion of magnesium must equal the intestinal absorption, or about 100 mg/day. Thus the fractional excretion of magnesium ($Mg_{excreted} \div Mg_{filtered}$) is about 4% under normal conditions.[241] With magnesium depletion, the fractional excretion of magnesium can fall to less than 1%, and with magnesium loading, rise to match the excess in the filtered load.[241] This modulation in magnesium excretion is largely due to changes in plasma magnesium concentration.

The major site of renal magnesium reabsorption (60%–70% of the filtered load) is the TAL. This tubular segment is responsible for most of the modulation in magnesium excretion. Magnesium reabsorption here is largely passive and depends on a lumen-positive voltage generated by the (diuretic-inhibitable) Na-K-2Cl transporter channel and potassium recycling via the renal outer medullary potassium channels.[241] This explains why loop diuretics increase urinary magnesium excretion and tend to cause hypomagnesemia. Other factors that inhibit magnesium reabsorption in the TAL include volume expansion, hypercalcemia, hypophosphatemia, and to a lesser extent, metabolic acidosis. Conversely, volume depletion, hypocalcemia, and metabolic alkalosis increase magnesium reabsorption. About 10% of filtered magnesium is reabsorbed in the distal convoluted tubule. Reabsorption at this site is inhibited by thiazide diuretics and stimulated by potassium-sparing diuretics such as amiloride.[303]

Magnesium plays a vital role in cellular physiology. It catalyzes more than 300 enzymatic reactions and is an integral part of all adenosine triphosphate–dependent reactions.[306] It is involved in synthesis of proteins; energy-rich compounds, electron, and proton transporters; DNA and ribonucleic acid transcription; translation of messenger RNA and regulation of mitochondrial function.[306,310] There is evidence that magnesium helps regulate intracellular calcium concentration, especially in vascular smooth muscle, and thereby affects vascular tone.[310] In vitro studies suggest a role for magnesium in inflammation and immunity, although clinical confirmation is lacking.[310]

Assessment of Body Magnesium Status

Because extracellular magnesium accounts for only about 1% of total body magnesium, plasma magnesium is a poor reflection of body magnesium status. Nonetheless, magnesium status is most commonly assessed by measuring plasma magnesium levels. Like calcium, magnesium circulates in the plasma in bound and free (ionized Mg^{2+}) forms, the latter being the metabolically active form. Determination of ionized magnesium is clinically impractical, and there is no reliable correlation with serum albumin concentration. Moreover, the relationship between low ionized magnesium concentration and increased morbidity and mortality in critically ill patients has yet to be clearly established.[311–313] Thus, the available literature does not support the superiority of the measurement of ionized magnesium over the cheaper and widely available total serum magnesium levels.

The magnesium loading test has been proposed as a more sensitive measure of total body magnesium stores than the plasma magnesium concentration. In theory, magnesium-depleted individuals will translocate more of the administered magnesium load into cells and excrete a lower proportion in the urine over 24 hours.[281,303,310] Because the test requires a 24-hour urine collection and must be limited to patients who have normal renal function and who are not taking medications that affect magnesium excretion (see later text), the test is often impractical in the critical care setting.

Hypomagnesemia

Epidemiology

Patients with malnutrition, chronic alcoholism, those with congestive heart failure using loop or thiazide diuretics, patients in the postoperative period (especially after open heart surgery), and patients with cancer are at higher risk than the general ICU population.[303–305,314]

Causes

The causes of hypomagnesemia can be divided into four main categories: (1) insufficient intake, (2) renal loss, (3) extrarenal loss, and (4) redistribution (Box 54.12).

The renal causes can be distinguished from the others by measuring 24-hour urinary magnesium excretion or, more practically, the fractional excretion of magnesium (FE_{Mg}), calculated as follows[303]:

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100,$$

where U_{Mg} and P_{Mg} are the urine and plasma concentrations of magnesium, respectively, and U_{Cr} and P_{Cr} are the urine and plasma concentrations of creatinine. (P_{Mg} is multiplied by 0.7 as this represents the ultrafilterable fraction of magnesium.) A 24-hour urinary magnesium excretion of more than about 25 mg or FE_{Mg} greater than 2% is consistent with renal hypomagnesemia.[238,303] Most hypomagnesemia in critically ill patients is multifactorial.

Deficient Intake

The prevalence of hypomagnesemia in individuals with chronic alcoholism is approximately 20% to 30%. Hypomagnesemia in alcoholic individuals is multifactorial and results from decreased dietary intake, increased renal loss, and acute pancreatitis.[303] Parenteral nutrition is an important cause of hypomagnesemia in the ICU. Patients receiving parenteral nutrition have a higher daily magnesium requirement for unknown reasons.[238]

• BOX 54.12 Causes of Hypomagnesemia

Deficient Intake
- Magnesium-deficient parenteral nutrition
- Protein-calorie malnutrition
- Alcoholism

Renal Loss
- Drug-induced
  - Loop diuretics
  - Thiazide diuretics
  - Aminoglycosides
  - Amphotericin b
  - Cis-platinum
  - Cetuximab
  - Foscarnet
  - Pentamidine
- Volume Expansion
- Osmotic diuresis (e.g., hyperglycemia)
- Alcohol
- Hypercalcemia
- Tubular dysfunction
  - Recovery from acute tubular necrosis
  - Bartter syndrome
  - Gitelman syndrome

Gastrointestinal
- Small intestine resection
- Inflammatory bowel disease
- Jejunoileal bypass surgery
- Diarrhea
- Steatorrhea
- Malabsorption syndromes
- Proton pump inhibitors

Redistribution
- Acute pancreatitis
- Hungry bone syndrome

Gastrointestinal Losses

Diarrheal fluid contains a high concentration of magnesium—up to 16 mg/dL[238,310]—and hypomagnesemia is a common finding in patients with acute or chronic diarrhea from any cause. Because intestinal absorption of magnesium occurs primarily in jejunum and ileum, conditions such as celiac disease, inflammatory bowel disease, extensive small bowel resection, and jejunoileal bypass surgery for obesity are frequently associated with intestinal magnesium wasting.[303] The prolonged use of proton pump inhibitors increases the risk of hypomagnesemia in the general population[315] as a result of reduced GI absorption; however, the exact mechanism remains unclear.[316]

Renal Losses

Medications are perhaps the most important cause of renal magnesium wasting in critically ill patients. Loop diuretics are commonly used at high doses. Aminoglycosides may cause asymptomatic hypomagnesemia 3 to 4 days after initiation of therapy; typically

it resolves after cessation of therapy.[238,317] Almost all patients who receive cisplatin develop renal magnesium wasting and hypomagnesemia, which may persist for months after discontinuation of therapy.[318] Most patients who receive IV pentamidine therapy develop renal magnesium wasting and hypomagnesemia that may last for 1 to 2 months after cessation of the therapy.[238] The renal magnesium wasting associated with chronic alcohol use may take up to a month to resolve with abstinence.[303]

Redistribution

Hypomagnesemia is reported in up to 20% of patients with acute pancreatitis.[305,310] The proposed mechanism is saponification of necrotic fat with magnesium and calcium. The mechanism of hypomagnesemia with the hungry bone syndrome (following parathyroidectomy for hyperparathyroidism) is rapid bone uptake of magnesium during remineralization.

Clinical Manifestations

Hypomagnesemia in critically ill patients has been associated with a twofold increase in mortality, even after adjustment for severity of illness.[319] (The observation that magnesium supplementation has not been shown to improve outcome[303] suggests that hypomagnesemia may be a marker for pejorative conditions not captured by severity of illness scores.)

The signs and symptoms of hypomagnesemia are cardiovascular, neuromuscular, and metabolic and are shown in Box 54.13.[238,303,306,310] There is little evidence that hypomagnesemia is associated with arrhythmias in otherwise healthy individuals. In the setting of acute myocardial ischemia, however, even mild hypomagnesemia has been associated with increased frequency of ventricular arrhythmias.[303] Results of recent large clinical trials, however, have shown no benefit to magnesium supplementation in this setting in the absence of overt hypomagnesemia.[310] Torsades de pointes is a malignant ventricular arrhythmia associated with magnesium deficiency or drugs that prolong the QT interval. Magnesium is the treatment of choice. Magnesium supplementation after cardiopulmonary bypass may reduce the frequency of ventricular ectopy.

The hypocalcemia associated with hypomagnesemia is caused by both hypoparathyroidism and bone resistance to PTH. Hypokalemia is caused by hypomagnesemia-induced renal potassium wasting and will not resolve until the hypomagnesemia is corrected.[320,321]

Treatment

In patients who have malignant cardiac arrhythmias (ventricular fibrillation or torsades de pointes) or seizure attributed to hypomagnesemia, intravenous magnesium must be given immediately (2 g of magnesium sulfate over minutes).

Less urgent cases, but those in which signs and symptoms are present, may be treated with magnesium sulfate 6 g IV in the first 24 hours followed by 3 to 4 g daily for the next 2 to 6 days.[238,303,310] Because translocation of magnesium into cells is a slow process and because urinary excretion is proportional to the plasma magnesium level, more rapid infusion rates are associated with urinary magnesium wasting that defeats the purpose of the therapy. Effective intravenous infusions should be given over 8 to 12 hours.[303] For patients with impaired renal function, the dose should be reduced by 50% to 75% and serum magnesium levels should be monitored frequently. Patients should be monitored closely for symptoms and signs of hypermagnesemia (see the following text).

Patients with refractory hypokalemia in the setting of hypomagnesemia, who are receiving high doses of potassium, must be monitored closely for the development of hyperkalemia once the magnesium has been replenished.

For mild asymptomatic hypomagnesemia, patients who can tolerate oral medication should receive oral magnesium salts (e.g., magnesium chloride, 500 mg slow-release tablets, 10–12 per day in divided doses). High doses of oral magnesium salts may cause diarrhea.

• BOX 54.13 Clinical Manifestations of Hypomagnesemia

Cardiovascular

Ventricular arrhythmias
- Torsades de pointes
- Ventricular fibrillation; premature ventricular contractions
- Increased digitalis toxicity

Conduction disturbances
- Prolonged QT interval
- Prolonged QRS duration
- ST depression
- Peaked T wave

Neuromuscular
- Muscle weakness
- Tetany
- Horizontal and vertical nystagmus
- Choreoathetoid movements
- Seizures

Metabolic

Hypokalemia, refractory
Hypocalcemia, refractory

Hypermagnesemia

Causes

Hypermagnesemia is much less common than hypomagnesemia. Patients with normal renal function have a prodigious capacity to excrete excess magnesium through the kidneys.[238] Thus hypermagnesemia is seen only in patients with compromised renal function who are receiving enteral or parenteral magnesium, or in patients with normal renal function receiving massive exogenous magnesium (e.g., treatment for preeclampsia and eclampsia).[238] The causes of hypermagnesemia are shown in Box 54.14.

• BOX 54.14 Causes of Hypermagnesemia

Patients With Renal Insufficiency

Magnesium-containing antacids (e.g., magnesium aluminum hydroxide)
Magnesium-containing laxatives or enemas (e.g., magnesium citrate)

Patients With Normal Renal Function

Treatment of preeclampsia or eclampsia
Treatment of hypomagnesemia

Miscellaneous

Hypothyroidism
Hyperparathyroidism
Addison disease
Lithium treatment

• BOX 54.15 Clinical Manifestations of Hypermagnesemia

Cardiovascular
- Hypotension
- Facial flushing
- Bradycardia
- Sinoatrial or atrioventricular heart block
- Asystole

Gastrointestinal
- Nausea and vomiting
- Ileus

Neuromuscular
- Hyporeflexia
- Flaccid skeletal muscle paralysis
- Respiratory muscle weakness and paralysis
- Lethargy
- Coma

Urinary retention

Clinical Manifestations

The clinical manifestations of hypermagnesemia (Box 54.15) are largely due to the effect on the heart, nerve, and smooth muscle. Initial manifestations, with plasma concentrations of 4 to 6 mg/dL, include nausea and vomiting, hypotension, and flushing. More severe effects, including death,[322] are seen with levels exceeding 6 mg/dL.

Treatment

Treatment of hypermagnesemia depends on the severity of symptoms and the patient's renal function. Patients with adequate renal function and mild asymptomatic hypermagnesemia require no treatment except to remove all sources of exogenous magnesium. The half-time of elimination of magnesium is about 28 hours.[238] Magnesium excretion may be enhanced by saline solution infusion and the use of loop diuretics.[238] (Care must be taken to prevent hypokalemia and metabolic alkalosis.) Patients with symptomatic hypermagnesemia, especially those with cardiovascular manifestations, require urgent treatment. The recommended therapy is calcium gluconate 1 g IV over 5 minutes.

Patients with acute or chronic renal failure and symptomatic hypermagnesemia require dialysis to remove excess magnesium. Hemodialysis removes magnesium efficiently, yielding a 30% to 50% reduction in predialysis serum magnesium levels after a 3- to 4-hour treatment.[238]

Phosphorus

Phosphorus has an essential role in normal physiology. It is necessary for skeletal integrity; energy economy (formation of high-energy phosphate bonds); nucleic acid, lipid, and protein structure; cell signaling; and buffering.[241] It is not surprising, therefore, that disorders of phosphorous homeostasis have diverse manifestations.[323–325] Hypophosphatemia is considerably more common in hospitalized and critically ill patients than hyperphosphatemia.

Normal Phosphorus Homeostasis

Total body phosphorus amounts to about 700 g in an adult. About 85% resides in the skeleton, about 15% in soft tissues, and only about 1% in blood.[240] Circulating phosphorus is mostly in the form of inorganic phosphates. The normal plasma concentration of phosphorus is 2.5 to 4.5 mg/dL, also expressed as a phosphate concentration of 0.9 to 1.45 mmol/L. (Phosphate concentration should not be expressed in milliequivalents per liter because the average valence of plasma phosphates, a mixture of HPO_4^{2-} and $H_2PO_4^-$, changes with pH.[326]) Of that circulating phosphorus, about 75% is free and ultrafilterable; 25% is protein bound.[241]

A normal adult diet includes about 1000 mg of phosphorus per day. Stool contains about 300 mg, so the net absorption (mostly in the small intestine under the influence of vitamin D) is about 70%. The dietary and secreted phosphorus may be bound into insoluble, nonabsorbable salts by cations such as Al^{3+}, Ca^{2+}, and Mg^{2+}. Thus the kidney is responsible for excreting about 700 mg phosphorus per day. Almost all phosphorus reabsorption takes place in the proximal tubule. The most important regulators of renal phosphorus excretion are PTH, fibroblast growth factor (FGF)-23, and dietary phosphorus content. PTH increases phosphorus excretion.[240] FGF-23, a phosphatonin released by osteocytes and osteoblasts in bone, increases urinary phosphorus excretion.[327] Renal excretion of phosphorus is proportional to the dietary intake. Other factors that increase renal phosphorus excretion include extracellular volume expansion, acute hypercalcemia, diuretics, and glucocorticoids.[240,241] Acid-base disorders have a variable effect on phosphorus reabsorption depending on their direction and duration[240,241] with one exception: respiratory alkalosis causes a marked decrease in renal phosphorus excretion by causing redistributive hypophosphatemia[324] (see the following text).

Phosphorus homeostasis depends on PTH, FGF-23, and vitamin D. PTH and FGF-23 cause phosphaturia by decreasing renal proximal tubule reabsorption. Active vitamin D inhibits PTH release. Vitamin D activation (1-α hydroxylation) in the kidney is inhibited by FGF-23 and hyperphosphatemia. This, in turn, reduces intestinal phosphorus absorption and allows increased PTH secretion, causing phosphaturia and returning plasma phosphorus toward normal. Hypophosphatemia reverses this physiology, allowing increased gut absorption and reduced renal excretion of phosphorus.

Hypophosphatemia

Hypophosphatemia is common in critically ill patients. It has been reported in 29% of adult surgical patients (and 45% of patients with one or more risk factors for hypophosphatemia), and—liberally defined—in 76% of pediatric ICU patients.[328] Patients with malnutrition, uncontrolled diabetes mellitus, sepsis, and chronic alcoholism are at high risk for hypophosphatemia.[329] It is associated with a marked increase in mortality in patients with sepsis,[330] and serum phosphorus concentration is inversely correlated with APACHE II (acute physiology, age, and chronic health evaluation) score after liver resection.[331] In these situations, the serum phosphorus concentration probably is a marker of severity of illness. If severe, however, hypophosphatemia itself may cause serious complications.

Causes of Hypophosphatemia

The causes of hypophosphatemia classically are divided into three general categories: (1) redistribution from the extracellular to the intracellular space, (2) increased renal excretion, and (3) decreased intestinal absorption (Box 54.16). It is important to recognize that many factors have several different effects on phosphorus homeostasis.

• BOX 54.16 Causes of Hypophosphatemia

Redistribution
Acute respiratory alkalosis
Refeeding syndrome
Treatment of diabetic ketoacidosis
Hungry bone syndrome—postparathyroidectomy
Leukemia

Increased Renal Excretion
Hyperparathyroidism
Vitamin D deficiency or resistance
Volume expansion
Postobstructive diuresis
Recovery from acute tubular necrosis
Fanconi syndrome
Postrenal transplantation
Drugs
  Acetazolamide
  Corticosteroids
Inherited disorders
Tumor-induced osteomalacia

Decreased Intestinal Absorption
Malnutrition
Phosphate-binding medications
Chronic diarrhea
Chronic alcoholism

• BOX 54.17 Clinical Manifestations of Hypophosphatemia

Skeletal muscle
  Weakness
  Rhabdomyolysis
Decreased cardiac output
Hematologic
  Erythrocytes
  Decreased 2,3-diphosphoglycerate
  Decreased tissue oxygen delivery
  Spherocytosis
  Hemolysis
  Impaired leukocyte function
  Impaired platelet function
Neurologic
  Anorexia
  Irritability
  Confusion
  Paresthesias
  Ataxia
  Seizure
  Coma
Skeletal
  Bone pain
  Pseudofractures
  Osteomalacia
Insulin resistance

Redistribution
Respiratory alkalosis causes intracellular phosphate shift (by stimulating glycolysis) and can cause severe symptomatic hypophosphatemia. Respiratory alkalosis is commonly encountered in ICU patients owing to sepsis, liver failure, and in patients requiring mechanical ventilation; in the last case, the degree of hypophosphatemia is proportional to the pH.[238,332] Sepsis is commonly associated with hypophosphatemia, probably owing to hyperventilation and respiratory alkalosis. Rapid refeeding of patients with malnutrition may result in significant hypophosphatemia owing to an insulin-mediated intracellular phosphate shift. In one study of ICU patients, refeeding hypophosphatemia developed in 34% of patients after 48 hours of starvation and was predicted by the prealbumin concentration. Profound hypophosphatemia (<1 mmol/dL) occurred in 10% of patients.[333] Patients with anorexia nervosa, uncontrolled diabetes mellitus, chronic malnutrition, and chronic alcoholism are at a particularly high risk of developing refeeding syndrome. Leukemia in the leukemic phase[334] and with rapid leukocyte reconstitution after bone marrow transplant[335] have been reported to cause severe redistributive hypophosphatemia.

Diabetic ketoacidosis is associated with phosphorus efflux from cells and increased urinary phosphate excretion, resulting in severe total body phosphorus depletion (often with a deceptively normal presenting serum phosphorus concentration).[324] Initiation of insulin therapy in such patients results in intracellular phosphate shift and can result in profound, symptomatic hypophosphatemia.[324]

Increased Renal Excretion
Any cause of primary hyperparathyroidism will cause phosphaturia and tend to cause hypophosphatemia. Hyperparathyroidism caused by hypocalcemia or vitamin D deficiency or resistance is similarly associated with hypophosphatemia. The exception is the secondary hyperparathyroidism of chronic kidney disease, in which hyperphosphatemia owing to decreased renal phosphorus elimination is characteristic. Vitamin D deficiency or resistance also causes hypophosphatemia from decreased intestinal phosphate absorption. Extracellular volume expansion increases the filtered phosphorus load and dilutes the luminal concentration of phosphorus, resulting in phosphaturia. Ethanol and glycosuria both decrease proximal tubule phosphate reabsorption.[238,324] All diuretic drugs, but particularly those with proximal tubular effects such as acetazolamide and, to a lesser degree, thiazides, cause phosphaturia.

Decreased Intestinal Absorption
Salts of Al^{3+} and Ca^{2+}, formulated for oral administration as antacids or as phosphate-binding medications, can cause malabsorptive hypophosphatemia. Chronic diarrhea and steatorrhea may cause reduce intestinal phosphate absorption directly and by way of vitamin D deficiency and cause hypophosphatemia.

The hypophosphatemia commonly associated with chronic alcohol ingestion is multifactorial. Dietary phosphorus deficiency, malabsorption, antacid ingestion, hypocalcemia and secondary hyperparathyroidism, hypomagnesemia, and an ethanol-induced renal tubular defect all have been implicated.[324]

Clinical Manifestations

Important clinical manifestations of hypophosphatemia are shown in Box 54.17. Most patients are asymptomatic until plasma phosphorus falls below 1.5 mg/dL or about 0.5 mmol/L. The most severe manifestations, such as hemolysis, spontaneous rhabdomyolysis, seizure, or coma, are not commonly seen with phosphorus above 1 mg/dL (0.3 mmol/L). Acute clinical manifestations are thought to be largely due to altered cellular energy economy.[238,240,323,324]

Treatment

The therapy of hypophosphatemia starts with its prevention. In critically ill patients, this depends on recognition and correction of the factors that lead to hypophosphatemia. The astute clinician will be able to anticipate the development of hypophosphatemia (in refeeding, for example), monitor the patient appropriately, and supplement phosphorus accordingly. Patients receiving total parenteral nutrition should receive adequate phosphorus for their level of renal function (see Chapter 78).[326]

The exact method of phosphorus supplementation in hypophosphatemia depends on the severity of the disturbance and the patient's underlying condition. In mild to moderate hypophosphatemia (>1.5 mg/dL or about 0.5 mmol/L) oral replacement is usually sufficient. Skim milk is an excellent source of phosphorus and provides 900 mg/L of inorganic phosphate. In patients who cannot tolerate milk, oral sodium phosphate, formulated to provide 250 mg of phosphate in each tablet, can be used. (Fleet Phospho soda was once recommended for phosphate supplementation but is no longer available due to safety concerns.[260]) Supplementation should continue for several days to replenish phosphorus deficits adequately. Administration of sufficient doses of oral phosphorus preparations very commonly causes diarrhea, limiting its usefulness.

Patients with severe hypophosphatemia (<1.5 mg/dL), or those for whom the enteral route is not an option, require intravenous phosphorus repletion. In such patients, the recommended dose is 2.5 to 5.0 mg (0.08–0.16 mmol)/kg body weight over 6 hours; doses at the higher end of the range are reserved for profound, symptomatic hypophosphatemia.[240,326] A recent study used a more aggressive, weight-based protocol in critically ill patients and found it to be safe and effective.[336] Clinicians should recognize that the administered intravenous phosphorus can complex with circulating calcium, leading to a decrease in ionized calcium (with attendant hypotension and tetany) and metastatic calcification. The use of potassium salts of phosphate for repletion of phosphorus deficits has been associated with dangerous hyperkalemia. For that reason, potassium deficits and phosphorus deficits should be treated separately.[326]

Hyperphosphatemia

Hyperphosphatemia (plasma phosphorus >5.0 mg/dL or a phosphate concentration >1.6 mmol/L) most often is associated with renal dysfunction. Massive influx of phosphorus into the extracellular space, however, either from endogenous sources or exogenous, can overwhelm normal renal excretory mechanisms and lead to severe hyperphosphatemia.

Causes of Hyperphosphatemia

Hyperphosphatemia may be caused by (1) redistribution of phosphorus from the intracellular to the extracellular space, (2) increased phosphorus intake, and (3) decreased renal excretion of phosphorus (Box 54.18). It is important to recognize that most hyperphosphatemia is multifactorial.

• BOX 54.18 Causes of Hyperphosphatemia

- Redistribution
  - Tumor lysis syndrome
  - Rhabdomyolysis
  - Pancreatitis
  - Respiratory acidosis
  - Lactic acidosis
  - Diabetic ketoacidosis
- Increased Intake
  - Phosphate-containing enemas and laxatives
  - Intravenous phosphate
  - Hypervitaminosis D
- Decreased renal excretion
  - Acute renal failure
  - Chronic kidney disease
  - Hypoparathyroidism
- Pseudohyperphosphatemia

Redistribution

Hyperphosphatemia is a common complication of the tumor lysis syndrome.[72] Similarly, rhabdomyolysis often is associated with hyperphosphatemia, especially when it is complicated by acute renal failure.[74,337] Less commonly recognized causes of redistributive hyperphosphatemia include acute and chronic respiratory acidosis, acute pancreatitis,[338] DKA,[339] and lactic acidosis.[340]

Increased Intake

Exogenous administration of phosphorus is unlikely to cause hyperphosphatemia unless renal function is compromised. Several cases have been reported of potentially life-threatening hyperphosphatemia and hypocalcemia after the use of phosphate-containing laxatives and enemas, especially in children and elderly patients.[261,263,264,341,342] Overly aggressive parenteral phosphorus supplementation can cause hyperphosphatemia. Hypervitaminosis D causes increased intestinal uptake of phosphorus and a decrease in PTH, both of which predispose to hyperphosphatemia.

Decreased Renal Excretion

Acute renal failure is associated with elevated phosphate levels caused by the inability of the kidneys to excrete phosphate load. This is particularly pronounced in patients in whom acute renal failure is caused by the tumor lysis syndrome or rhabdomyolysis. Advanced chronic kidney disease (glomerular filtration rate < 25 mL/min) commonly is associated with hyperphosphatemia. Such patients are particularly susceptible to developing severe and life-threatening hyperphosphatemia if they are exposed to an acute increase in serum phosphate levels. Hypoparathyroidism of any cause is associated with impaired renal phosphorus excretion.

Pseudohyperphosphatemia

Spurious increases in the measured plasma phosphorus concentration are reported to be caused by contamination of the blood sample with phosphate-buffered saline solution as a diluent for heparin[343] or during sample processing by the laboratory.[344] Even microliter volumes of the contaminant can cause significant elevations in the measured phosphorus.[343] Paraproteinemia can also cause psuedophyperphosphatemia.

Clinical Manifestations

Phosphate complexes with circulating calcium, reducing the concentration of ionized calcium. Thus most of the clinical consequences of hyperphosphatemia are those of hypocalcemia (see previous text). In addition, ectopic deposition of calcium phosphate salts can occur, especially when the calcium-phosphorus product exceeds 70 mg/dL.[240] Such ectopic calcification in the heart can cause conduction and rhythm disturbances.[345]

Because phosphate is an "unmeasured ion," hyperphosphatemia causes increases in the anion gap. Extreme hyperphosphatemia can cause shocking elevations in the anion gap. One case of hyperphosphatemia from Phospho-Soda intoxication (serum phosphorus 62.5 mg/dL) was associated with an anion gap of 51 mmol/L.[346] To estimate the contribution of phosphorus to the anion gap, one must know not only the plasma concentration of phosphorus but also the pH, because the valence of phosphate varies with pH—from 1.8 mEq/mmol at pH 7.4 to 1.6 mEq/L at pH 7.0.[326] Because extreme hyperphosphatemia can be caused by lactic or ketoacidosis (see previous text), an elevated anion gap in the setting of hyperphosphatemia should never be attributed to the hyperphosphatemia itself without further investigation.

Treatment

Treatment of hyperphosphatemia consists of reducing the phosphate intake and enhancing the removal of excess phosphate. If the patient is taking an oral diet, dietary phosphate should be restricted to less than 800 mg/day. Oral phosphate binders can be added with meals to decrease intestinal phosphate absorption.

Patients with normal renal function can be treated with saline solution diuresis to increase renal phosphate excretion. Acetazolamide can be added to enhance phosphaturia, taking care to avoid a metabolic acidosis. Patients with severe hyperphosphatemia with coexisting renal failure may require renal replacement therapy in the form of intermittent or continuous hemodialysis.

Key Points

- Acid-base disorders often provide a window into underlying pathology. Optimal diagnosis of acid-base disorders requires familiarity with the rules of normal compensation and the pitfalls characteristic of critical illness.
- Acute hyperkalemia may result from exogenous potassium administration or redistribution from cells. Acute hypokalemia always is caused by redistribution.
- Patients, particularly women, are predisposed to catastrophic hyponatremia if hypotonic fluids are administered in the postoperative period.
- The treatment of acute symptomatic hyponatremia is largely independent of its cause, whereas the treatment of chronic hyponatremia depends critically on the underlying pathophysiology.
- Hypernatremia in hospitalized patients should be considered iatrogenic, reflecting insufficient recognition of the causes of water loss and inadequate water replacement in vulnerable patients.
- Plasma calcium concentration, corrected for the plasma albumin concentration, correlates poorly with ionized calcium in critically ill patients. If possible, ionized calcium should be directly measured when considering disorders of calcium homeostasis.
- The clinical manifestations of many metabolic disorders have common features (e.g., hypocalcemia, hypomagnesemia, hyperphosphatemia, metabolic alkalosis), relating to their overlapping pathophysiology.

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Review Questions

1. Which of the following statements regarding the treatment of lactic acidosis with sodium bicarbonate is most accurate?
   a. Administration can result in hypercalcemia.
   b. There is a risk of paradoxical worsening of intracellular acidosis.
   c. Treatment of lactic acidosis in patients with arterial pH less than 7.3 has been shown to improve hemodynamic parameters but not survival.
   d. Administration is likely to reduce lactate production.
   Answer: b. Treatment of lactic acidosis with sodium bicarbonate will cause an increase in carbon dioxide generation, which may lower intracellular pH. By raising extracellular pH, bicarbonate administration will reduce ionized calcium (answer a incorrect). Despite the theoretical appeal of raising extracellular pH, studies have not shown any improvement in hemodynamic parameters or survival (answer c incorrect). By causing systemic alkalinization, bicarbonate administration is likely to cause an increase in lactate generation rate (answer d incorrect).
2. You are evaluating a 50-year-old patient in the intensive care unit (ICU). The patient was admitted with sepsis from a urinary source and has been intubated and receiving pressors (norepinephrine and dopamine) for the past 3 days. His past medical history includes diabetes and benign prostatic hyperplasia.

   On examination his vital signs are within normal limits and he appears to be comfortable and in no distress. His laboratory findings are as follows: sodium 143 mEq/L, potassium 5.8 mEq/L, chloride 108 mEq/L, bicarbonate 24 mEq/L, glucose 90 mg/dL, blood urea nitrogen (BUN) 12 mg/dL, and creatinine 0.9 mg/dL (baseline 0.7 mg/dL). All electrolyte values were normal yesterday. Arterial blood gas shows pH 7.38, partial pressure of carbon dioxide (P_{CO_2}) 41 mm Hg, and partial pressure of arterial oxygen (Pa_{O_2}) 180 mm Hg. Urinary electrolytes include the following: urinary sodium 87 mEq/L, urinary potassium 35 mEq/L, and urinary chloride 110 mEq/L. Which of the following is the most likely explanation for the elevated potassium level?
   a. Norepinephrine treatment
   b. Type 4 renal tubular acidosis (RTA)
   c. Starvation ketosis
   d. Pseudohyperkalemia
   Answer: d. There are various causes for hyperkalemia in critically ill patients, including excessive potassium load, translocation of potassium across cellular membrane, and inability to eliminate excess balance. Norepinephrine treatment has not been associated with hyperkalemia (as opposed to succinylcholine or digitalis) (answer a incorrect), and the presence of normal laboratory findings on the previous day makes intravenous (IV) RTA less likely (answer b incorrect). There is no evidence of ketosis with no acidosis, no anion gap, and normal serum glucose (answer c incorrect). Pseudohyperkalemia is the most likely explanation because of normal laboratory findings the day before without change in clinical status. Pseudohyperkalemia has several possible causes, including hemolysis and fist clenching with a tourniquet in place during phlebotomy (answer d correct).
3. A 55-year-old man with small cell lung cancer and syndrome of inappropriate antidiuretic hormone secretion (SIADH) was admitted with seizure and hyponatremia with a sodium level of 107 mmol/L on admission. A 3% sodium chloride (NaCl) infusion is started at 80 mL/h and after 6 hours the sodium level is 122 mmol/L.
   Which of the following next steps is most appropriate at this point?
   a. Stop the 3% NaCl infusion and monitor sodium level every 4 hours.
   b. Stop the 3% NaCl infusion and start a 0.9% infusion at 160 mL/h.
   c. Stop the 3% NaCl and give hydrocortisone 100 mg 3 times a day.
   d. Stop the 3% NaCl, start 5% dextrose in water (D_5W) and desmopressin to lower the sodium level.
   Answer: d. Patients with acute symptomatic hyponatremia need to be treated with an infusion of 3% saline solution to rapidly increase the plasma sodium concentration and prevent cerebral edema. The sodium goal is 6 mmol/L in the first 24 hours as a more rapid rise is unnecessary and can induce osmotic demyelination syndrome. This patient had a very rapid increase in the sodium level; therefore, the sodium concentration must be lowered. This can be best achieved using desmopressin and D_5W (choice d). Monitoring chemistry (choice a), administration of normal saline solution (answer b) may result in even more rapid increase in sodium. Hydrocortisone (answer c) has no role.
4. Which of the following is not a preferred treatment for hypercalcemia?
   a. Plicamycin
   b. Calcitonin
   c. Hemodialysis
   d. Zoledronic acid
   Answer 4: a Treatment of hypercalcemia includes calcium elimination and reduced bone resorption. Zoledronic acid is one of the most efficacious bisphosphonates used to treat hypercalcemia (answer d incorrect). Calcitonin rapidly reduces calcium levels but its effects dissipate within 72 hours (answer b incorrect). Hemodialysis can be used in certain cases to treat refractory hypercalcemia (answer c). Despite its effect on calcium level, the use of plicamycin is discouraged because of its side effect profile (renal liver and bone marrow toxicity) (answer a correct).
5. Which of the following electrolyte abnormalities can cause an elevated anion gap?
   a. Hypercalcemia
   b. Hypernatremia
   c. Hyperphosphatemia
   d. Hypermagnesemia
   Answer: c. The anion gap is the difference between measurements of positively charged and negatively charged particles. In cases of elevated calcium (answer a), sodium (answer b), or magnesium (answer d), there is a concomitant increase in measured negative charges, thus not increasing the anion gap. The presence of hyperphosphatemia can cause large elevations in the anion gap because it is an unmeasured anion.
6. A cachectic homeless man is admitted to the intensive care unit (ICU) obtunded, hypotensive, and hypoxemic. Initial plasma laboratory findings are as follows: sodium 130 mmol/L, potassium 3.6 mmol/L, chloride 96 mmol/L, bicarbonate 13 mmol/L, glucose 62 mg/dL, blood urea nitrogen (BUN) 48 mg/dL, creatinine 1.8 mg/dL. A chest x-ray demonstrates

several spiculated nodules within both lung fields. He is intubated and treatment with intravenous normal saline solution containing dextrose, thiamine, and folic acid is started. Which of the following electrolyte disturbances would the patient be at the highest risk of developing with the described treatment?

a. Hypernatremia
b. Hyperkalemia
c. Hypermagnesemia
d. Hypercalcemia
e. Hypophosphatemia

Answer: e. This patient has risk factors and physical findings of long-standing malnutrition and is at risk of developing the refeeding syndrome as a result of endogenous insulin secretion in response to dextrose. Hypernatremia is unlikely to develop with isotonic fluids (answer a incorrect), and insulin-mediated potassium entry into cells would most likely result in hypokalemia rather than hyperkalemia (answer b incorrect). Hypermagnesemia would likely not occur without excessive magnesium ingestion (answer c incorrect), and as the metabolic acidosis (likely ketoacidosis) corrects, the blood pH will rise, thus placing him at risk for hypocalcemia owing to displacement of albumin-bound protons with calcium (answer d incorrect). Hypophosphatemia can occur as the result of insulin-mediated phosphorus entry into cells (answer e correct), and this may be life-threatening if appropriate replenishment is not provided.

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Acute Diabetic Emergencies, Glycemic Control, and Hypoglycemia

FARAH MORGAN AND STEVEN T. KAUFMAN

CHAPTER OUTLINE

Diabetes Mellitus: Epidemiology and Classification

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State
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- Pathophysiology
- Precipitating Factors
- Presentation
- Diagnosis
- Management
- Prevention

Glycemic Control in the Intensive Care Unit
- Epidemiology and Significance of Hyperglycemia
- Synopsis of Trials of Glycemic Control
- Intravenous Insulin Protocols
- Technical Issues in Measuring Glucose
- Current Guidelines for Glycemic Control

The Effect of Parenteral Nutrition, Enteral Nutrition, and Glucocorticoids on Glycemic Control
- Subcutaneous Insulin Use in the Hospitalized Patient

Hypoglycemia
- Physiologic Response to Hypoglycemia
- Hypoglycemia in Patients With Diabetes or Who Receive Insulin
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Diabetes Mellitus: Epidemiology and Classification

In 2015, 415 million people worldwide were living with diabetes mellitus (DM) with a projected increase to over 642 million by 2040.[1] Twelve percent of the global health expenditure is spent treating DM and its complications,[1] yet despite this expenditure on health care, 5 million people died from DM in 2015.[1] In the United States, 29.1 million people have DM but more than 25% of them are not yet diagnosed.[2] An additional 86 million people have prediabetes, and 90% of these patients are unaware of the 15% to 30% risk of developing DM over the next 5 years.[2] The medical costs for those in the United States with DM are 2.3 times higher than for those who do not have DM.[3] Diabetes remains the primary cause of all new cases of kidney failure and nontraumatic lower extremity amputation and is the seventh leading cause of death in the United States.[4,5]

The 2016 American Diabetes Association Guidelines classified diabetes into the following categories[6]:

1. Type 1 diabetes
2. Type 2 diabetes
3. Gestational diabetes
4. Specific types of diabetes related to other causes

Patients with DM have a relative insulin deficiency (type 2 DM) or absolute insulin deficiency (type 1 DM). Type 1 DM is caused by autoimmune β-cell destruction, which typically leads to absolute insulin deficiency. Type 2 DM is caused by insulin resistance in the liver, skeletal muscle, and adipose tissue along with a decline in insulin secretion that results in a state of relative insulin deficiency. This accounts for 90% to 95% of DM in the United States. Obesity, lack of physical activity, and unhealthy diet increase the risk of type 2 DM. Although most type 2 DM is diagnosed in adults, children are at increased risk as well owing to the formerly stated risk factors. The rise of type 2 DM in those younger than 20 years of age parallels the increased prevalence in obesity in children.[4,7] Low socioeconomic status and members of minority races and ethnic groups—African Americans, Native Americans, Hispanics, Pacific Islanders, and Asian Americans—are at greatest risk for developing type 2 DM and have a higher risk of developing the microvascular complications of diabetes.[8]

Gestational diabetes (GDM) represents diabetes diagnosed in the second or third trimester of pregnancy that is not overt DM,[6] whereas women detected to have DM in their first trimester would be considered to have pregestational type 2 DM.[6] Women with GDM have up to a 69% risk of GDM with subsequent pregnancies[9] and a 17% to 63% risk of developing type 2 DM within 5 to 16 years.[9,10] All women with a history of GDM should undergo lifelong screening for type 2 DM[6, 9,10] beginning with glucose testing at 6 to 8 weeks postpartum and continuing every 3 years.[10]

Other forms of diabetes include neonatal diabetes, maturity-onset diabetes of the young, diabetes related to abnormalities in the exocrine pancreas, such as cystic fibrosis, drug-induced diabetes, partial or total pancreatectomy, or pancreatitis.[6]

Insulin deficiency can be absolute resulting from β-cell destruction (autoimmune, pancreatitis, or surgical excision) or relative resulting from insulin resistance.[11] In the absence of insulin (relative or absolute deficiency) tissues are unable to use glucose and sense a state of "starvation," leading to further increase in glucose through stimulation of glycogenolysis and gluconeogenesis. In this setting, amino acids and free fatty acids (FFAs) serve as fuel for gluconeogenesis resulting in ketogenesis.[12] The actions of insulin are shown in Box 55.1.

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), the two hyperglycemic emergencies in patients with diabetes,[13] are states of decompensated hyperglycemia. In DKA, insulin deficiency and increased counterregulatory hormones lead to abnormal lipid and carbohydrate metabolism that results in hyperglycemia and ketosis.[13] The diagnosis of DKA is made when the following criteria are met: serum glucose above 250 mg/dL, serum pH less than 7.3, bicarbonate less than 18 mEq/L, positive ketones, and anion gap above 10 mEq/L.[13]

HHS is a state of relative insulin deficiency with adequate insulin to prevent lipolysis and ketogenesis. A decrease in pH related to ketone formation causes the lethargy and nausea of DKA. Without these symptoms, patients with HHS present with more pronounced hyperglycemia, dehydration, and hyperosmolality.[13] The diagnosis of HHS is made when the following criteria are met: plasma glucose greater 600 mg/dL, pH greater than 7.3, bicarbonate greater than 18 mEq/L, small or negative ketones, and serum osmolality greater than 320 mOsm/kg.[13] Table 55.1 lists the diagnostic criteria for DKA and HHS.

Epidemiology

DKA is a possible fatal complication of uncontrolled DM, particularly type 1 DM. Mortality for DKA has decreased to less than 1% but reaches 5% for elderly adults or those with life-threatening illnesses.[13,14] DKA account for 500,000 hospitalizations per year with patients younger than 45 years of age having far higher hospitalization rates compared with older patients.[15,16] The 3.4-day average length of hospital stay for DKA causes a significant economic

• BOX 55.1 Actions of Insulin on Target Organs

Adipose Tissue
Increased glucose entry
Increased fatty acid synthesis
Increased glycerol phosphate synthesis
Increased triglyceride deposition
Activation of lipoprotein lipase
Inhibition of hormone-sensitive lipase

Liver
Decreased ketogenesis
Increased protein synthesis
Increased lipid synthesis
Decreased glucose output via increased glycogen synthesis and decreased gluconeogenesis

Muscle
Increased glucose entry
Increased glycogen synthesis
Increased amino acid uptake
Increased protein synthesis in ribosomes
Decreased protein catabolism
Decreased release of gluconeogenic amino acids
Increased ketone uptake
Increased K^+ uptake

General
Increased cell growth

From Barrett KE, Barman SM, Boitano S, et al. Endocrine functions of the pancreas and regulation of carbohydrate metabolism. In: Barrett KE, Barman SM, Boitano S, Brooks H, eds. Ganong's Review of Medical Physiology. *23rd ed. New York: McGraw-Hill; 2010, chap. 21, 316–336.*

TABLE 55.1 Diagnostic Criteria for Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Criterion	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.3	7–7.24	<7	>7.3
Serum bicarbonate (mEq/L)	15–18	10–<15	<10	>15
Urine ketones[a]	Positive	Positive	Positive	Small
Serum ketones[a]	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)[b]	Variable	Variable	Variable	>300
Anion gap	>10	>12	>12	Variable
Alteration in sensorium or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

[a]Nitroprusside reaction method.
[b]Calculation: 2 [measured Na^+] + [glucose]/18.
Copyright ©2004 American Diabetes Association. Modified from Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in diabetes. *Diabetes Care.* 2004:27(suppl 1):S94–S102; used with permission from the American Diabetes Association.

burden with an estimated annual direct and indirect cost of $2.4 billion.[16,17] DKA is the most common cause of death in children and adolescents with type 1 DM.[13,18,19]

DKA is most common in patients with absolute insulin deficiency such as type 1 DM or pancreatogeneous diabetes, although it can also occur in type 2 DM in two scenarios: (1) acute glucose toxicity and (2) ketosis-prone (or "flatbush") diabetes. About 35% of cases of DKA occur in patients with type 2 DM and in 50% of these patients, it was the initial manifestation of diabetes.[16]

Acute hyperglycemia causes glucose toxicity that leads to reduced β-cell insulin secretion. As the β-cell production of insulin falls, glucose levels further increase, exacerbating the process.[20] Insulin secretion recovers as the glucose levels are lowered, thereby correcting the toxicity. Ketosis-prone diabetes occurs more commonly in African Americans and Hispanics[12,13,16,20] who are obese and have a strong family history of DM.[21–23] Although patients with ketosis-prone type 2 diabetes present in a ketotic, insulin-deficient state, many patients are able to restore insulin secretory capacity and discontinue insulin within a few months of treatment.[21]

HHS, formally known as hyperglycemic hyperosmolar nonketotic state, is the most serious diabetic emergency in type 2 DM. It is characterized by severe dehydration, hyperglycemia and hyperosmolality.[13,24] HHS most commonly occurs in elderly adults with type 2 DM but it can also occur in younger adults and even children. Although the incidence of HHS is 1 in 1000 or less than 1%, the severity of the illness is better characterized by the 10% to 20% mortality rate.[12,16,24] Severe dehydration, advanced age, and other comorbid conditions are associated with increased mortality.[13]

Pathophysiology

DKA is a result of insulin deficiency and elevated counterregulatory hormones (glucagon, growth hormone, cortisol, and catecholamines). In the absence of insulin the liver, adipose tissue, and skeletal muscle are unable to use glucose and sense a state of "starvation." The resulting gluconeogenesis and glycogenolysis worsen the hyperglycemia.[12,13,25] The combination of insulin deficiency and increased counterregulatory hormones leads to an increase in lipolysis and release of FFAs into the circulation. Ketone bodies (acetoacetate and β-hydroxybutyrate) are formed by hepatic oxidation of these FFA.[13] Ketone bodies are weak acids that deplete the body of bicarbonate, leading to development of acidosis.[16]

Hyperglycemia-induced osmotic diuresis causes a net loss of potassium, chloride, sodium, and phosphate. Potassium is shifted to the extracellular space but cannot reenter the cell in the setting of insulinopenia as insulin is needed to drive potassium intracellularly. Despite an increase in extracellular potassium, net potassium balance is negative because of renal losses[16] (Fig. 55.1).

HHS, as DKA, is characterized by insulinopenia and an increase in counterregulatory hormones. However, unlike DKA, there is adequate insulin to prevent lipolysis and the development of ketone bodies and acidemia.[25,26] In contrast to DKA, the higher hepatic and circulating insulin and lower glucagon levels prevent ketogenesis.[24] Owing to the lack of ketoacidosis, hyperglycemia manifests over days, leading to osmotic diuresis and severe dehydration.[25] Glucosuria initially prevents severe hyperglycemia but a decrease in glomerular filtration rate from hypovolemia reduces the ability to eliminate glucose in the urine. The result is severe hyperglycemia and hyperosmolality.[24]

Precipitating Factors

The most common precipitating factors for DKA and HHS are infection and omission of antidiabetic therapy, although a precipitating factor may not be identified in up to 20% to 30% of cases.[27] New-onset type 1 DM or discontinuation of insulin in an established patient with type 1 DM is the precipitating factor in up to 50% of admissions for DKA.[27] In addition, omission or reduction of insulin as a means of weight control may account for up to 20% of recurrent DKA in young women with DM[13,28]—a condition termed "diabulimia."[29]

Forty percent to 60% of HHS is caused by infection, most commonly pneumonia (40%–60%) and urinary tract infection (5%–16%).[24] Other medical illness, such as stroke, myocardial infarction (MI), or trauma, can lead to HHS by increasing counterregulatory hormones and/or decreasing access to water. Drugs such as glucocorticoids, atypical antipsychotics, and thiazide diuretics may lead to metabolic decompensation resulting in HHS.[24] Up to 20% of patients presenting with HHS do not have a previous diagnosis of DM.[24] The precipitating factors of DKA are listed in Table 55.2.

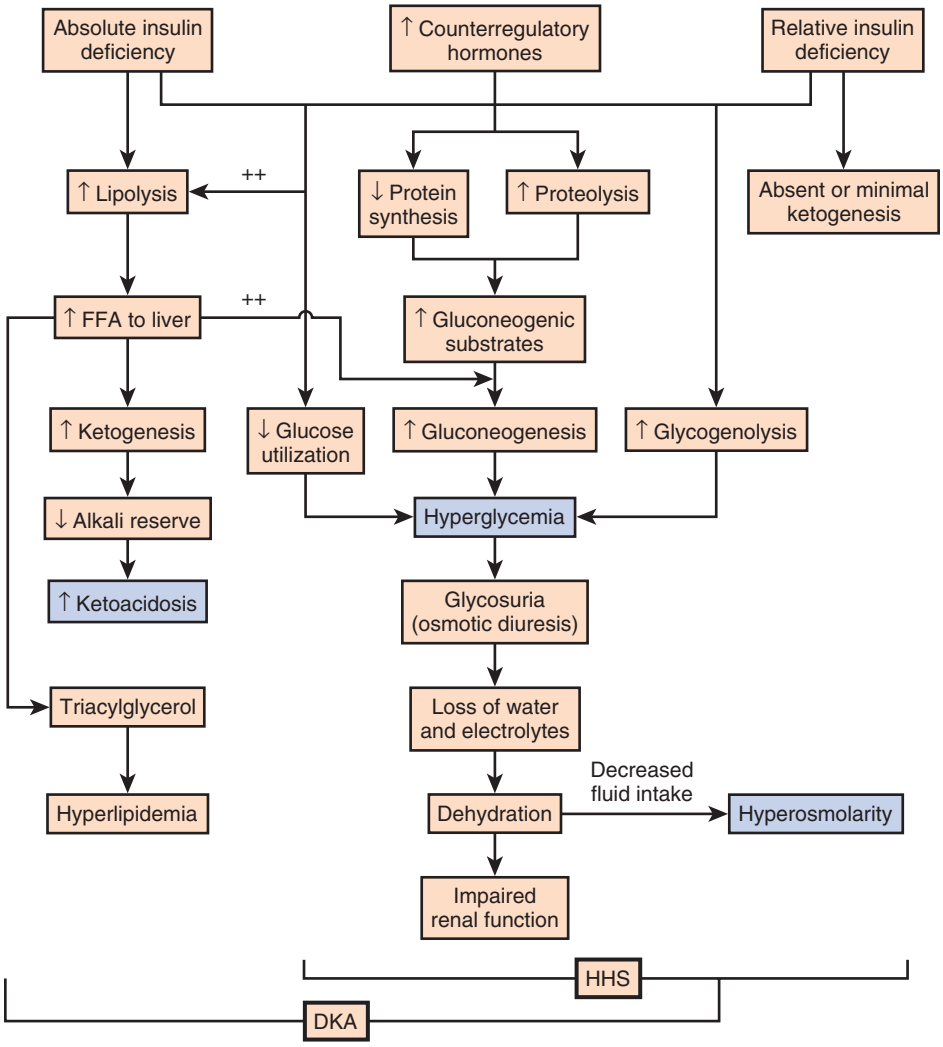
Presentation

Patients with DKA and HHS present with classic symptoms of hyperglycemia: polyuria, polydipsia, and blurry vision, along with symptoms of volume depletion: weakness, fatigue, somnolence, headache, and anorexia related to volume depletion.[30] In addition, patients with DKA also have ketosis-related symptoms: nausea, vomiting, and abdominal pain.[27] DKA develops quickly, frequently within 24 hours, whereas HHS develops insidiously over days or weeks.[12] Both can be subtle or fulminant. Because DKA and HHS can be the presenting signs of DM, a high clinical suspicion is needed to make the appropriate diagnosis and institute timely treatment. Mental status can be normal or altered in DKA if acidosis is severe, whereas the severity of mental status change in HHS can vary from lethargy and somnolence to coma. Clinical signs of DKA and HHS are those of volume depletion and include hypotension, tachycardia, and dry mucous membranes.[30] Patients with DKA may have Kussmaul respirations (rapid deep breathing) and a fruity odor to their breath as a result of acetone (derived from acetoacetate).

Diagnosis

The diagnosis of DKA is made by a pH less than 7.3, bicarbonate less than 18 mEq/L, anion gap greater than 10 mEq/L, glucose level greater than 250 mg/dL, and ketonemia.[24] Diabetic ketoacidosis must be differentiated from other causes of anion-gap metabolic acidosis without ketosis (lactic acidosis, hyperchloremic acidosis, and salicylate toxicity) as well as from other ketotic states (ketotic hypoglycemia, alcoholic ketosis, starvation ketosis, isopropyl alcohol, and hyperemesis).[16]

Although most patients will have a glucose level above 250 mg/dL, DKA can occur in the setting of lower or even euglycemic glucose levels, including pregnant patients owing to increased counterregulatory hormones[27,31,32] and those with poor oral intake and dehydration. Similarly, in patients with gastric losses of hydrogen ions (H^+), bicarbonate can be normal in DKA.[33] Euglycemic DKA has been noted with sodium glucose cotransporter inhibitors used to treat type 2 DM.[34] Patients at greatest risk are those with type 2 DM who are using insulin along with a sodium glucose



• **Fig. 55.1** Pathogenesis of diabetic ketoacidosis *(DKA)* and hyperglycemic hyperosmolar state *(HHS)*: stress, infection, or insufficient insulin. *FFA,* Free fatty acid. (From Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32:1335–1343.)

TABLE 55.2 Causes of Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome[12,13,16,25]

Etiologic Factor/Condition	Diagnoses With Comments
Inadequate insulin	Nonadherence, inadequate insulin regimen, insulin pump failure or omission of insulin, new-onset diabetes
Infections	Any moderate to severe infectious process Most commonly, pneumonia, urinary tract infection, sepsis
Acute medical conditions	Myocardial infarction, pancreatitis, cerebrovascular accident
Interference with glucose metabolism or insulin secretion	Thiazide diuretics, corticosteroids, second-generation (atypical) antipsychotics, FK506 (tacrolimus), glucagon, sympathomimetic agents (albuterol, terbutaline, dobutamine)
Endocrine disturbance	Pheochromocytoma, hyperthyroidism, acromegaly, hemochromatosis
Substance abuse	Cocaine
Nutritional factors	Parenteral nutrition

cotransporter inhibitor who omit insulin and those with an acute illness or decreased oral intake.[34] Additional causes of euglycemic DKA include hepatic insufficiency, starvation ketosis, alcoholic ketoacidosis, and reduction in the glucose before resolution of the acidosis.

Ketones are most often measured in the laboratory by the nitroprusside method, which reacts with acetoacetate and acetone, the less prominent ketones in DKA.[35] β-Hydroxybutyrate is converted to acetoacetate as DKA is treated; hence the nitroprusside method of measuring ketones can result in false-negative ketone levels at presentation and false-positive ketone levels during recovery. By definition, ketone levels are positive in DKA, whereas ketone levels are mildly elevated or absent in HHS. (A serum β-hydroxybutyrate level greater than 3.8 mmol/L is consistent with DKA.[36]) Serum β-hydroxybutyrate is useful for diagnosis and determination of recovery of DKA but serial measurements do not aid management.[12,35]

Serum sodium is often low on presentation because of the osmotic shift of water from the intracellular to extracellular space, causing dilutional hyponatremia. The sodium level should be corrected for glucose by adding 1.6 mEq/L to the sodium for every 100-mg/dL increase in glucose above 100 mg/dL. This estimates the sodium level once the glucose level is corrected.[13] A normal or elevated admission serum sodium level in the setting of hyperglycemia is indicative of profound dehydration and water deficit.[13]

The diagnosis of HHS is based on a glucose level greater than 600 mg/dL, serum osmolality greater than 320 mOsm/kg, and the absence of significant ketosis.[24] A significant number of patients with HHS present with normal mental status; therefore alteration in mental status is no longer part of the diagnostic criteria for HHS.

Osmolality can be calculated using glucose and sodium: [2(measured Na) + glucose/18].[17,24,35] Previous equations included urea; however, the osmotic contribution of urea is not significant.[24] Serum osmolality is generally normal in DKA but is often profoundly elevated in HHS because of the marked volume depletion that results from osmotic diuresis.

The serum potassium level may be low, normal, or elevated in DKA and HHS.[13] Insulin deficiency and acidosis decrease cellular uptake of potassium, although hyperosmolality enhances cellular efflux of potassium.[13] Large amounts of potassium shift from the intracellular space to the extracellular space and are then lost in the urine. Regardless of the serum potassium level, all patients with DKA and HHS have substantial depletion of total body potassium.

Evaluation of DKA and HHS should include measurement of electrolytes, phosphorus, blood urea nitrogen, creatinine, urinalysis, complete blood cell count, hepatic enzymes, hemoglobin A_{1c} (HbA_{1c}), serum ketones, and electrocardiogram. A thorough history should be taken to determine the precipitating cause. A chest radiograph should be considered because of the high incidence of pneumonia as a precipitating factor of HHS.[12,24] Additional workup testing should be based on the clinical evaluation.

Serum amylase and lipase levels can be elevated in up to 25% of patients with DKA,[16] although clinicians should be aware that acute pancreatitis does occur in 10% to 15% of cases of DKA.[37] Leukocytosis, present in up to 50% of patients who present with DKA and HHS owing to increased catecholamine release,[38,39] is proportional to the degree of acidosis, hypercortisolemia, and elevated catecholamines.[16] Although leukocytosis does tend to correlate with the severity of DKA, an elevated white blood cell count should prompt evaluation for infection.[12,38]

Management

DKA and HHS require management of fluids, electrolyte replacement, and insulin. DKA in pregnancy is a medical emergency with up to a 9% fetal death rate.[27] The management of DKA and HHS in adults is detailed in Fig. 55.2.

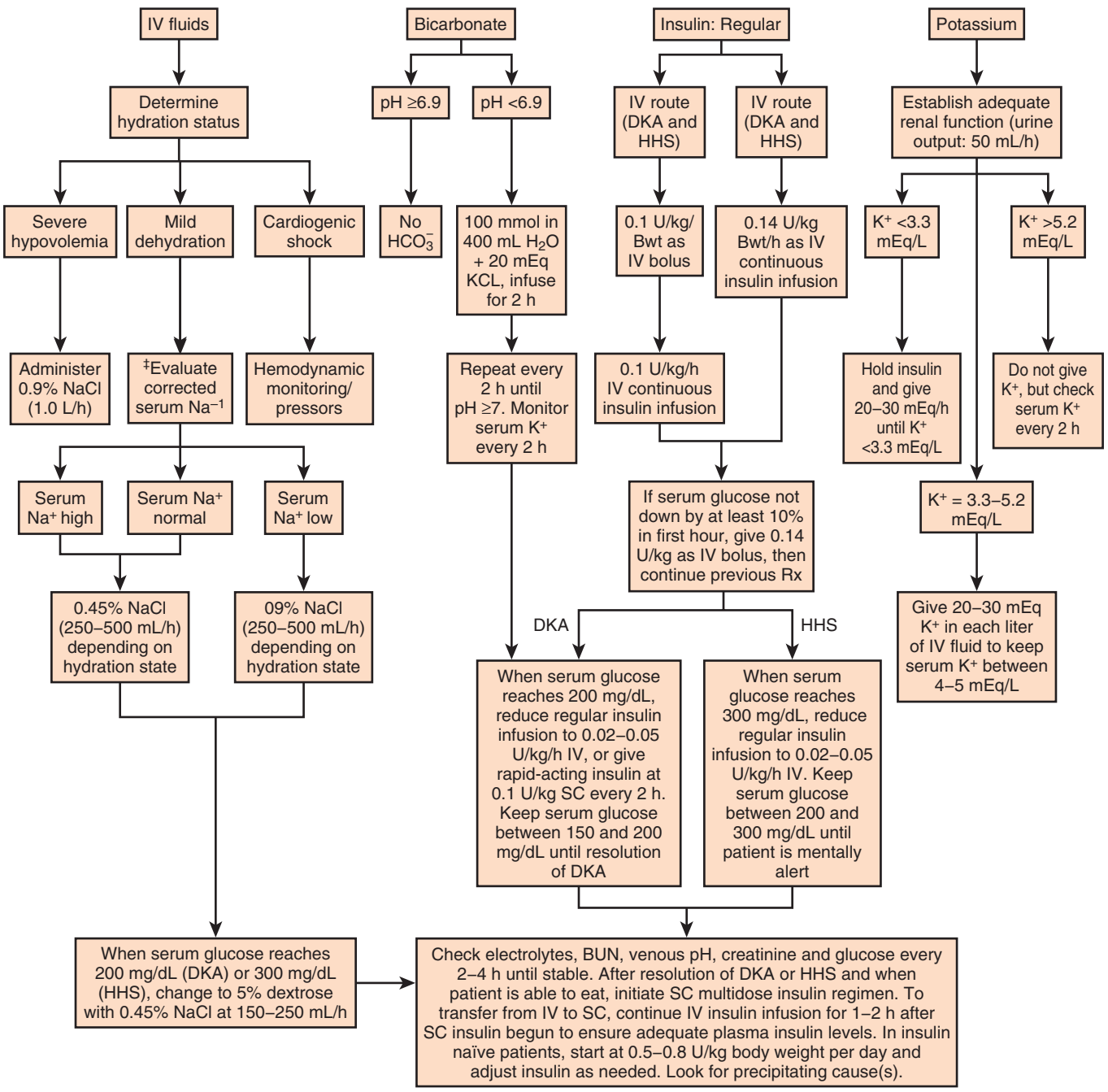
Fluid Replacement

Fluids are essential in the treatment of DKA and HHS to restore tonicity, replete intravascular volume, improve renal and tissue perfusion, and help to reduce the plasma osmolality.[25] Normal saline solution is infused at 15 to 20 mL/kg per hour over the first 2 hours with the subsequent rate of fluid resuscitation based on the state of hydration, serum electrolytes, and assessment of hemodynamic status. Patients with HHS will have a larger fluid deficit than those with DKA and may require fluid rates maintained at 500 mL/h to correct 50% of the fluid deficit within the first 12 hours.[25] Higher rates have not proven beneficial.[25] Saline solution should be continued if the patient is hypotensive. In patients who are hypernatremic or eunatremic, 0.45% normal saline solution can be used at a rate of 250 to 500 mL/h for subsequent fluid.[13,25,35] Patients who remain hyponatremic should continue to receive normal saline solution; 50% of the fluid deficit should be replaced within the first 12 hours and the remainder over the ensuing 12 hours.[25,35] Patients with congestive heart failure or risk of volume overload may need more cautious fluid replacement and appropriate monitoring. Dextrose is added to the fluids once the plasma glucose level falls below 200 to 250 mg/dL. This allows continued infusion of insulin for correction of the ketoacidosis.[13,25,35]

Insulin

In patients with moderate to severe DKA or DKA with mental status changes, intravenous insulin is the treatment of choice. Serum potassium must be greater than 3.3 mEq/L before initiating insulin. A continuous intravenous infusion is usually initiated with a bolus of 0.1 U/kg followed by a rate of 0.1 U/kg per hour.[40] Alternatively, the rate may be started at 0.14 U/kg per hour[16,35] without a bolus. Subcutaneous insulin may be used while intravenous (IV) access is being obtained. In the setting of anasarca, intramuscular insulin may be preferred until the IV access is established. Trials of rapid-acting subcutaneous insulin administered every 1 to 2 hours for DKA have proven the effectiveness of subcutaneous insulin regimens in the non-ICU setting for mild DKA. Subcutaneous and intramuscular insulin in mild DKA produces similar resolution of ketoacidosis and restoration of euglycemia, although trial data for more severe ketoacidosis and DKA in ICU patients are lacking.[13,41] Subcutaneous and intramuscular insulin may be appropriate for mild DKA but should not be used in the setting of moderate or severe DKA.[13,41] During an insulin infusion, point of care (POC) glucose should be monitored hourly initially and then decreased to every 2 hours as the patient's hyperglycemic and acidosis stabilize. The infusion should result in reduction of glucose by 50 to 75 mg/dL per hour. More rapid correction is not necessary and may be harmful. When the plasma glucose level falls below 200 to 250 mg/dL, the infusion rate should be reduced to 0.02 to 0.05 U/kg per hour and dextrose added to the IV fluids to allow time for resolution of the acidosis.[13] The insulin rate should be titrated to maintain the glucose level between 150 and 200 mg/dL until DKA is resolved.[13]

Resolution of DKA is defined by a glucose level less than 200 mg/dL with two of the following: anion gap 12 mEq/L or



• **Fig. 55.2** Protocol for the management of adult patients with diabetic ketoacidosis *(DKA)* or hyperglycemic hyperosmolar state *(HHS).* DKA diagnostic criteria: blood glucose 250 mg/dL, arterial pH 7.3, bicarbonate 15 mEq/L, and moderate ketonuria or ketonemia. HHS diagnostic criteria: serum glucose greater than 600 mg/dL, arterial pH greater than 7.3, serum bicarbonate greater than 15 mEq/L, and minimal ketonuria and ketonemia. Notes: †15 to 20 mL/kg/hour; ‡serum Na should be corrected for hyperglycemia (for each 100 mg/dL glucose, add 1.6 mEq to sodium value for corrected serum value). *BUN,* Blood urea nitrogen; *Bwt,* body weight; *HCO_3^-,* bicarbonate; *IV,* intravenous; *K^+,* potassium ion; *Na^+,* sodium ion; *NaCl,* sodium chloride; *SC,* subcutaneous. (From Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32:1335–1343.)

lower, serum bicarbonate 15 mEq/L or higher, and venous or arterial pH greater than 7.3. Resolution of HHS is defined by normalization of effective serum osmolality to less than 310 mmol/kg and return to normal mental status.[13,17] Once DKA or HHS is resolved, insulin is transitioned to a subcutaneous regimen. To avoid recurrence of DKA, subcutaneous insulin must be overlapped with the insulin drip for at least 2 hours. The home insulin regimen may be restarted in individuals with controlled DM before admission.[13] Previous diabetes control can be assessed with HbA_{1c} testing. In patients not previously using insulin, the subcutaneous insulin dose should be extrapolated from the last 6 to 8 hours of the insulin infusion rate. It is important that the patient is at a steady state and not taking pressors before making this estimation.[42,43] The subcutaneous insulin regimen is calculated from the mean insulin rate during the steady-state period. To find the total daily dose of insulin, the mean insulin rate is multiplied by 20 to allow for a 20% reduction in the calculated dose. Half of the total daily dose should be administered as long-acting (basal insulin) such as NPH, glargine, degludec, or detemir and 50% should be administered as short-acting insulin such as regular, aspart, glulisine, or lispro to control meal-related hyperglycemia.[43] A detailed guide for successful transition to subcutaneous insulin is listed in Box 55.2.

Potassium

Serum potassium concentration is often elevated as a result of extracellular shift of potassium. This shift is a result of insulin deficiency, acidemia, and hypertonicity.[16] Patients with low or low-normal serum potassium levels on presentation have a severe total-body potassium deficit.[13,16,25] Insulin should not be given unless the serum potassium is greater than 3.3 mEq/L to avoid cardiac arrhythmias.[17] Patients who present with hypokalemia require cardiac monitoring, aggressive potassium replacement, and close monitoring of potassium levels.[13] During treatment of DKA and HHS with insulin and fluids, serum potassium levels rapidly fall. Potassium repletion begins when the serum potassium falls below 5.0 mEq/L[24] by adding 20 to 30 mEq KCl in each subsequent liter of IV fluids to maintain the potassium level between 4 and 5 mEq/L.[17,25] More cautious replacement is necessary in the setting of renal insufficiency. Electrocardiography at evaluation and cardiac monitoring is important in DKA and HHS owing the multiple cardiac effects of both hyperkalemia and hypokalemia.

Bicarbonate

Replacement of bicarbonate is rarely recommended in the management of DKA, and even suggestions for use in patients with pH of 6.9 or lower lack evidence from randomized clinical trials. Bicarbonate may worsen hypokalemia and increase the risk of cerebral edema.[16,17] Replacement is achieved by administering 100 mmol (2 ampules) of sodium bicarbonate in 400 mL of water with 20 mEq KCL at a rate of 200 mL/h.[16,17,35] This may be repeated every 2 hours until the pH is above 7.[35] In patients with a pH above 7.0, replacement of bicarbonate offers no improvement in outcomes or rate of recovery and is not recommended.[17]

• BOX 55.2 Important Steps in Transition From Insulin Infusion to Subcutaneous Insulin

Step 1: Is the patient stable enough for transition?

Hypotension, active sepsis, use of pressors, and intubation are contraindications to transition because these factors are recognized to be associated with unreliable subcutaneous insulin absorption, with continued need for the most flexible dosing because of frequently changing insulin requirements.

Step 2: Does the patient need to switch to scheduled subcutaneous insulin?

Yes:	No:
Type 1 DM—all patients	Type 2 DM in patients with a recent mean infusion rate <0.5 unit/h
Type 2 DM in patients on home insulin regimen	Stress hyperglycemia or previously unrecognized DM if infusion rate <1 unit/h or if HbA_{1c} is near normal
Type 2 DM in patients with a recent mean infusion rate ≥0.5 unit/h	

Step 3: If transition is needed, calculate a TDD of insulin. The TDD is an estimate of the 24-h insulin requirement when the patient is receiving full nutrition.

- Determine mean insulin infusion rate from last 6 to 8 h.
- Calculate 24-h insulin dose based on this rate, and reduce the 24-h dose by 20%.
  - Multiply hourly insulin infusion rate by 20 (80% of 24) to arrive at a safety-adjusted 24-h insulin dose.
- Determine if this total is the TDD or basal dose based on current nutrition.
  - If the infusion was providing both the basal and nutritional needs of the patient (i.e., continuous tube feeds), this will be the TDD.

OR

  - If the infusion was not covering significant nutrition, this *could* be the basal insulin dose.

Step 4: Construct a basal/bolus regimen tailored to the patient's nutritional situation, building safeguards for any changes in nutritional intake and uncertainties about reliability of intake. Several options are again available.

- *Basal*: glargine, detemir, degludec, or NPH
  1. Dose is 40% to 50% of TDD.

  OR

  2. Adjusted 24-h intravenous requirement can be given as all basal.
- *Nutritional*: The remainder of TDD is scheduled nutritional insulin in divided doses. In general, these doses need to be adjusted down for <100% nutritional intake, and the orders should allow for administering nutritional insulin just AFTER observed meal to allow an assessment of intake. Several options are available for estimating the initial doses:
  1. Use 50% of the TDD as nutritional coverage, and divide this amount by 3 to determine the scheduled meal dose. Hold if patient does not eat more than 50% of each meal.
  2. Use a more conservative start of 0.1 to 0.2 × basal dose for each meal.
  3. Use carbohydrate counting to cover nutritional intake.

Step 5: Be sure to give subcutaneous insulin BEFORE the infusion stops.

- Basal glargine and detemir ideally are given at least 2 h before infusion is discontinued.
- Shorter lead times (30 min) are possible if rapid-acting insulin is given with basal insulin.

DM, *Diabetes mellitus;* HbA_{1c}, *hemoglobin A_{1c} (glycosylated hemoglobin);* TDD, *total daily dose.*

Modified from O'Malley CW, Emanuele, M, Halasyamani L, et al. Bridge over troubled waters: safe and effective transitions of the inpatient with hyperglycemia. J Hops Med. *2008;3(5 suppl):S55–S65.*

Phosphate

Like potassium, phosphate is shifted to the extracellular space in the response to acidosis and osmotic diuresis leads to urinary phosphate loss.[16] Despite total-body phosphate deficits, phosphate levels are often normal or elevated on presentation because of the extracellular shifts.[13,16] As insulin therapy allows phosphate to reenter the cell, hypophosphatemia develops.[16] Complications of hypophosphatemia are rare but include respiratory and skeletal muscle weakness, reduced cardiac output, and decreased tissue oxygen delivery.[16,35] Although routine replacement of phosphate is not recommended or supported by trial data, serum phosphate should be monitored and replaced if the phosphate concentration falls below 1.0 mg/dL or in those with possible complications of hyperphosphatemia such as cardiac dysfunction, anemia, or respiratory depression.[13,16] Replacement is usually achieved by administering potassium phosphate, 20 to 30 mEq/L added to replacement fluids. Other potassium replacement requires adjustment if potassium phosphate is added to avoid overzealous correction of potassium. Serum calcium should be monitored in patients receiving phosphate owing to the risk of hypocalcemia.[35] The maximal rate of phosphate repletion should not exceed 4.5 mmol/h.[13]

Complications of the Management of Hyperglycemic Emergencies

The most common complications of the management of DKA and HHS in adults are hypoglycemia, hypokalemia, and hypophosphatemia. Frequent monitoring of glucose and addition of dextrose to the IV fluids once glucose falls below 250 mg/dL helps to prevent hypoglycemia. Frequent monitoring, and appropriate fluid and electrolyte replacement help prevent any complications related to electrolyte disturbances and volume depletion.

In children with DKA, cerebral edema is a feared complication that occurs in less than 1% of children. The mortality rate is 20% to 50% and 15% to 35% of survivors are left with permanent neurologic sequelae.[44] The pathophysiology is poorly understood.[44] Postulated mechanisms for cerebral edema include osmotically driven intracellular water shift when plasma osmolality declines too rapidly, ketone bodies affecting vascular integrity, and hypoxemia.[16] Risk factors include higher osmolality and serum urea nitrogen at presentation, pH less than 7.1, partial pressure of carbon dioxide less than 20 mm Hg, greater than 50 mL/kg of fluid administered within the first 4 hours of treatment, initiation of insulin before rehydration bolus, and treatment with bicarbonate.[12,13,25] Early symptoms are headache and vomiting that progress to decreased arousal and altered mental status.[25] Special attention to rate and tonicity of fluids is especially important in the pediatric population as DKA is treated to avoid rapid correction of glucose and osmolality.[44]

Prevention

Many cases of DKA and HHS are preventable through proper education and effective communication with a health care provider. Education regarding sick day management for all patients with DM and caregivers is paramount to preventing DKA (Box 55.3). In contrast, held basal insulin, less frequent glucose monitoring, a lack of correction scale insulin, and dehydration facilitate the onset of DKA. Ketones should be monitored by urine dipstick if glucose is greater than 240 mg/dL. This allows recognition of impending ketoacidosis, which may guide insulin therapy and prevent hospitalization.[13,45] Patients with insulin pumps require a prescription for basal insulin in the event of a pump failure. Patients should have printed instructions about when to contact their treating physician.

Unfortunately, cessation of insulin because of its high cost is also a common cause of DKA. Insulin discontinuation and poor adherence to therapy account for more than half of DKA in minority populations.[13,46] This may be due to the high cost of insulin, limited access to health care, and low health literacy. Improving diabetes care in this population requires recognition of the many barriers that affect health care in these populations.

• BOX 55.3 Sick Day Management Protocol for Diabetic Patients[120,121]

Examples of "Sick Day" Scenarios

- Feeling sick or presence of fever for 2 days or longer without getting better
- Vomiting or diarrhea for more than 6 h

Management

General Measures

- Check blood sugar levels at least every 4 h, but when values are changing quickly, check more often.
- Check urine or blood ketones.
- Modify usual insulin regimen according to a plan developed by the diabetes physician or team.
- Maintain adequate food and fluid intake. If your appetite is poor, aim for consumption of 50 g of carbohydrate every 3–4 h. If you are nauseous, high-carbohydrate liquids, such as regular (not diet) soft drinks or juice, or frozen juice bars, sherbet, pudding, creamed soups, or fruit-flavored yogurt usually are tolerated. Broth also is a good alternative.

Taking Medications When You Are Sick

- If you are eating: Continue taking your pills for diabetes or your insulin. Your blood sugar may continue to rise because of your illness.
- If you are nauseous or vomiting or otherwise cannot take your medicines:
  - Continue to take your long-acting insulin (Lantus, Levemir, NPH).
  - Call your doctor and discuss whether you need to adjust your short- or rapid-acting insulin dose (regular, lispro [Humalog], aspart [Novolog], glulisine [Apidra]) or your other diabetes medicines.

Examples of When to Call Physician or Diabetes Team

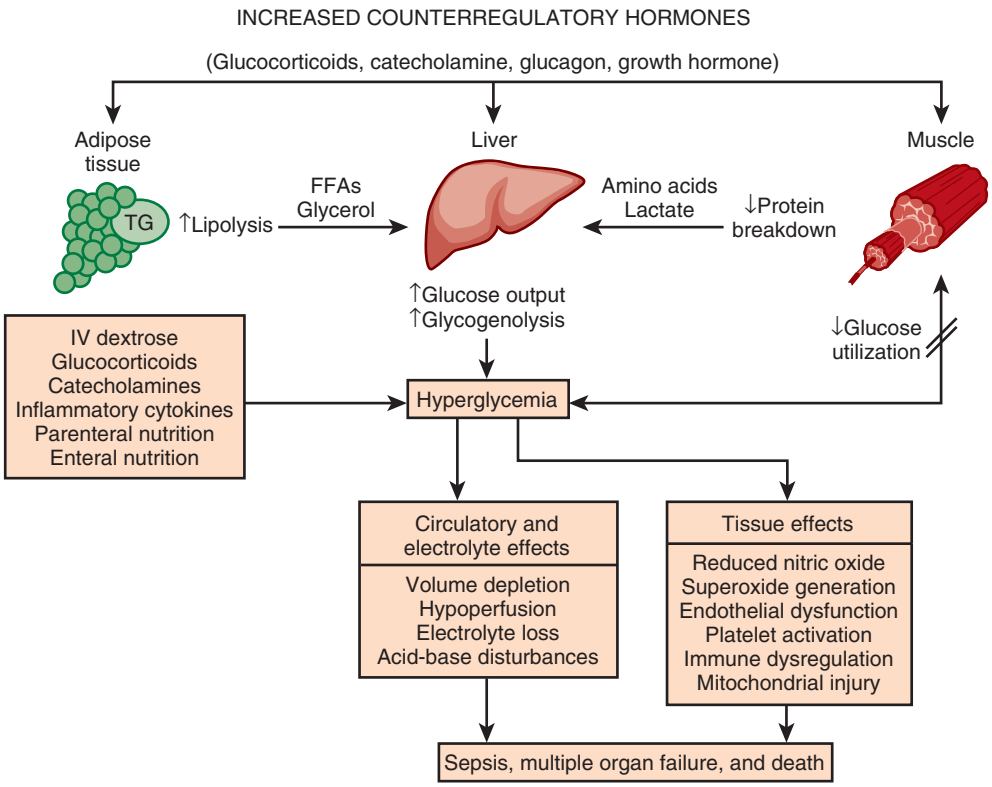
- If glucose levels are higher than 240 mg/dL despite taking extra insulin according to a sick day plan
- If you take diabetes pills and blood sugar is still above 240 mg/dL before meals and remains there for more than 24 h
- If symptoms/signs develop that might signal diabetic ketoacidosis or dehydration, such as dizziness, trouble breathing, fruity breath, or dry and cracked lips or tongue

DKA, *Diabetic ketoacidosis.*

Glycemic Control in the ICU

Epidemiology and Significance of Hyperglycemia

Mortality follows a J-shaped association for glucose levels in the hospital with increased mortality in those with hyperglycemia and those with hypoglycemia.[47,48] Acute hyperglycemia was once regarded as an adaptive response to critical illness, though this idea was challenged by several reports of an increased risk associated with hyperglycemia[49,50] and the noted benefits of improved glucose control in patients with acute MI, stroke, coronary artery bypass surgery, and critical illness.[49,51,52,53]



• **Fig. 55.3** Pathogenesis of stress hyperglycemia. Stress hyperglycemia results from increased hepatic glucose production and impaired glucose utilization in peripheral tissues. Excess counterregulatory hormones (glucagon, cortisol, catecholamines, and growth hormone) increase lipolysis and protein breakdown (proteolysis), and impair glucose utilization by peripheral tissues. Hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate, and worsening hyperglycemia. At the cellular level increased blood glucose levels result in mitochondrial injury by generating reactive oxygen species and endothelial dysfunction by inhibiting nitric oxide production. Hyperglycemia increases levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin 6, leading to immune system dysfunction, and increases plasminogen activator inhibitor-1 and fibrinogen, causing platelet aggregation and hypercoagulable state. These changes can eventually lead to increased risk of infection, impaired wound healing, multiple organ failure, prolonged hospital stay, and death. *FFA,* Free fatty acids; *TG,* triglycerides. (From Farrokhi F, Smiley D, Umpierrez GE. Glycemic control in non-diabetic critically ill patients. *Best Pract Res Clin Endocrinol Metab.* 2011;25:813–824.)

Hyperglycemia in hospitalized patients occurs in those with known or undiagnosed DM. Stress hyperglycemia is seen in up to 17% of critically ill patients with previously normal glucose tolerance (Fig. 55.3).[54–56] Hyperglycemia from any source is associated with increased in-hospital mortality compared with those with normoglycemia.[48] Although glucose typically normalizes after resolution of the acute illness in those with stress-induced hyperglycemia, patients with stress-induced hyperglycemia are almost twice as likely to develop DM in the future compared with those with normoglycemia.[55,56]

Synopsis of Trials of Glycemic Control

Early observational studies of patients with MI, stroke, and critical illness revealed that acute hyperglycemia is associated with increased in-hospital mortality in patients with and without DM.[50,52,57] Results of the first randomized controlled trial confirmed observational studies in patients with DM with MI[53] showing improved prognosis with insulin-glucose infusions compared with conventional therapy.[53] The landmark prospective randomized controlled trial, published by Van den Berge in 2001, evaluated intensive insulin therapy (IIT) (glucose target 80–110 mg/dL) versus conventional treatment (glucose target 180–200 mg/dL) for hyperglycemia in a surgical intensive care unit.[58] IIT was associated with a dramatic reduction in mortality, septicemia, length of stay in the ICU, and number of transfusions required.[58] However, results of this single-center study were not able to be reproduced in randomized, controlled multicenter trials or in the medical ICU setting,[59–61] suggesting that the effects seen in the Van den Berge study may be specific to surgical ICU patients.

Hypoglycemia, the foremost obstacle in the use of IIT, increases mortality.[60–63] In the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study, a multicenter international randomized trial of intensive glucose control in the ICU, those treated to intensive targets had increased mortality.[64] The VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) trial stopped early because of an increased rate of severe hypoglycemic events and a trend toward prolonged ICU stay in the IIT-treated group.[61]

In addition, patients with larger glycemic variability have an increased odds ratio of hospital mortality, particularly in nondiabetic patients with sepsis.[65] Advances in glucose monitoring and delivery may play a future role in minimizing variability.[66–68] Fig. 55.4 summarizes key studies that have evaluated inpatient intensive glycemic control.

Based on the analysis of the available studies, it is suggested to initiate insulin in critically ill patients when glucose levels exceed 180 mg/dL and to treat to a target glucose level of 140 to 180 mg/dL.[47] Certain populations, including those with acute ischemic cardiac or neurologic events and those undergoing coronary artery bypass grafting, may benefit from more intensive targets such as 110 to 140 mg/dL if this can be achieved without significant hypoglycemia.[47,54] More recent studies have been unable to demonstrate a reduction in perioperative complications in patients undergoing coronary artery bypass grafting who are treated with IIT (glucose goal 100–140 mg/dL).[69] Some of these discrepancies may be partially accounted for by evidence that those without a previous history of DM may benefit from IIT intensive insulin therapy, whereas patients with known preexisting DM have little to no significant benefit from IIT.[69,70]

Intravenous Insulin Protocols

An insulin infusion is the preferred way to manage persistent hyperglycemia in the majority of critically ill patients in the ICU, whereas subcutaneous insulin may be appropriate in those critically ill patients who are able to eat. IV insulin should be started when the glucose level reaches 180 mg/dL.[54] Insulin infusion protocols should be developed by an interdisciplinary team involving endocrinologists, intensivists, nurses, and pharmacists and should allow for hourly adjustment of insulin based on POC glucose readings.[71,72] POC glucose levels should be measured every 1 to 2 hours while an insulin infusion is used to allow titration of the infusion with an upper target of glucose of 180 mg/dL. Once the glucose level and insulin rate are stable, glucose can be measured every 4 hours.[73] An insulin infusion must also be adjusted for nutrition status. Patients receiving an insulin infusion are usually not eating or drinking (NPO) or are receiving total parenteral nutrition or continuous tube feeds. If total parenteral nutrition or tube feeds are withheld, the infusion should be reduced by 50%.[72] In the rare instance when a patient is eating, consideration should be given to use of subcutaneous rapid-acting insulin with meals. This avoids titration of the insulin drip related to postprandial hyperglycemia.[72] When used properly, insulin infusion protocols have a low rate of hypoglycemia.[72]

Technical Issues in Measuring Glucose

Control of hyperglycemia and prevention of hypoglycemia in the ICU is largely dependent on our ability to accurately measure glucose levels. Glucometers have a 15% error compared with laboratory glucose at euglycemic ranges with higher errors at the low range of glucose values (<50 mg/dL) and at the high range of glucose values (>500 mg/dL).[74–76] Changes in pH, anemia, hypothermia, and hypoperfusion affect glucometer accuracy.[77–79] Peripheral vasoconstriction from pressors decreases peripheral glucose values compared with laboratory glucose values.[77,80] Anemia falsely elevates POC measurements, thereby increasing the risk of missing hypoglycemia in up to 10% of patients.[81] POC glucose from arterial blood correlates best with central laboratory glucose testing with decreasing accuracy for venous and the greatest variability for capillary samples.[77,79,81]

Continuous glucose monitors (CGMs) may offer another modality for measuring glucose in the ICU. CGMs use an electrochemical sensor placed subcutaneously to measure glucose every 1 to 10 minutes in the interstitial space in the outpatient setting. The accuracy of CGMs in the ICU and hospital setting may make them more effective in identifying asymptomatic hypoglycemia compared with POC glucose monitoring,[82–85] although without large randomized trial data, there is insufficient evidence to support use of CGMs in critically ill patients.[86,87]

Current Guidelines for Glycemic Control

Several medical associations, including the American Association of Clinical Endocrinologists, Endocrine Society, American Diabetes Association, and Surviving Sepsis Campaign, recommend maintaining glucose between 140 mg/dL and 180 mg/dL in ICU patients, and initiating insulin in the ICU for a glucose level higher than 180 mg/dL.[54,73]

The Effect of Parenteral Nutrition, Enteral Nutrition, and Glucocorticoids on Glycemic Control

Critically ill patients are particularly susceptible to hyperglycemia related to parenteral and enteral nutrition owing to the high concentration of carbohydrates in the feeding preparations combined with altered carbohydrate metabolism in the setting of increased stress and increased levels of counterregulatory hormones.[88]

Because total parenteral nutrition (TPN) and peripheral parenteral nutrition (PPN) are likely to cause hyperglycemia in those with previously controlled DM, IV or subcutaneous insulin should be initiated when TPN/PPN is started.[54] Adding insulin to parenteral nutrition prevents hypoglycemia if the nutrition is discontinued but is impractical for frequent insulin adjustments. When nutrition is held, the IV or subcutaneous insulin should be reduced or dextrose-containing intravenous fluids should be started to prevent hypoglycemia. Although nonstandardized amounts of dextrose are often initiated, when nutrition is held or discontinued, the rate of dextrose-containing IVF can be calculated based on the glucose concentration in the nutrition to minimize hypoglycemia.

Glucose levels should be monitored for at least 48 hours in all patients receiving glucocorticoids.[89,90] In those already using insulin, early insulin adjustments are necessary to avoid hyperglycemia.[54] An insulin infusion is appropriate for moderate to severe steroid-induced hyperglycemia, whereas initiation of subcutaneous insulin at a dose of 0.3 to 0.5 units/kg body weight can be used for less severe hyperglycemia.[91] To avoid hypoglycemia, insulin doses need to be reduced as steroid doses are lowered.[54]

Subcutaneous Insulin Use in the Hospitalized Patient

Insulin is the treatment of choice for hospitalized patients with hyperglycemia. Oral agents and noninsulin injectables are not appropriate in the hospital because of alterations in nutrition and various contraindications. An insulin infusion is preferable in the ICU for moderate to severe hyperglycemia, although subcutaneous insulin regimens can be ordered based on the nutritional status of the patient. Table 55.3 lists the onset, peak, and duration of action of available subcutaneous insulin preparations.

Title	*N*	Setting	Blood Plasma Sups (mEq/L [mmol]) Intensive	Blood Plasma Sups (mEq/L [mmol]) Conventional	Blood Glucose Achieved [mg/dL 9mmol/L][b] Intensive	Blood Glucose Achieved [mg/dL 9mmol/L][b] Conventional	Primary Outcome	End Point Rate (%) Intensive	End Point Rate (%) Conventional	ARR (%)[c]	RRR (%)[c]	Odds Ratio (95% CI)
DIGAMI (ref. 33),1995	620	CCU (AMI)	126–196 (7–10.9)	Usual care	173 (9.6)	211 (11.7)	1-Year mortality	18.6	26.1	7.5	29[d]	NR
Van den Berghe et al. (ref. 5), 2001	1548	SICU	80–110 (4.4–6.1)	180–200 (10–11)	103 (5.7)	153 (8.5)	ICU mortality	4.6	8.0	3.4	42	0.58 (0.38–0.78)[d]
DIGAMI 2 (ref. 34), 2005	1253	CCU (AMI)	126–180 (7–10) (groups 1 and 2)	Usual care (group 3)	164 (9.1)	180 (10)	2-Year mortality	Group 1, 23.4; group 2, 21.2	Group 3, 17.9	__[e]	__[e]	NR
Van den Berghe et al. (ref. 16), 2006	1200	MICU	80–110 (4.4–6.1)	180–200 (10–11)	111 (6.2)	153 (8.5)	Hospital mortality	37.3	40.0	2.7	7.0	0.94 (0.84–1.06)[e]
HI-5 (ref. 35), 2006	240	CCU (Ami) (GIK)	72–180 (4–10)	Usual care <288	149 (8.3)	162 (9)	6-Month mortality	7.9	6.1	–1.8[e]	–30[e]	NR
GuControl (ref. 27), 2007[f]	1101	ICU	80–110 (4.4–6.1)	140–180 (7.8–10)	118 (6.5)	144 (8)	ICU mortality	16.7	15.2	–1.5	–10	1.10 (0.84–1.44)[e]
Gandhi et al. (ref. 36), 2007	399	Operating room	80–110 (4.4–6.1)	<200 (<11)	114 (6.3)	157 (8.7)	Composite[g]	44	46	2	4.3	1.0 (0.8–1.2)[e]
VISEP (ref. 13), 2008	537[h]	ICU	80–110 (4.4–6.1)	180–200 (10–11)	112 (6.2)	151 (8.4)	28-Day mortality	24.7	26.0	1.3	5.0	0.89 (0.58–1.38)[e,i]
De La Rosa et al. (ref. 28), 2008[f]	504	SICU MICU	80–110 (4.4–6.1)	180–200 (10–11)	117 (6.5)	148 (8.2)	28-Day mortality	36.6	32.4	–4.2[e]	–13[e]	NR
NICE-SUGAR (ref. 14) 2009	6104	ICU	81–108 (4.5–6)	≤180 (≤10)	115 (6.4)	145 (8.0)	3-Month mortality	27.5	24.9	–2.6	–10.6	1.14 (1.02–1.28)[d]

[a]ARR, absolute risk reduction; CCU, coronary care unit; GIK, glucose-insulin-potassium; MICU, medical ICU; NR, not reported; RRR, relative risk reduction; SICU, surgical ICU. [b]Mean morning blood glucose concentrations (except for GluControl, which reported mean overall blood glucose concentrations). [c]Intensive group versus conventional group. [d]$P < 0.05$. [e]Not significant ($P < 0.05$). [f]Presented as abstract only. [g]Composite of death, sternal infection, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure at 30 days. [h]Only patients with sepsis. [i]Personal communication, Dr. Frank Brunkhorst.

• **Fig. 55.4** Summary data of selected randomized controlled trials of intensive insulin therapy in critically ill patients (>200 randomized patients). *AMI,* Acute myocardial infarction; *ARR,* absolute risk reduction; *CI,* confidence interval; *CCU,* coronary care unit; *GIK,* glucose-insulin-potassium; *MICU,* medical intensive care unit; *NR,* not reported; *RRR,* relative risk reduction; *SICU,* surgical intensive care unit. (From Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care.* 2009;32:1119–1131; *Endocr Pract.* 2009;15:353–369.)

TABLE 55.3 Onset, Peak, and Duration of Action of Currently Available Insulin Preparations

Insulin Preparation	Onset of Action	Peak Action	Duration of Action
Lispro	5–15 min	1–2 h	4–6 h
Aspart	5–15 min	1–2 h	4–6 h
Glulisine	5–15 min	1–2 h	4–6 h
Regular	30–60 min	2–3 h	6–10 h
NPH	2–4 h	4–10 h	12–18 h
Detemir	2 h	Relatively peakless	12–24 h
Glargine	2 h	Relatively peakless	20–24 h
Degludec	2 h	Relatively peakless	33–42 h

In patients who are NPO, a long-acting basal insulin such as detemir, glargine, or degludec is appropriate. Insulin degludec is one of the newer ultralong-acting basal insulins. It lasts longer than 24 hours and is dosed once daily similar to glargine.[92,93] Detemir is dosed every 12 to 24 hours given its shorter duration of action. NPH can be dosed every 12 hours or every 8 hours with or without a small dose of regular insulin as an acceptable basal insulin regimen for a patient who is NPO, although because of its greater peak effect, it may increase the risk of hypoglycemia. Glucose should be monitored every 4 to 6 hours and insulin and fluids with dextrose adjusted as needed.

Patients who are eating should have prandial insulin added to one of the previous basal insulin regimens. Lispro, aspart, and glulisine are the preferred prandial insulins as opposed to regular insulin because of their shorter onset and duration of action, which better mimics physiologic insulin.

For patients with preexisting DM who are using oral hypoglycemic and/or noninsulin agents, the total daily dose of insulin should be calculated based on the age, glomerular filtration rate, and weight of the patient. Patients older than 70 years or those with a glomerular filtration rate less than 60 mL/min should be started on a regimen 0.2 to 0.3 U/kg body weight per day, whereas those younger than 70 years and with normal renal function can be started on 0.4 to 0.5 U/kg body weight per day.[91] The total dose should be split to give 50% as basal insulin and 50% as nutritional insulin.[91] Alternatively, if a patient had previously adequate glucose control before hospitalization with a basal bolus insulin regimen, the patient's previous insulin regimen may be started. Premixed insulin should not be continued in the hospital owing to lack of flexibility. If a patient had good control with a premixed regimen as an outpatient, this can be converted to a basal bolus regimen by adding the total daily dose of insulin and administering 50% as basal insulin and 50% as nutritional insulin. If a patient previously used an insulin drip, this could also be used to calculate the total daily insulin regimen (see Box 55.2). It should be noted that when transitioning from glargine or levemir to insulin degludec or NPH, patients may require up to 20% to 30% less basal insulin.[94]

For patients receiving TPN or PPN, regular insulin may be added to the TPN/PPN at a dose of 1 unit of insulin per 15 g of carbohydrate.[95] Alternatively, basal insulin can be administered with rapid-acting correction every 4 hours.[54,91] This same regimen can be used for continuous enteral feeds. Patients receiving bolus enteral feeds generally require a basal insulin, such as glargine, detemir, degludec, or NPH, along with rapid-acting insulin with each bolus feeding as well as correctional insulin before each feeding. The bolus insulin and feeding should be no more frequent than every 4 hours.[54] Patients with nocturnal or cycled feeds should receive basal insulin in combination with a rapid-acting insulin at the start of tube feeds with rapid-acting insulin every 4 to 6 hours during feeding. The last dose of rapid-acting insulin should be at least 4 hours before discontinuation of the enteral feeds.[91]

Although correctional insulin is an important adjunct to a basal-bolus insulin regimen, it should not be used alone to manage hyperglycemia in the hospital.[96] Correctional insulin should be proportional to the total daily dose of insulin. Patients who require less total insulin also require less aggressive sliding scale regimens. The "rule of 1500" or the "rule of 1800" for more insulin-sensitive patients (type 1 DM, renal or hepatic insufficiency, elderly patients, and those with a body mass index less than 25 kg per m^2) can be used to estimate the glucose-lowering effect of 1 unit of insulin. The rule of 1500 formula estimates the correction using the total daily dose (TDD) of insulin. It is calculated as follows: 1500/TDD = expected mg/dL decrease in glucose from 1 unit of rapid-acting insulin.

TABLE 55.4 Clinical Symptoms of Hypoglycemia

Sympathoadrenal	Neuroglycopenic
Tremor	Tiredness or drowsiness
Palpitations	Difficulty thinking
Diaphoresis	Confusion
Nervousness	Blurred vision
Anxiety or apprehension	Slurred speech
Hunger	Dizziness, weakness
Pallor	Abnormal or belligerent behavior
	Seizure
	Coma or death

Hypoglycemia

Hypoglycemia is documented by Whipple's triad: symptoms and signs of hypoglycemia, a low plasma glucose concentration, and resolution of symptoms or signs after the plasma glucose is corrected. In the ICU, hypoglycemia, defined as a glucose level less than 70 mg/dL, leads to increased mortality hence limiting ability for tight glycemic control.[97–100] Severe hypoglycemia, defined by a blood glucose level less than 40 g/dL,[99] is common in intensive insulin protocols, occurring in 6.8% of patients in the NICE-SUGAR study.[64]

Physiologic Response to Hypoglycemia

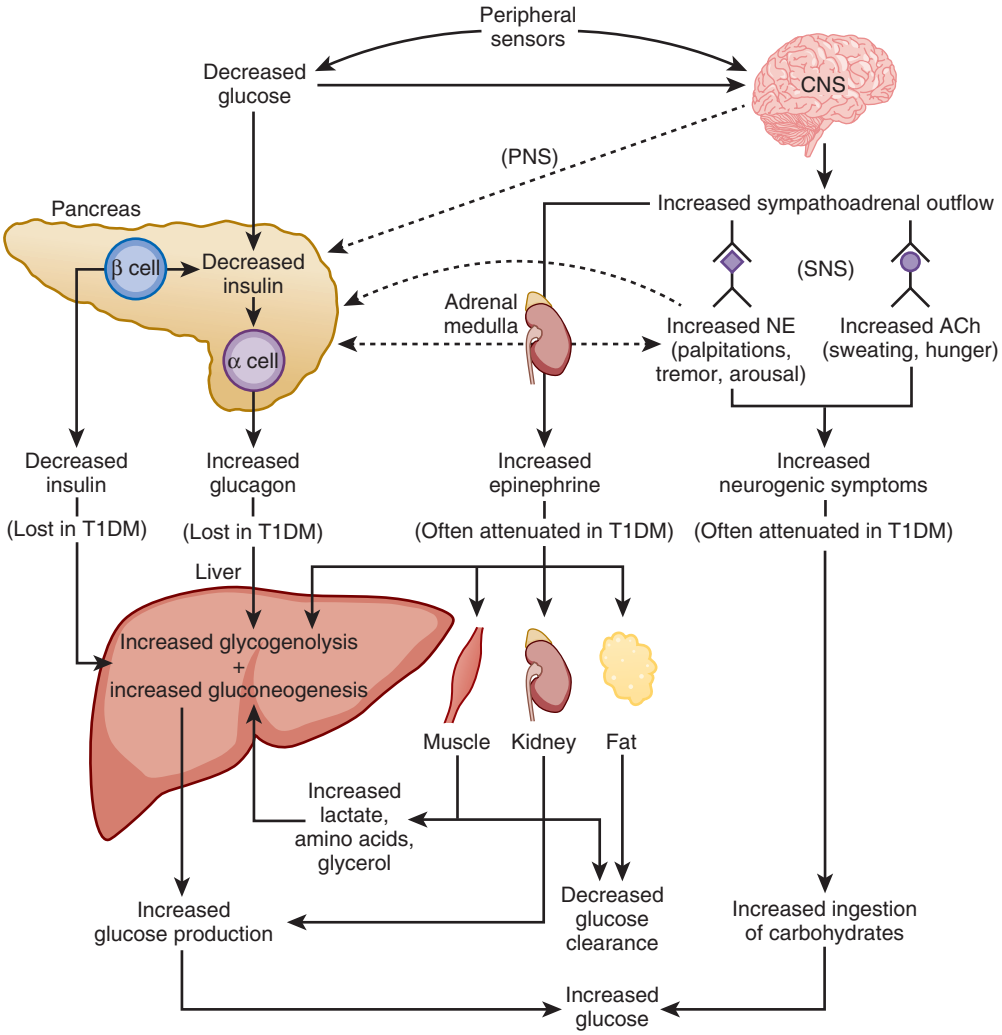
Symptoms of hypoglycemia can be divided into sympathoadrenal and neuroglycopenic responses. Sympathoadrenal activation causes tremulousness, palpitations, and anxiety from norepinephrine release[101,102] and sweating, hunger, and paresthesias from cholinergic stimulation.[101,102] As the glucose level drops below 50 mg/dL, the risk and severity of neuroglycopenic symptoms—warmth, weakness, fatigue, confusion, emotional lability, loss of consciousness, and seizures—increases[101] (Table 55.4).

The evolutionary importance in avoiding hypoglycemia is appreciated in the multiple redundant responses to signal and mount a response to a low blood glucose level. As glucose levels approach 81 mg/dL, insulin secretion is reduced. This reduction in insulin results in decreased glucose uptake by skeletal muscle and adipose tissue along with reduced inhibition of glucagon, leading to increased glycogenolysis in the liver, increased gluconeogenesis in the liver and kidney, and lipolysis in the adipose tissue.[102] At glucose levels of 65 to 70 mg/dL, there is an increase in glucagon and epinephrine secretion as well as an increase in cortisol and growth hormone. Increases in glucagon stimulate glycogenolysis and gluconeogenesis in the liver, providing a primary role in preventing hypoglycemia.[101,102] Epinephrine further reduces glucose utilization and stimulates hepatic gluconeogenesis and glycogenolysis as well as renal gluconeogenesis.[101–103] Epinephrine also mobilizes gluconeogenic substrates such as amino acids, lactate, and glycerol.[101] Epinephrine is a critical defense against hypoglycemia when glucagon secretion is deficient, such as in patients with prolonged type 1 DM.[101,102] Although glucagon and epinephrine act quickly—within minutes—cortisol and growth hormone limit glucose utilization over hours. Both cortisol and growth hormone prevent prolonged hypoglycemia by limiting glucose utilization and increasing glucose production.[101,104] When these mechanisms fail, hypoglycemia ensues and at glucose levels of 50 to 55 mg/dL, neurogenic and neuroglycopenic symptoms are present (Fig. 55.5).[101,105]

Hypoglycemia in Patients With Diabetes or Who Receive Insulin

Hypoglycemia that occurs in insulin-treated patients is the result of insulin excess in combination with altered carbohydrate availability, increased sensitivity to insulin, reduced clearance of insulin, increased glucose utilization, or compromised glucose counterregulation.[101]

Insulin secretagogues such as a sulfonylureas or meglitinides (glinides) stimulate endogenous insulin release through binding of adenosine triphosphate–sensitive potassium channels on the sulfonylurea receptor, resulting in depolarization of the β-cell membrane, opening of the voltage-gated calcium channels, calcium



• **Fig. 55.5** Physiologic and behavioral defenses against hypoglycemia in humans. *ACh,* Acetylcholine; *CNS,* central nervous system; *NE,* norepinephrine; *PNS,* parasympathetic nervous system; *SNS,* sympathetic nervous system; *T1DM,* type 1 diabetes; *α-cell,* pancreatic islet alpha cells; *β-cell,* pancreatic islet beta cells. (From Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. *J Clin Invest.* 2006;116:1470–1473, used with permission of the American Society of Clinical Investigation.)

influx, and eventually secretion of insulin.[106] Peak plasma concentrations of sulfonylureas occurs in 1 to 8 hours but the duration of action has a very wide range. Chlorpropamide, a long-acting sulfonylurea with 30% renal clearance, can have a duration of action of up to 60 hours in the setting of reduced renal clearance in kidney failure.[106] Glyburide, another long-acting sulfonlylurea, has a duration of action of 12 to 24 hours in therapeutic doses, although the half-life is prolonged in the setting of renal dysfunction owing to reduced renal clearance of active metabolites.[106] Second-generation sulfonylureas such as glipizide and glimepiride are less affected by renal dysfunction as they are metabolized to inactive metabolites that do not cause further hypoglycemia.[106] Glinides (repaglinide and nateglinide) have a more rapid onset and shorter duration of action and are therefore associated with less prolonged hypoglycemia.[107] Diabetes medications that affect insulin resistance and carbohydrate metabolism (metformin, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, amylin, incretin mimetics, bile acid sequestrants, or bromocriptine) typically do not cause hypoglycemia unless used in combination with insulin or an insulin secretagogue.

Hypoglycemia Unawareness (Hypoglycemia-Associated Autonomic Failure)

Recurrent hypoglycemia, particularly in the setting of exercise and sleep, blunt the normal adrenomedullary and sympathetic neural counterregulatory responses to hypoglycemia. This condition is known as hypoglycemia-associated autonomic failure (HAAF), or hypoglycemic unawareness.[103] This establishes a vicious cycle of recurrent hypoglycemia and further reduced hypoglycemic awareness.[102,108] The risk of severe hypoglycemia is markedly increased in patients with HAAF. Furthermore, the response to glucagon and epinephrine may already be blunted in the critically ill patient, further increasing the hypoglycemic risk in patients with HAAF.[108]

Loss of autonomic response to hypoglycemia is particularly important in patients with type 1 DM who lose α-cell production of glucagon over time.[102] The inability to regulate β-cell (insulin) and α-cell (glucagon) secretion increases the risk of iatrogenic hypoglycemic 25-fold. This is highlighted in the significant glycemic instability in patients after pancreatic surgery or severe pancreatitis.[11]

Management of Hypoglycemia in Diabetes

Appropriate treatment of hypoglycemia in the hospitalized patent requires standardized treatment regimens and protocols to avoid prolonged exposure to low glucose or rebound hyperglycemia. In a person who can tolerate oral intake, documented hypoglycemia should be treated with a measured amount of readily absorbable glucose (fruit juice, glucose tabs, or gel). For glucose levels of 50 to 69 mg/dL, the "rule of 15" applies; 15 g of glucose is administered with a repeat glucose measured in 15 minutes. Additional 15-g doses of glucose are given until the glucose level is greater than 70 mg/dL. If the initial measured glucose is less than 50 mg/dL, 20 to 30 g of readily absorbable glucose should be given.[109] Parenteral therapy with 25 g of 50% dextrose is necessary when neuroglycopenic symptoms are present or the patient is NPO.[101,109] Patients whose status is postbariatric surgery may have an ineffective response to oral glucose and should be treated with parenteral glucose. Because α-glucosidase inhibitors delay the breakdown and absorption of polysaccharides from the small intestine, patients taking these medications require oral glucose (a monosaccharide) rather than sucrose or lactose (disaccharides) to correct hypoglycemia.[110] Glucagon should be used in those with neuroglycopenic symptoms and no IV access, although it should be noted that those with depleted glycogen stores cannot respond to glucagon.

Appreciating the etiology of the hypoglycemia will help prevent further episodes. When hypoglycemia is secondary to a long-acting insulin, patients require dextrose-containing IVFs to prevent recurrent hypoglycemia. In the case of hypoglycemia secondary to a long-acting insulin secretagogue overdose, particularly glyburide, correction of glucose with carbohydrate intake alone commonly results in recurrent hypoglycemia. In this setting, octreotide, which reduces pancreatic insulin secretion, is a useful therapy and results in less recurrent hypoglycemia than conventional therapy (glucagon and dextrose).[106] The suggested dose of octreotide in this setting is 1 μg/kg every 12 hours to reduce insulin secretion.[106] In most cases, treatment can be stopped after 12 to 72 hours, but glucose monitoring should continue for at least 12 to 24 hours after cessation of treatment.[106]

Prevention of Hypoglycemia

Many episodes of hypoglycemia in the ICU are preventable with attention to changes in nutritional status, glucocorticoid adjustments, changes in pressor requirements, and the clinical status of the patient. Pressors, such as norepinephrine, result in hyperglycemia by reducing glucose utilization and stimulating hepatic gluconeogenesis and glycogenolysis,[101–103] whereas glucocorticoids increase glucose by decreasing skeletal muscle uptake of glucose and increasing glucose production.[101,104] Therefore reduction or cessation of pressors or glucocorticoids is expected to result in improvement in hyperglycemia and reduction in insulin requirements. Similar improvements in glucose are seen when a patient's clinical status improves, resulting in reduced endogeneous production of cortisol and epinephrine.

The single best predictor of hypoglycemia in the hospital is decreased nutrition.[111] Lowering or discontinuing nutrition without adjusting insulin is highly associated with hypoglycemia.[100] The hypoglycemia is exaggerated if a long-acting insulin is used to cover nutritional insulin requirements.[111] In addition, oral agents and premixed (i.e., 70/30 or 75/25) insulin should not be used in the hospital to treat hyperglycemia owing to interruptions in nutrition. Patients with poor oral intake require lower mealtime insulin doses, or mealtime insulin may be given within 15 minutes of completing the meal when the amount of oral intake is uncertain. Holding parenteral or enteral nutrition requires a decrease in basal insulin requirements and/or supplemental IV dextrose. Patients who are insulin dependent (i.e., those with type 1 DM) will progress to DKA without basal insulin; therefore basal insulin should be continued and IV dextrose supplemented as needed to avoid hypoglycemia. Nutrition can be calculated for precise dosing. For example, Glucerna 1.5 tube feeds (TF) has 133.1 g of carbohydrates per liter compared with 50 g of dextrose in 1 liter of 5% dextrose IVF. Allowing for differences in fiber, the D_5 IVF should be infused at approximately 2.7 times the TF rate to offer an equivalent amount of carbohydrates. Table 55.5 lists risk factors for hypoglycemia in hospitalized patients.

Hypoglycemia in Patients Without Diabetes

Because of counterregulatory mechanisms, hypoglycemia is very rare in patients without DM.[104] The differential diagnosis for hypoglycemia in patients without DM differs according to the clinical status of the patient: those who are otherwise healthy and those with an underlying illness (Table 55.6). Medications are the most common cause of hypoglycemia. Other etiologies include

TABLE 55.5 Risk Factors for Hypoglycemia in the Hospitalized Patient[111]

Risk Factor	Prevention
Initiation of insulin	Individualized insulin dosing
Inappropriate timing of mealtime insulin	Mealtime insulin boluses up to 15 min before or 15 min after meal
Overuse or overdosing of correctional doses of insulin	Individualized insulin dosing based on total daily insulin requirements
Change in nutrition	Standardized orders to adjust insulin or add intravenous fluids with dextrose
Reduction in corticosteroid dose	Adjust insulin doses as steroid dose is tapered

TABLE 55.6 Causes of Hypoglycemia in Adults

Ill or Medicated Individual	Seemingly Well Individual
1. Drugs Insulin or insulin secretagogue Alcohol Others 2. Critical illnesses Hepatic, renal, or cardiac failure Sepsis (including malaria) Inanition 3. Hormone deficiency Cortisol Glucagon and epinephrine (in insulin-deficient diabetes mellitus) 4. Non–islet cell tumor	1. Endogenous hyperinsulinism Insulinoma Functional cell disorders (nesidioblastosis) Noninsulinoma pancreatogenous hypoglycemia Post–gastric bypass hypoglycemia Insulin autoimmune hypoglycemia Antibody to insulin Antibody to insulin receptor Insulin secretagogue Other 2. Accidental or malicious administration of antidiabetic agents

From Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94:709–728.

TABLE 55.7 Examples of Medications Implicated as Causative Agents for Hypoglycemia[104]

Suspected Mechanism	Agent(s)
Accidental or malicious administration of antidiabetic agents	Insulins, sulfonylureas, glinides
Increased insulin or decreased clearance	Quinine, pentamidine, isoniazid, lithium, haloperidol, chloroquine, indomethacin
Decreased hepatic glucose output	Alcohol, unripe ackee fruit
Autoimmune	Isoniazid, interferon alfa, hydralazine, procainamide, sulfhydryl-containing drugs
Interactions with sulfonylureas	Phenylbutazone, colchicine, paracetamol
β-Cell toxicity	Pentaminide
Unknown mechanism	Sulfonamide, salicylates, warfarin, octreotide

critical illness, hormone deficiency, non–islet cell tumors, endogenous hyperinsulinemia, and accidental hypoglycemia (see Table 55.6). A list of drugs and suspected mechanisms of hypoglycemia can be found in Table 55.7. Patients with Whipple's triad (symptoms and signs of hypoglycemia, a low plasma glucose concentration, and resolution of symptoms or signs after the plasma glucose is corrected) require further evaluation.[104] A detailed history, examination, and clinical evaluation are required to elucidate the etiology of the hypoglycemia.

Habitual drinkers often consume alcohol over other forms of nutrition, depleting glycogen stores and forcing the body to rely on gluconeogenesis. Acute alcohol consumption reduces endogenous glucose production owing to inhibition of hepatic gluconeogenesis. This effect is worsened in patients with hepatic insufficiency. Despite these mechanisms, hypoglycemia occurs in few adults because of alcohol (1%–4%), although children who present with acute alcohol ingestion are at higher risk for hypoglycemia.[112,113]

Cortisol deficiency is associated with increased insulin sensitivity, reduced glucose production, and increased glucose disposal.[114] The pathophysiology that increases the risk of hypoglycemia in patients with untreated adrenal insufficiency is mitigated with doses of glucocorticoids concomitant to the level of illness.

Hospitalized patients are at risk for hypoglycemia related to poor nutrition, renal failure, heart failure, liver disease, advanced age, infections, and intensity of treatment regimens.[114–117] Hypoglycemia in hospitalized patients is associated with excess mortality.[115,116] In sepsis, the rate of glucose use exceeds that of production.[118] Initially, hyperglycemia results from an increase in stress hormones including glucagon and epinephrine, resulting in stimulation of insulin release and increased glucose utilization by skeletal muscle and adipose tissue. Hypoglycemia eventually develops as the result of reduced hepatic gluconeogenesis.[118] Malnutrition, and renal and liver failure further exacerbate the risk of hypoglycemia in sepsis. Renal failure leads to reduced renal gluconeogenesis and reduced clearance of insulin and secretagogues.[114,117] Similarly, liver failure reduces hepatic gluconeogenesis and glycogenolysis.[114] Thus multiorgan failure dramatically increases the risk of hypoglycemia.

Insulinomas are a rare cause of hypoglycemia with an annual incidence of 0.7 to 4 cases per million population.[114] Their incidence is highest in the fifth decade and 5% to 10% occur as part of multiple endocrine neoplasia type 1.[114] Patients typically present with recurrent spontaneous fasting hypoglycemia.[114] In contrast, patients with post–gastric bypass hypoglycemia have postprandial hypoglycemia.[119] Although the mechanism of post–gastric bypass hypoglycemia has not been completely established, it is thought to be at least partially related to rapid gastric emptying, which results in an excessive rise in glucose. The subsequent elevation in glucose stimulates an exaggerated glucagon-like peptide 1 response, which in turn stimulates insulin release and hypoglycemia.[119]

Approach to the Nondiabetic Patient With Hypoglycemia

Only patients with Whipple's triad should be evaluated for a hypoglycemic disorder.[104] A thorough review of the patient's clinical and laboratory data can often lead to the reason for hypoglycemia without a prolonged and costly workup. When the cause is identified, steps should be taken to avoid recurrent episodes of hypoglycemia. Hypoglycemia related to critical illness should be a diagnosis of exclusion.

When the cause of hypoglycemia is not evident, laboratory evaluation during an episode of spontaneous hypoglycemia is required. This includes measurement of plasma glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and a screen for oral hypoglycemic agents.[104] Insulin antibodies should be measured when antibody-induced hypoglycemia is suspected. Once samples for laboratory tests are drawn, 1 mg of glucagon should be administered IV to observe the response of plasma glucose.[104] Some patients may require a 72-hour fast to induce spontaneous hypoglycemia, although this is not recommended in a critically ill patient. A 72-hour fast protocol is listed in Fig. 55.6.

Once laboratory test results are received, they must be interpreted to determine the cause of hypoglycemia. Table 55.8 shows interpretation of the laboratory results. Patients with documented endogenous fasting or postprandial hyperglycemia with a negative screen for oral hypoglycemic agents and no circulating insulin antibodies should have computed tomography or magnetic resonance imaging scans or transabdominal ultrasonography to localize an insulinoma.[104]

Suggested protocol for a prolonged diagnostic fast

- Date the onset of the fast as the time of the last food intake.
- Discontinue all nonessential medications.
- Allow the patient to drink calorie-free beverages. Ensure that the patient is active during waking hours.
- Collect samples for plasma glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate every 6 h until the plasma glucose concentration is <60 mg/dL; at that point the frequency of sampling should be increased to every 1–2 h.
- Samples for plasma insulin, C-peptide, and proinsulin should be sent for analysis only in those samples in which the plasma glucose concentration is <60 mg/dL.
- End the fast when the plasma glucose concentration is <45 mg/dL and the patient has symptoms and/or signs of hypoglycemia (or if 72 h have elapsed without symptoms).
- The decision to end the fast before 72 h should not be based on a low plasma glucose concentration alone, in the absence of symptoms or signs, because some healthy individuals, especially women and children, have low glucose levels during prolonged fasting.
- Alternatively, the fast can be ended when the plasma glucose concentration is <55 mg/dL without symptoms or signs if Whipple's triad was documented unequivocally on a prior occasion.
- A low plasma glucose concentration is a necessary, albeit not in itself sufficient, finding for the diagnosis of hypoglycemia. Therefore, the decision to end the fast should be based on laboratory-measured plasma glucose concentrations, not those estimated with a point-of care.

• **Fig. 55.6** Suggested protocol for a prolonged diagnostic fast. (From Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94:709–728.)

TABLE 55.8 Patterns of Clinical and Serum Chemistry Findings After Fasting or a Mixed Meal

Symptoms/ Signs	Glucose (mg/dL)	Insulin (μU/mL)	C-peptide (nmol/L)	Proinsulin (pmol/L)	β-Hydroxy-Butyrate (mmol/L)	Glucose Increase After Glucagon (mg/dL)	Circulating Oral Hypoglycemic Agent	Antibody to Insulin	Diagnostic Interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Negative (positive)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Negative	Insulinoma, post–gastric bypass hypoglycemia
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Negative	Oral hypoglycemic agent
Yes	<55	≥3	≫0.2	≫5	≤2.7	>25	No	Positive	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Negative	IGF-mediated
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Negative	Not insulin (or IGF)-mediated

IGF, Insulin-like growth factor.

Key Points

- Despite advances in the management of critical illness, DKA and HHS remain life-threatening diabetic emergencies.
- DKA and HHS are often precipitated by interruption of insulin treatment, infection, or other acute illness, but may also be the initial presentation of diabetes.
- IV insulin is the treatment of choice for hyperglycemia in critically ill patients as it allows for frequent dose adjustments as necessary for the successful management of hyperglycemic emergencies.

- Attention to potassium replacement is essential to successful management of hyperglycemic emergencies.
- Target glucose in critically ill patients is 140 to 180 mg/dL, with attention given to avoidance of hypoglycemia.
- An HbA_{1c} test on admission distinguishes between stress hyperglycemia and previously unrecognized DM and helps guide therapy and the need for insulin therapy at the time of discharge.
- A physiologic insulin regimen, rather than oral hypoglycemics or sliding scale insulin alone, is the appropriate strategy for glucose control in the hospitalized patient.
- Recurrent hypoglycemia blunts the normal counterregulatory response in patients with type 1 DM and predisposes to severe hypoglycemia.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. A 64-year-old man presents to the emergency department with dizziness, nausea, vomiting, and abdominal pain. His past medical history is significant for type 2 diabetes, hypertension, and hyperlipidemia. Medications include insulin glargine 25 units nightly, metformin 1000 mg bid, lisinopril 10 mg daily, atorvastatin 10 mg daily, and canagliflozin 100 mg daily. He reports a recent upper respiratory tract infection with reduced appetite over the past several days. During this time, he held insulin glargine but continued his other medications. Laboratory evaluation is provided in the following table:

Evaluation	Level
Sodium	135 mmol/L
Potassium	5.3 mmol/L
Chloride	97 mmol/L
Carbon dioxide	12 mmol/L
Creatinine	1.3 mg/dL
Glucose	210 mg/dL
Lactate	2 mg/dL

Physical examination is significant for blood pressure of 110/60 mm Hg and heart rate of 113 beats/min. Cardiovascular examination reveals tachycardia. Lungs are clear, and the abdomen is mildly tender to palpation diffusely. There is reduced skin turgor and dry mucous membranes.

Which of the following medications should not be restarted upon discharge?

a. Metformin
b. Lisinopril
c. Canaglifozin
d. Glargine

Answer: c. Canaglifozin is the correct answer as the patient's presentation is consistent with euglycemic diabetic ketoacidosis (DKA) from sodium glucose cotransporter (SGLT-2) inhibitor. Metformin (answer a) is not the correct answer as the patient's creatinine is 1.3. Once his DKA is treated, this will likely improve further and metformin can be restarted safely. In addition, given that his lactate level is normal, his anion gap metabolic acidosis is not related to lactic acidosis from metformin. Lisinopril (answer b) is not correct as his blood pressure is likely low-normal owing to DKA and dehydration. He should safely be able to restart this upon discharge. Glargine (answer d) is incorrect as most patients with euglycemic DKA from SGLT-2 inhibitors have relative insulin deficiency and develop DKA in the setting of insulin cessation. This patient will need to be taking insulin after discharge.

2. A 56-year-old obese man was admitted and treated in the intensive care unit (ICU) for pneumonia and sepsis. On admission, his glucose level was elevated, requiring an insulin infusion during his ICU stay. A hemoglobin A_{1c} (glycosylated hemoglobin; HbA_{1c}) measured on admission was 8.5%, although he had no known history of diabetes. His current insulin infusion rate is 2 units/h and has been stable for the past 2 hours. Renal function has normalized. He passed a swallow study and is tolerating a full diet, although he has had more fluctuation in glucose since he started eating.

Which of the following is the most appropriate way to transition him away from the insulin drip?

a. Stop the insulin drip and start insulin on a sliding scale.
b. Stop the insulin drip and start metformin.
c. Start lantus 48 units nightly and stop the insulin drip 2 hours after it is given.
d. Start 0.4 units/kg body weight insulin divided as 50% long-acting and 50% short-acting and stop the insulin drip 2 hours after long-acting insulin.

Answer: d. Patients younger than 70 years of age with a normal glomerular filtration rate not previously on a stable insulin dose should be started on basal bolus insulin at a dose of 0.4 to 0.5 U/kg body weight divided as 50% basal and 50% mealtime insulin. Answer a is not correct because sliding scale only insulin is never appropriate for managing diabetes in the hospital. Answer b is not correct because oral agents and premixed insulin are not appropriate in the hospital because of potential changes in nutrition and medical status. Answer c is not correct because the patient's insulin dose should not be calculated based on his insulin drip as his insulin drip has not been stable for at least 6 hours. In addition, basal insulin therapy without mealtime insulin is not appropriate in this patient given that he is eating.

3. A 75-year-old man is admitted to the ICU after a Whipple procedure performed for pancreatic cancer. He has a history of preexisting diabetes using metformin and glipizide before admission. After surgery, his glucose levels remained below 150 mg/dL until tube feeds were started. Blood sugars levels have been controlled for the past 48 hours with NPH 14 units every 8 hours while receiving Glucerna 1.5 at 60 mL/h (about 191 g carbohydrates over 24 hours). This morning he developed abdominal distention and tube feeds were held an hour ago (at 9 am) with plans for a computed tomography scan of the abdomen. He received his morning dose of NPH at 8 am. The current glucose level is 100 mg/dL. Which of the following is the most appropriate plan to prevent hypoglycemia?

a. Give an ampule of 50% dextrose (D50) now and monitor glucose hourly until tube feeds can be restarted.
b. Start D5 normal saline solution at 160 mL/h.
c. Start D10 at 45 mL/h.
d. No intervention is needed because the glucose level is currently normal.

Answer: b. The patient is receiving Glucerna 1.5 with 191 g carbohydrates over 24 hours. This is about 7 to 8 g of carbohydrates per hour. The equivalent amount of carbohydrates should be delivered with dextrose-containing fluids to prevent hypoglycemia given that the patient has already received insulin. Administering D5 in normal saline solution at 160 mL/h will provide the equivalent amount of carbohydrates per hour. Answer a is not correct as the patient is not hypoglycemic and so does not require D50 now. In addition, if no further glucose is given, he is very likely to develop hypoglycemia. Answer c is not correct as D10 at 45 mL/h would provide only 4.5 g of glucose per hour. Answer d is not correct as the patient is at significant risk of hypoglycemia with the change in nutrition.

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Adrenal Insufficiency in the Critically Ill Patient

WALTER MICKEY, FARID SADAKA, AND STEVEN J. TROTTIER

CHAPTER OUTLINE

Incidence and Prevalence
- Pathophysiology
- Glucocorticoid Synthesis
- Glucocorticoid Actions

Etiology and Pathogenesis
- Autoimmune Disease
- Infectious Disease
- Acquired Immunodeficiency Syndrome
- Neoplasia
- Medications
- Adrenal Hemorrhage
- Etiology of Secondary Adrenal Insufficiency

Clinical Features

Diagnosis
- Laboratory Findings
- Diagnostic Tests

Critical Illness–Related Corticosteroid Insufficiency

Management
- Preexisting Adrenal Insufficiency
- Hemodynamically Stable Patient
- Hemodynamically Unstable Patient
- Severe Sepsis and Septic Shock

Etomidate

Summary

Adrenal insufficiency (AI) is by far the most common adrenal disorder seen in the intensive care unit (ICU) and is the focus of this chapter. It occurs more frequently in critically ill patients than in general hospitalized patients and represents a true emergency that requires rapid diagnosis and treatment. If missed, the condition can be fatal. In addition, because critical illness is often the precipitant of overt AI, the intensivist may have the first and only chance to make the diagnosis.[1]

Primary AI results from a subtotal or complete destruction of the adrenal cortex (>90%) and results in cortisol, aldosterone, and androgen deficiency. Multiple causes of primary AI include autoimmune destruction (Addison disease), polyendocrine deficiency syndrome, infections (e.g., tuberculosis, fungus), vascular compromise, primary or metastatic cancer, amyloidosis, and surgical removal of the adrenal glands.

Secondary AI is much more common than primary AI and can be traced to a lack of adrenocorticotropic hormone (ACTH). Without ACTH to stimulate the adrenal glands, production of cortisol falls but aldosterone secretion remains intact. The most common cause of secondary AI is the inadvertent abrupt withdrawal of therapeutic exogenous corticosteroids. Another cause of secondary AI is the surgical removal of benign or noncancerous, ACTH-producing tumors of the pituitary gland (Cushing syndrome). In this case, the source of ACTH is suddenly removed, and replacement hormones must be taken until normal ACTH and cortisol production resumes.

Less commonly, secondary AI occurs when the pituitary gland reduces or ceases production of ACTH. This can occur for a variety of reasons, including tumors or infections of the area, loss of blood flow to the pituitary, radiation for the treatment of pituitary tumors, total or subtotal removal of the hypothalamus, and surgical removal of the pituitary gland.

The term "relative adrenal insufficiency" has been replaced in recent literature by "critical illness–related corticosteroid insufficiency" (CIRCI),[2,3] which is characterized by corticosteroid activity that is inadequate for the severity of the illness of a patient.

Patients at risk of AI vary from young athletes using steroids to persons taking adrenal extracts for "adrenal fatigue syndrome." Also at risk are those receiving chronic topical glucocorticoid treatment for dermatologic disorders. Patients who are using glucocorticoids and inhibitors (such as itraconazole, diltiazem) of cytochrome 450 (CYP) 3A4 are at risk as well.[4] For all these reasons the intensivist must understand clinical problems associated with the hypothalamic-pituitary-adrenal (HPA) axis and the use of glucocorticoid hormones.

Incidence and Prevalence

The actual incidence of acute AI is unknown. The incidence of HPA axis failure varies depending on the criteria used to make the diagnosis and the patient population studied. At least 90% of both adrenal glands must be destroyed before clinical and biochemical manifestations of AI occur. The overall incidence of AI is estimated to be as high as 60% in patients with severe sepsis and septic shock.[5] Secondary AI may be more common than primary AI. The clinical presentation of secondary AI is relatively nonspecific and often resembles other conditions common in the ICU. Hence

it is not uncommon to attribute the clinical features resulting from acute AI to commonly seen medical conditions in the ICU.[6]

Pathophysiology

To understand the pathogenesis of adrenal diseases one must understand the physiology of the adrenal glands and the causes that result in the disruption of the physiologic process.

The adrenal glands are pyramid-shaped, each weighing about 5 to 10 g, and are located just superior to their respective kidneys. The left adrenal gland is usually slightly more cephalad than the right gland. Each adrenal gland is composed of an inner medulla and outer cortex. These layers are embryologically, anatomically, and physiologically distinct. The adrenal cortex is responsible for the secretion of multiple steroid hormones. The adrenal medulla is responsible for the secretion of catecholamines.

The adrenal cortex is composed of three zones: the outer zona glomerulosa, inner zona fasciculata, and zona reticularis. The zona glomerulosa secretes the mineralocorticoid aldosterone in response to angiotensin, ACTH, and a high circulating potassium concentration. The zona fasciculata and zona reticularis secrete glucocorticoids and adrenal androgens.

The principal mineralocorticoid is aldosterone, which is regulated not only by ACTH but also by serum sodium and potassium levels and by the renin-angiotensin system.[7,8] Mineralocorticoids exert their primary effect on distal renal tubule cells, resulting in renal sodium retention at the expense of potassium loss in the urine. A third major class of adrenal steroids is the sex hormones: dehydroepiandrosterone (DHEA), DHEA-sulfate, and androstenedione. Like the glucocorticoids, ACTH primarily regulates these steroid hormones. They function mainly as precursors for the primary circulating androgen, testosterone, and may also undergo separate conversion to estrogen hormones. In critically ill patients, glucocorticoids are the steroid hormones of greatest concern and therefore remain the focus of the remainder of this discussion.

Glucocorticoid Synthesis

Glucocorticoid synthesis is regulated by (1) a negative feedback mechanism involving cortisol and adrenal steroids, (2) a diurnal rhythm, and (3) stress. The hypothalamus and the pituitary gland closely regulate adrenal hormone production. Corticotropin-releasing hormone (CRH) is produced in the hypothalamus and acts on specialized cells in the pituitary, stimulating production of ACTH, which serves, in turn, to stimulate adrenal cortical cells to produce numerous steroid hormones, including cortisol. Adrenal hormones have a negative influence at the level of the hypothalamus and the pituitary, inhibiting CRH and ACTH release. The adrenal gland in turn ceases its secretory activity until the cortisol concentration returns to normal. When serum cortisol levels are below normal, secretion of CRH and ACTH increases, stimulating the adrenal glands to produce cortisol until its level normalizes. Therefore abnormalities in circulating serum levels of adrenal steroid hormone can be caused by either adrenal or hypothalamic pituitary disease. Because ACTH possesses α-melanocyte–stimulating hormone activity, excessive production of ACTH is associated with hyperpigmentation.

Cortisol is normally secreted in a diurnal pattern. The circulating cortisol level is increased in the morning hours, at approximately 8 a.m. Serum cortisol concentrations decrease throughout the remainder of the day.[9] Similarly, the serum cortisol response to ACTH stimulation also varies in a circadian rhythm. Afternoon responsiveness is much greater because of the decreased circadian level of cortisol at that time. In addition, cortisol is secreted in a series of pulses rather than in a continuous fashion. These factors contribute to make interpretation of a random cortisol level and the ACTH-stimulated value difficult.

"Stress" (exemplified by sepsis, major surgery, or trauma) also affects glucocorticoid synthesis.[10–12] The *stress response* is characterized by continuous ACTH secretion despite a high serum cortisol concentration. Stress overrides all other regulatory mechanisms of cortisol secretion by the adrenal cortex and increases cortisol secretion irrespective of the time of day or the current serum cortisol concentration. The mechanism by which the HPA axis is regulated during stress is not clearly understood. Periventricular neurons in the hypothalamus respond to stress by increasing the levels of CRH messenger ribonucleic acid.[13,14] It has been shown that production of the cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α also plays an important role in the regulation of the HPA axis.[15–19] The cortisol secretion that occurs because of the activation of the HPA axis causes an inhibitory effect not only on the secretion of CRH and ACTH but also on the liberation of interleukins.[20] Thus there is a functional loop between immune activation and regulation of the HPA axis during stress.

The stress response is biphasic, consisting of an early phase in which both ACTH and cortisol are elevated and a late phase in which the serum cortisol level is elevated but the serum ACTH level is paradoxically low.[8] This is explained by the fact that endothelin and atrial natriuretic peptide are both elevated in severe illnesses. Endothelin increases cortisol production by the adrenals, whereas the atrial natriuretic peptide inhibits ACTH production by acting at the hypothalamic-pituitary level. Vasopressin and angiotensin II can increase ACTH secretion during stress conditions, such as sepsis and septic shock.

Acute respiratory failure causes a 50% to 100% rise in serum cortisol concentration. A twofold to sixfold rise occurs with septic shock and after surgical procedures and trauma. The rise in serum cortisol correlates positively with severity of illness[6] and negatively with survival.[7]

The normal daily output of cortisol by the adrenal glands is 20 to 30 mg. The normal adrenal gland secretes about 10 to 12 times the normal daily output of cortisol when under maximal physiologic stress. Hence approximately 200 to 300 mg of hydrocortisone or its equivalent is considered a daily "stress dose" of glucocorticoid.

Glucocorticoid Actions

After uptake of free hormone from the circulation, the effects of cortisol and aldosterone are mediated by binding to intracellular receptors termed the glucocorticoid receptor and the mineralocorticoid receptor.

Cardiovascular Effects

Glucocorticoids help to maintain vascular tone and cardiac contractility. The presence of glucocorticoids is important to the physiologic effects of catecholamines on vascular smooth muscle. Glucocorticoids affect blood pressure by different mechanisms, including direct action of glucocorticoids on the vasculature, permissive effects of the glucocorticoids on the vasopressor action of catecholamines, glucocorticoid-induced decrease in the levels of prostaglandin E_2 and kallikrein (vasodilators), and reduction of nitric oxide–mediated endothelial dilatation. Angiotensinogen synthesis is increased by glucocorticoids.[21] Glucocorticoids increase the synthesis of β-adrenergic receptors, reverse β_2-adrenergic receptor

dysfunction, and increase the coupling of the receptor with the second messenger system.[22]

Two hemodynamic states have been described during acute AI:

1. Low cardiac output, high systemic vascular resistance shock is caused by both decreased myocardial contractility and decreased preload.
2. High cardiac output, low systemic vascular resistance shock mimics septic shock.[23] It appears that patients with AI present initially with a combination of cardiogenic shock and hypovolemic shock. Intravascular volume expansion with intravenous (IV) fluids results in an increase in cardiac output and a lowering of systemic vascular resistance. The hemodynamic profile that one observes is dependent on the timing of hemodynamic assessment during the course of treatment in an individual patient. Thus the hypotension of AI can mimic cardiogenic, hypovolemic, or septic shock (depending on when the hemodynamic assessment was made) and may be poorly responsive or unresponsive to treatment with fluids and vasopressors in the absence of glucocorticoid therapy.

Metabolic Effects

Glucocorticoids increase blood glucose concentrations through their action on glycogen, protein, and lipid metabolism. A major action is on gluconeogenesis. Glucocorticoids increase hepatic glycogen and glucose by inducing the synthesis of hepatic enzymes and increasing the availability of gluconeogenic substrates. This is because of glucocorticoid-induced proteolytic activity on peripheral tissues, which causes mobilization of glycogenic amino acid precursors from peripheral supporting structures, such as bone, skin, muscle, and connective tissue, because of protein breakdown and inhibition of protein synthesis. Glucocorticoids decrease the peripheral uptake and utilization of glucose. They have a permissive effect on other hormones such as glucagon and catecholamines, thus serving to increase the circulating glucose concentration, which in turn increases insulin secretion, at the expense of protein and lipid catabolism.

Glucocorticoids increase lipolysis both directly and indirectly by action on other hormones. Glucocorticoids regulate fatty acid mobilization by enhancing activation of cellular lipase by lipid-mobilizing hormones (e.g., catecholamines, pituitary peptides). They elevate free fatty acid levels in the plasma and enhance any tendency to ketosis. Glucocorticoids stimulate peripheral protein metabolism, using the amino acid products as gluconeogenic precursors. Muscle protein synthesis is reduced, and thus glucocorticoids cause muscle atrophy.

Renal Effects

Glucocorticoids bind to the mineralocorticoid receptors in renal tubules and increase sodium reabsorption and excretion of potassium and hydrogen ions. Glucocorticoids increase the glomerular filtration rate, proximal tubular epithelial sodium transport, and free water clearance. Hyponatremia during AI can be secondary to the glucocorticoid inhibitory effect on vasopressin.[21]

Immunologic Effects

Glucocorticoids suppress immunologic responses, and this is the basis for their use in the treatment of autoimmune and inflammatory disorders. In the peripheral blood, they redistribute lymphocytes from the intravascular compartment to the lymphoid pool in the spleen, lymph nodes, and bone marrow. They therefore decrease lymphocyte counts, but neutrophil counts increase after glucocorticoid administration. Eosinophil counts fall as the result of eosinophil apoptosis. Glucocorticoids inhibit immunoglobulin synthesis and cytokine production from lymphocytes. Glucocorticoids also inhibit monocyte differentiation into macrophages.[21] Glucocorticoids mediate antiinflammatory effects by decreasing the release of inflammatory mediators such as histamine, cytokines, and prostaglandins. The immunologic actions of glucocorticoids are significant only in circumstances in which they are present in supraphysiologic amounts, such as markedly increased endogenous production or exogenous administration.

Gastrointestinal Effects

It has been postulated that CRH inhibits the release of motilin, a duodenal hormone that is responsible for the initiation of peristaltic contractions, which begin in the stomach and propagate distally. Glucocorticoids decrease CRH production and thus inhibit gastric and intestinal motility. This could explain the vomiting, constipation, and abdominal pain observed in cortisol deficiency. Glucocorticoids can also increase risk of peptic ulcer disease and pancreatitis.

Calcium Metabolism

Glucocorticoids lower serum calcium levels by several mechanisms. They inhibit calcium absorption from the gut, decrease renal calcium reabsorption (which results in hypercalciuria), and promote a shift of calcium from the extracellular compartment to the intracellular compartment. Glucocorticoids inhibit osteoblast function and cause osteoporosis, which occurs in approximately 50% of patients who require long-term use of glucocorticoids.[24] Avascular necrosis is a dreaded complication. It mainly affects the femoral head and causes pain and collapse of the bone, often necessitating hip replacement. Glucocorticoid-induced osteocyte apoptosis has been implicated in the pathogenesis of the condition, and the lack of a direct role for an interrupted blood supply suggests that the term osteonecrosis may be preferable to avascular necrosis.[21]

Other Effects

Glucocorticoids have many other effects, including the ability to produce significant mood changes and even psychosis in some patients. Glucocorticoids have been associated with neuronal death, especially in the hippocampus. Glucocorticoids have an association with cataract formation and increased intraocular pressure both by increasing aqueous humor production and decreasing drainage. They also negatively affect the production and action of a number of other hormones, including insulin, thyroid hormones, and gonadal hormones.

Aldosterone secretion is regulated mainly by the renin-angiotensin system. The most potent modulator of this system is renal perfusion. Hyperkalemia inhibits production of renin but increases the synthesis of aldosterone. Aldosterone increases sodium reabsorption in the collecting tubules and at the same time causes potassium and hydrogen ion excretion. This is mediated by the sodium ion–potassium ion (Na^+/K^+) pump in the presence of the enzyme Na^+/K^+-adenosine triphosphatase (ATPase) and results in sodium and water retention and an increase in intravascular volume.[21]

Hyperkalemia, hyponatremia, non–anion gap metabolic acidosis, hemoconcentration, and hypovolemia provide important clinical clues to the diagnosis of primary AI. Because ACTH is not a potent regulator of aldosterone secretion, secondary AI is usually not associated with hyperkalemia. Hyponatremia and hypovolemia may be present in secondary AI but not to the degree found in primary AI. The renin-angiotensin system is activated during AI and serves as a defense mechanism to improve the low intravascular

volume and the altered vasomotor tone that results from aldosterone and cortisol deficiency.[25,26]

Etiology and Pathogenesis

Causes of primary AI are shown in Box 56.1.

Autoimmune Disease

Autoimmune adrenalitis (Addison disease) is currently the most common cause of primary AI in the Western world and accounts for up to 80% of cases.[21] AI may occur as isolated disease or as part of a polyglandular autoimmune syndrome associated with thyroiditis, diabetes mellitus (Schmidt syndrome), hypogonadism, vitiligo, and pernicious anemia.[27,28] Autoimmune AI is more common in women than men and usually occurs in the third to fifth decades of life. The mean duration of symptoms before diagnosis is approximately 3 years. In this disorder high levels of circulating autoantibodies attack the cytoplasm of adrenal cortical cells and inhibit synthesis of glucocorticoids.[27,29]

• BOX 56.1 Causes of Primary Adrenal Insufficiency

- Autoimmune (idiopathic) 80% (most common cause)
- Infections
  - Tuberculosis (second most common cause)
  - *Pneumococcus* infection
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
  - *Meningococcus* infection
  - Cryptococcosis
  - Candidiasis
  - *Torulopsis* infection
  - Cytomegalovirus infection
- AIDS
- Neoplasia
  - Metastatic carcinoma
  - Lymphoma
- Infiltrative diseases
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
- Adrenal hemorrhage
- Sepsis
- Anticoagulants
- Coagulopathy
- Trauma
- Prior surgery
- Difficult pregnancy
- Vasculitis
- Postadrenal venography
- Medications
  - Ketoconazole
  - Phenytoin
  - Phenobarbital
  - Rifampin
  - Etomidate
  - Fluorouracil
  - Metyrapone
- Miscellaneous
  - Irradiation
  - Bilateral adrenalectomy
- Congenital conditions

Infectious Disease

Worldwide, infectious diseases are the most common cause of primary AI.[21]

Tuberculosis

Primary AI results from adrenal gland destruction by *Mycobacterium tuberculosis*. This infection currently accounts for less than 20% of cases.[30] This usually occurs in the presence of tuberculosis elsewhere in the body, especially with involvement of the lungs, genitourinary system, and gastrointestinal system. AI is usually manifest years after the initial presentation of tuberculosis.[31] The mean duration of symptoms of AI before diagnosis is 6 to 9 months. AI secondary to tuberculosis occurs with equal frequency in men and women. In contrast to autoimmune adrenalitis, tuberculosis-induced adrenal disease is not associated with other endocrine diseases. In addition, with tuberculosis the adrenal glands are enlarged and may be calcified. In contrast, the adrenal glands in autoimmune adrenalitis are usually atrophied and noncalcified.

Fungal Disease

Fungal disease can also cause primary AI. *Histoplasma capsulatum* is the most common organism. As seen in tuberculosis, fungal infection is usually disseminated and involves organs other than the adrenal glands. Adrenal involvement may be seen during the active phase or may develop years later after the disease has become "inactive." Sarosi and colleagues[32] reported that more than 50% of patients with disseminated histoplasmosis had AI, and AI was the most common cause of death.

Acquired Immunodeficiency Syndrome

Patients with AIDS are at risk of developing AI by several different mechanisms. Fungal infections are more common in this patient population, and disseminated disease may involve the adrenal glands. Similarly, mycobacterial infection, cytomegalovirus infection, and Kaposi sarcoma may cause involvement of the adrenal glands in up to 50% of patients.[3] In addition, sepsis and spontaneous adrenal hemorrhage are also seen in this group of patients. Because patients with human immunodeficiency virus infection now survive longer, an increased incidence of AI is likely.

Neoplasia

Neoplastic metastasis to the adrenal glands has been found on autopsy in 27% to 40% of patients who die of malignancy.[33–36] Yet metastatic carcinoma accounts for less than 1% of cases of primary AI.[33] This finding is explained by the tremendous functional reserve possessed by the adrenal glands. More than 90% of the adrenal gland must be destroyed before hypofunction occurs. Many patients with metastasis to the adrenals do not develop hormonal deficiency.[37] The most common neoplasms involving the adrenal glands are lung cancer, breast cancer, melanoma, and lymphoma.[35] AI usually occurs in the setting of widespread metastatic disease and is rarely the initial manifestation of malignancy.

Medications

Certain medications can cause AI. Of particular interest to the intensivist are ketoconazole, phenytoin, phenobarbital, rifampin, and etomidate. Ketoconazole decreases glucocorticoid synthesis and is also a glucocorticoid receptor antagonist. Although some

of the newer antifungal drugs (e.g., itraconazole and fluconazole) tend to be safer, AI that occurs after treatment with high doses has been reported, especially during states of increased glucocorticoid requirement, such as the severe stress associated with critical illness. Etomidate decreases glucocorticoid production even after a single injection. Phenytoin, rifampin, and barbiturates increase the catabolism of glucocorticoids. These medications can precipitate acute AI by decreasing glucocorticoid production or function in a patient who has compromised adrenal reserve.[28]

Adrenal Hemorrhage

Adrenal hemorrhage is an important but uncommon cause of AI in the ICU. The association of adrenal hemorrhage with fulminant sepsis was first described with *Neisseria meningitidis* (Waterhouse-Friderichsen syndrome). Infections with *Streptococcus pneumoniae, Staphylococcus* species, *Pseudomonas* species, and *Haemophilus influenzae* type b can also cause this syndrome.[28]

Besides the infectious causes, other conditions may predispose to adrenal hemorrhage, including severe illness (particularly cardiac disease), coagulopathy, anticoagulant therapy, thromboembolism, burns, and trauma.[38] Under these circumstances the typical signs and symptoms of AI are often mistaken for those of other common conditions. Typical settings include the patient who is in the first or second postoperative week or a patient who has recently started anticoagulation therapy. Common findings include abdominal, back, flank, or chest pain; nausea; vomiting; fever; altered mental status; orthostatic hypotension; and a sudden drop in the hematocrit level. The hemodynamic crisis associated with adrenal hemorrhage occurs 1 to 3 days after the initial hemorrhage.

Etiology of Secondary Adrenal Insufficiency

Causes of secondary AI are shown in Box 56.2. Secondary AI occurs because of a decrease in ACTH caused by either hypothalamic-pituitary disease or suppression of the HPA axis as a result of glucocorticoid therapy. The most common cause today is discontinuation of corticosteroid therapy. Nearly 1% of people in the general population (2.5% of those who are older than 70 years of age) are treated with long-term regimens of glucocorticoids for inflammation related to chronic disease.[28] Chronic glucocorticoid therapy leads to HPA axis suppression with resulting secondary AI if glucocorticoids are abruptly discontinued. With the exception of AI because of discontinuation of chronic glucocorticoid therapy, secondary adrenocortical insufficiency is much less common than primary AI. Isolated ACTH deficiency is rare, and ACTH is the last pituitary hormone to be impaired by enlarging sellar and suprasellar tumors.

Most patients admitted to the ICU with secondary AI have recently received steroid therapy or have taken steroids within the year before admission. No clear evidence indicates that detailing the duration or dose of steroid therapy predisposes patients to adrenal suppression. Doses of 25 mg of prednisone twice a day for 2 days, 12.5 mg/day for 6 months, or 5 mg/day for 5 years have all been shown to cause adrenal suppression. On the other hand, studies have shown that prednisone in doses less than 40 mg/day given every morning for 5 to 7 days did not cause adrenal suppression.[39]

As a practical guideline, in anyone who has received more than 20 mg of prednisone a day for more than 3 weeks adrenal function should be considered suppressed until proved otherwise.[40] If glucocorticoids have been given to a patient for more than 1 to 2 weeks, the regimen should be tapered to allow time for the adrenal glands to recover function. AI can occur in response to stress as long as 1 year after steroids are discontinued. All such patients should be evaluated for adrenal function and should be treated with stress doses of steroids during the interim period.

Patients with liver diseases may have AI. Signs of AI are present in 33% of patients with acute liver failure, 65% of patients with chronic liver disease and sepsis, and 92% of patients who have undergone a liver transplantation.[41] In patients with cirrhosis, AI is reported during sepsis and septic shock and is associated with increased mortality. Consequently, the term "hepatoadrenal syndrome" was proposed. Corticosteroid replacement in this patient population has yielded conflicting results, however. Patients with liver diseases should be carefully monitored for symptoms and signs of adrenal insufficiency.[42]

Another potential problem is hypopituitarism related to brain injury. Pituitary dysfunction occurs in up to 30% of patients with brain injury and may not appear until months or years after the traumatic incident.[43]

• BOX 56.2 Causes of Secondary Adrenal Insufficiency

Glucocorticoid therapy (most common cause of secondary adrenal insufficiency)
Neoplastic
- Pituitary adenoma
- Meningioma
- Craniopharyngioma
- Metastatic carcinoma
- Breast
- Lung
- Gastrointestinal
- Lymphoma
- Leukemia

Vascular
Pituitary apoplexy
Sheehan syndrome
Sickle cell disease
Intracranial aneurysm
Cavernous sinus thrombosis
Vasculitis
Eclampsia
Infection
- Tuberculosis
- Fungal infection
- Malaria
- Actinomycosis
- Viral infection

Autoimmune disorders
Infiltrative disorders
Sarcoidosis
Hemochromatosis
Irradiation
Head trauma and pituitary surgery
Isolated adrenocorticotropic hormone deficiency

Clinical Features

Common symptoms and signs of AI are shown in Box 56.3. The symptoms, signs, and general laboratory findings seen in AI are nonspecific. However, when taken together they form a pattern of findings that should suggest the possibility of AI. Clinical features can be divided into acute AI and chronic AI. Patients with acute

• BOX 56.3 Common Symptoms and Signs of Adrenal Insufficiency

Symptoms

- Weakness
- Fatigue
- Anorexia
- Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, constipation, and weight loss)
- Orthostatic symptoms
- Myalgias
- Arthralgias

Signs

- Weight loss
- Orthostatic hypotension
- Hyperpigmentation
- Vitiligo
- Confusion/psychosis

AI share many characteristics with patients who have chronic AI, but the symptoms are usually more severe in the acute setting.

The most common complaints associated with chronic adrenal insufficiency are fatigue, weight loss, and gastrointestinal complaints, including nausea, vomiting, and diarrhea. More than half of patients with chronic AI experience postural hypotension. Less commonly patients may develop arthralgias, myalgias, and psychiatric disease, including depression, memory impairment, delirium, and psychosis. Decreased axillary and pubic hair as well as amenorrhea can be seen in women of childbearing age. Patients with primary AI may have hyperpigmentation of the tongue, buccal mucosa, palmar creases, and scar tissue. This is caused by increased production of melanocyte-stimulating hormone, a cleavage product of proopiomelanocortin, which is the precursor for ACTH. Hyperpigmentation is notably absent in secondary AI. The classic presentation of acute AI is a patient with unexplained hemodynamic instability who is unresponsive to intravascular volume resuscitation and use of vasopressors. The associated symptoms are generally nonspecific and are the same as chronic AI. Abdominal pain is common and in the case of adrenal hemorrhage or infarct may mimic an acute surgical abdomen. If the underlying problem is autoimmune adrenalitis, the patient may have vitiligo, pernicious anemia, or one of the other associated endocrinopathies.

Diagnosis

The diagnosis of AI demands a high index of suspicion. The classic symptoms, signs, and laboratory findings of AI are not commonly seen. The consequences of missing the diagnosis can be lethal, but if the diagnosis is made the condition can usually be treated easily. If the diagnosis of AI is being considered, the patient's history should be carefully reviewed for use of steroids (including inhaled corticosteroids), exposure to tuberculosis, use of anticoagulant therapy, presence of sepsis, or history of cancer that may have metastasized to the adrenal glands. Patients taking high doses of steroids can develop AI when subjected to stress. Given that the major manifestations of acute adrenal crisis (i.e., shock) are related primarily to mineralocorticoid deficiency, it is important to recognize that patients receiving glucocorticoid therapy can still develop adrenal crisis if mineralocorticoid supplementation is inadequate.

• BOX 56.4 Common Laboratory Findings in Adrenal Insufficiency

- Hyponatremia
- Hyperkalemia
- Acidosis
- Prerenal azotemia
- Hypoglycemia
- Lymphocytosis
- Eosinophilia

Laboratory Findings

Although the laboratory evaluation of patients with suspected AI is essential, the utility of this evaluation is variable. In a patient with acute worsening of a chronic hypoadrenal state, the common laboratory findings shown in Box 56.4 are more likely to be present and are likely to be more pronounced. In a patient with acute adrenal insufficiency as the result of adrenal infarct or hemorrhage the classic laboratory abnormalities are unlikely to be seen. Although their absence does not exclude the diagnosis, when the typical laboratory abnormalities are present the possibility of adrenal insufficiency should be entertained. Electrolyte abnormalities depend on the type of deficiency: a combined glucocorticoid and mineralocorticoid deficiency (typically seen in primary AI) or an isolated glucocorticoid deficiency (characteristic of secondary AI).

Patients who have a combined deficiency may show hyponatremia, hyperkalemia, decreased serum bicarbonate, and increased blood urea nitrogen. This is primarily caused by the mineralocorticoid deficiency, which leads to renal sodium loss, potassium retention, and dehydration with acidosis and prerenal azotemia. In patients with concomitant kidney injury hypercalcemia may also be seen. It has been suggested that eosinophilia may serve as a marker for adrenal insufficiency; however, this finding is neither sensitive nor specific for AI and should not be relied upon. Patients with secondary adrenocortical deficiency usually have milder electrolyte abnormalities. Their normal adrenal glands are able to produce sufficient amounts of mineralocorticoid even in the absence of ACTH stimulation. They usually have mild hyponatremia with normal potassium levels, and they show little evidence of dehydration. Patients with AI may also have hypoglycemia, which occurs as a result of increased utilization of glucose and decreased gluconeogenesis in the face of glucocorticoid deficiency.

Diagnostic Tests

When there is a high suspicion of AI, hormonal testing is necessary to confirm the diagnosis. The utility of hormonal testing, particularly in the setting of critical illness, is controversial. Furthermore, in the setting of suspected adrenal crisis treatment and testing should be performed concomitantly; however, treatment should not be delayed to allow for testing. The laboratory evaluations most commonly used to detect AI in critically ill patients are the random serum cortisol level and the rapid ACTH stimulation test.

Serum Cortisol Level

The biochemical diagnosis of AI is controversial and is based on the demonstration of decreased cortisol production. Potential pitfalls in the measurement of cortisol levels arise when considering the

effects of critical illness on cortisol production, transport, and utilization. Most clinical laboratories routinely measure total cortisol levels, which may not accurately reflect the physiologic activity of cortisol. Critical illness results in a loss of cortisol-binding globulin with a subsequent decrease in the physiologically inactive protein-bound cortisol and an increase in the physiologically active free cortisol. Experts have recently suggested that measurement of free cortisol levels makes more physiologic sense, but studies have not helped establish diagnostic thresholds for free cortisol levels.[44] To further complicate the matter tissue levels of cortisol measured by microdialysis do not appear to strongly correlate with either free or total serum cortisol levels.[45] In addition, variability of cortisol assays can confound the diagnosis of AI.[46]

Given the controversy in diagnosis, the following recommendations have been suggested. A randomly measured serum cortisol level that exceeds 44 μg/dL makes the diagnosis of adrenocortical deficiency unlikely.[5] This information alone may be insufficient as it has been suggested that patients with septic shock who have high baseline cortisol levels (>34 μg/dL) and an increase of less than 9 μg/dL have a high mortality risk.[47] Serum cortisol levels should increase significantly in patients with normal adrenal function who are in shock and critically ill. The finding of a random serum cortisol level of less than 10 μg/dL in this setting is highly suggestive of compromised adrenal function and should prompt treatment or a confirmatory ACTH stimulation test.[5]

The interpretation of random serum cortisol levels can be effected by several commonly used drugs in the ICU. Antifungal agents such as fluconazole have the ability to impair cortisol synthesis. Propofol produces a temporary reduction in serum cortisol levels but does not seem to inhibit adrenal responsiveness to ACTH. Etomidate, on the other hand, is associated with a reduced serum cortisol concentration despite ACTH stimulation.[48] Treatment with hydrocortisone or cortisone can alter measurements as these agents are detected by most assays used for the measurement of cortisol. Dexamethasone is not detected by most assays and should not interfere with measurements. Treatment with any corticosteroid for more than 2 to 3 days may cause suppression of the HPA axis and thus may alter the outcome of biochemical measurements.

Rapid ACTH Stimulation Test

The ACTH stimulation test measures the response of the adrenal gland to stimulation by exogenous ACTH. This test can be performed at any time of the day because the normal diurnal variation of cortisol is lost in the setting of critical illness. Two major forms of this test are used: low-dose (1 μg) and high dose (250 μg). Clinically, the majority of testing is accomplished using high-dose ACTH stimulation. For both methods the procedure is the same. A baseline serum cortisol level is obtained. Cosyntropin (synthetic ACTH) is then administered intravenously followed by a sample for cortisol level drawn 60 minutes after ACTH administration.

Many recommendations have been made regarding interpretation of ACTH stimulation testing results. When used in the evaluation primary adrenal insufficiency peak cortisol levels less than 18 μg/dL at 30 or 60 minutes after the administration of ACTH are indicative of adrenal insufficiency.[49] It has been suggested that a rise in serum cortisol of less than 9 μg/dL is indicative of AI; however, studies have been unable to consistently demonstrate that this adequately predicts a response to treatment with steroids in critically ill patients.[5]

A few studies have compared low-dose and high-dose ACTH stimulation tests in critically ill patients; however, these study sizes are small.[50,51] Further research is required before definitive recommendations regarding the use of low-dose versus high-dose ACTH stimulation testing can be made.

Interpretation of the results from an ACTH stimulation test performed in critically ill patients who may have sustained recent injury to the hypothalamus or pituitary gland (traumatic brain injury, intracerebral hemorrhage, cerebrovascular accident, postpartum hypopituitarism, and so on) should be done with caution. In these situations the adrenal glands may continue to exhibit a normal response to exogenous ACTH administration for up to 3 weeks after the injury.[43]

The rapid ACTH stimulation test is a relatively simple test for evaluating AI; however, it does not differentiate between primary and secondary AI. To differentiate between primary and secondary AI, a basal plasma ACTH determination is made. An ACTH level more than two times the upper limit of normal is consistent with primary AI.[49] Historically, a 24- to 48-hour infusion of ACTH has been used to distinguish primary and secondary AI. Failure of the adrenal glands to appropriately increase cortisol production after prolonged infusion of ACTH is indicative of primary AI as the atrophic adrenal glands should still be capable of increasing production in response to the prolonged stimulus. Given the availability and accuracy of ACTH measurements, the prolonged stimulus is not often necessary or recommended in the critically ill patient.

After the diagnosis of primary AI is established, appropriate investigation for mineralocorticoid insufficiency should be pursued. Simultaneous measurements of plasma renin activity and aldosterone levels can provide valuable information regarding mineralocorticoid insufficiency.[49] These tests are technically challenging, however, and it is often not feasible to correctly perform these measurements in the intensive care setting.

Critical Illness–Related Corticosteroid Insufficiency

The term critical illness–related corticosteroid insufficiency (CIRCI) describes HPA axis dysfunction in critical illness, which is defined as a cellular corticosteroid activity that is inadequate for the severity of the patient's illness. The use of the term relative adrenal insufficiency is no longer recommended by some authors.

Despite no conclusive evidence of benefit, in the 1950s, 1960s, and into the 1970s cortisol at low doses over days was often used in patients with severe manifestations of sepsis to counter the AI that was assumed to be present. This practice was based on autopsy studies that revealed adrenal necrosis in patients with severe infections. The subsequent recognition of the systemic effects of inflammation in sepsis and the discovery that the majority of patients in septic shock had normal or increased cortisol levels led to a paradigm shift in treating septic shock with massive doses of steroids given for a short period of time. This practice was based on animal studies showing that large doses of steroids given before boluses of endotoxin prevented death.[46] Clinical trials testing the utility of several large doses of steroids in patients with septic shock failed to show benefit.[52,53] One study in patients with septic shock demonstrated that regardless of baseline cortisol level, the inability to raise the cortisol level following ACTH stimulation by at least 10 μg/dL signified poor prognosis.[47] In this poor prognostic group, the higher the baseline cortisol level with failure to produce a 10-μg/dL increase, the worse the prognosis. There is currently no consensus regarding the diagnostic criteria for CIRCI.

Management

Once the diagnosis of AI is made, a search for the cause should be initiated as the patient is being stabilized. Appropriate evaluation for a potential infectious etiology (tuberculosis, fungal infections, and so on) should be pursued as indicated by the patient's history and exposures. An abnormal prothrombin time, partial thromboplastin time, or platelet count may point to an unsuspected coagulopathy suggesting the possibility of adrenal hemorrhage. Antiadrenal antibodies are found in about 70% of patients with autoimmune adrenal disease and in less than 0.1% of normal subjects.[54] Adrenal calcification can be seen in 53% of cases of tuberculosis and can be identified via computed tomography (CT) scan of the abdomen.[55]

Management of AI can be best accomplished by identifying the degree of acuity and severity of the patient's illness at the time of presentation.[56]

Preexisting Adrenal Insufficiency

Patients who are known to have AI or who have received glucocorticoid therapy in the past year should receive stress doses of corticosteroids during critical illnesses and during surgical procedures. The typical regimen is administration of a hydrocortisone 100-mg IV bolus followed by 200 mg/24 h (either as continuous infusion or in divided IV doses). Attention should be paid to providing adequate intravascular volume expansion with isotonic crystalloid solutions. Five percent dextrose in isotonic saline solution may be used in the hypoglycemic patient. Once the acute insult has resolved, the hydrocortisone should be tapered to a maintenance dose. The typical replacement dose is 15 to 25 mg of hydrocortisone or 3 to 5 mg prednisolone daily.[49] If concurrent mineralocorticoid deficiency is present, 50 to 100 μg/day of fludrocortisone should be prescribed.

Patients with known AI scheduled for operation should continue the existing steroid dose before surgery. The morning of the procedure hydrocortisone 100 mg is given intravenously. During the operation a 100-mg hydrocortisone infusion is given. After surgery 100 mg of hydrocortisone is administered intravenously every 8 hours during the first postoperative day. The dose is then tapered to the baseline steroid dose over the next 3 to 4 days.

Adequate instruction is important in this group of patients. Patients with AI should be advised to wear a medical alert bracelet. These patients should be provided with a parenteral form of glucocorticoid and taught to self-administer the drug in case of emergency. They should be taught about the clinical situations in which increased amounts of glucocorticoids are required.

Hemodynamically Stable Patient

A patient who is suspected of having AI and who is hemodynamically stable should be managed in the following manner. A serum cortisol level and a rapid ACTH stimulation test should be performed before initiation of stress doses of corticosteroids. Hypovolemia should be treated with isotonic saline solution. If the diagnosis of AI is confirmed, hydrocortisone 50 to 100 mg should be administered as an IV infusion every 6 to 8 hours.

Hemodynamically Unstable Patient

Acute AI is a life-threatening emergency and requires immediate and aggressive therapy. The treatment of a patient with suspected AI and who is hemodynamically unstable should not be delayed to allow for biochemical testing of adrenal function. Patients should be resuscitated with isotonic fluids, vasopressors as indicated, and receive parenteral glucocorticoids. Blood samples should be obtained for assessment of baseline serum cortisol concentration, electrolytes, glucose, blood urea nitrogen, and creatinine.

The dose of hydrocortisone is 100 mg IV bolus followed by 50 to 100 mg IV every 6 hours. After the patient's condition has stabilized, the hydrocortisone is tapered at 25 to 50 mg/day until a maintenance dose of 30 mg/day is achieved.

Vigorous intravascular volume expansion with isotonic saline solutions is recommended. Volume resuscitation is usually initiated with 0.9% normal saline solution. Dextrose 5% in saline solution can be added to prevent hypoglycemia. The patient's fluid, electrolyte, and glucose status should be carefully monitored during resuscitation. In general, patients with acute AI have a deficit that is approximately 20% of their extracellular space. The rapidity of infusion depends on the patient's hemodynamic status and the presence or absence of underlying cardiovascular disease. Typical methods of assessing volume responsiveness including physical examination, noninvasive cardiac output monitoring, focused critical care echocardiography, and frequent assessment of markers of perfusion (lactic acid, urine output, and so on) should be used. Vasopressors may be necessary in the initial stages to maintain an adequate blood pressure to ensure tissue perfusion. In general, if the hypotension is caused by AI, improvement in blood pressure should be seen within 6 hours of corticosteroid therapy.

Mineralocorticoid administration is usually not required initially during acute AI, because the large doses of hydrocortisone provide adequate mineralocorticoid activity. Once the acute event has resolved and the hydrocortisone is tapered to less than 100 mg/day, mineralocorticoids may need to be started. Fludrocortisone is recommended at a dose of 0.05 to 0.20 mg/day. Excess mineralocorticoids can cause congestive heart failure, hypokalemia, and metabolic alkalosis.

In patients with concurrent hypothyroidism, glucocorticoid replacement should begin before thyroid hormone replacement. Administration of thyroid hormone increases the metabolism of glucocorticoids. Thus treatment with thyroid hormone before glucocorticoid therapy might worsen the hypoadrenal state and precipitate AI.

Reversal of the underlying cause of adrenal dysfunction is an important aspect of treatment. The precipitation of acute adrenal failure is provoked by another acute process and thus the causes of both primary and secondary AI should be sought. Prophylactic use of antibiotics is not beneficial, but specific infections should be treated aggressively with appropriate antibiotic therapy.

Severe Sepsis and Septic Shock

Six randomized clinical trials suggest that replacement of moderate-dose hydrocortisone (200–300 mg/day) decreases the need for vasopressor support in patients with septic shock.[2,57] Among them, the two larger trials were better powered to detect a survival difference but had differing results. These differences were attributed in part to varying demographics and other factors. In the Corticosteroid Therapy of Septic Shock (CORTICUS) study, hydrocortisone did not decrease the mortality rate in either responders or nonresponders to ACTH, but the patients who received hydrocortisone had more rapid resolution of shock, which has also been seen in other studies. These results were different from those

in the Annane study, in which the nonresponders to ACTH had both a reduction in mortality rate and reversal of shock.[57] The differences were attributed in part to the fact that in the Annane study, the patients enrolled were sicker, patients had higher Simplified Acute Physiology (SAPS II) scores, and time to enrollment differed (8 hours vs. 72 hours in the CORTICUS study). The CORTICUS study was published some years after the Annane study; it is possible that variations in the supportive care of the critically ill with advances in the care of the patients with sepsis could have made it difficult to show a mortality rate difference in the CORTICUS study. More patients in the CORTICUS study had a surgical source of sepsis, and thus source control may have played a bigger role in improving outcomes. In addition, fludrocortisone was not administered in the CORTICUS study. The duration of steroid therapy was different in the two studies, and this could have caused the dissimilar results. In addition, the CORTICUS study had a higher rate of superinfection. Compounding all these issues is the difficulty surrounding the accurate diagnosis of AI.[57,58] However, in a recent study, the addition of enteral fludrocortisone did not result in a significant improvement in hospital mortality rates.[59]

In the trials previously mentioned, there was resolution of shock in both responders and nonresponders to ACTH stimulation. As such the most recent Surviving Sepsis Guidelines available at the time of this writing recommend that the ACTH stimulation test not be used to determine who to treat with glucocorticoids. These guidelines recommend that patients with shock unresponsive to adequate fluid resuscitation and vasopressor support should be treated with IV hydrocortisone.[60]

Once initiated, hydrocortisone should ideally be continued for about 7 days. At the present time, the optimum duration of therapy is not clear, but data from studies would suggest that abrupt discontinuation of hydrocortisone could precipitate a rebound inflammatory response and recurrent shock. The ideal dose of steroid should help decrease the proinflammatory responses and at the same time minimize adverse effects, such as interference with wound healing, and decrease any negative impact on immune function. From studies, it appears that adverse effects of myopathy and superinfections are more common with doses greater than 200 to 300 mg/day of hydrocortisone. Hydrocortisone can be administered as a bolus dose or as a continuous infusion. Continuous infusions tend to cause less glycemic fluctuations.

To date, no studies document an improved outcome with corticosteroid use in the absence of septic shock. The recently published Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial investigated the use of hydrocortisone to prevent the development of septic shock in patients with sepsis. In this multicenter, randomized, placebo-controlled trial, there was no difference in the rate of development of septic shock between patients treated with a 50-mg bolus followed by a 200-mg continuous infusion of hydrocortisone and those who received placebo. This study also failed to demonstrate any difference in mortality, ICU length of stay, total days of mechanical ventilation, and organ dysfunction.[61]

Etomidate

Etomidate is a drug increasingly used as an induction agent for endotracheal intubation. It has the advantage of not causing hemodynamic instability. This drug inhibits the 11β-hydroxylase enzyme that converts 11-deoxycortisol into cortisol in the adrenal gland and can cause AI. This adverse event has been described with single-bolus and continuous infusions.

A 2015 Cochrane Library systematic review and meta-analysis concluded that a single induction dose of etomidate was associated with AI as evidenced by the results of ACTH stimulation testing. The review also concluded that there is no strong evidence that the use of single-dose etomidate increases mortality in critically ill patients. Furthermore, etomidate was not found to be associated with increased ICU length of stay, hospital length of stay, duration of mechanical ventilation, or duration of vasopressor use.[62] The authors of this review judged the conclusions to be based on a moderate quality of evidence and recommend that further trials be designed to better answer this question.

Summary

Management of acute AI involves prompt diagnosis and immediate treatment to prevent cardiovascular collapse and death. A high index of suspicion is necessary because the condition can be lethal if missed. Therapy with stress doses of corticosteroids should be initiated when there is a high index of suspicion. The side effects of a short course of high-dose corticosteroids in a critically ill patient are minor compared with the possible consequence of cardiovascular collapse and death.

Key Points

- AI is a true emergency and requires rapid diagnosis.
- Common symptoms of AI include weakness, fatigue, and loss of appetite.
- The classic presentation of acute AI is a patient with unexplained hemodynamic instability who is unresponsive to intravascular volume resuscitation and use of vasopressors. AI can mimic cardiogenic, hypovolemic, or septic shock.
- Secondary AI is more common than primary AI. The most common cause of secondary AI is discontinuation of corticosteroid therapy.
- Patients who have taken 20 mg of prednisone per day or its equivalent for a period longer than 3 weeks during the past year should be considered to be adrenal insufficient until proven otherwise.
- Autoimmune disease is currently the most common cause of primary AI and accounts for approximately 80% of cases. The second most common cause of primary AI is adrenal gland destruction by *Mycobacterium tuberculosis*.
- Ketoconazole, phenytoin, phenobarbital, rifampin, and etomidate can cause AI.
- Therapy with stress doses of corticosteroids should be initiated even before the confirmation of the diagnosis when there is a high index of suspicion. The side effects of a short course of high-dose corticosteroids in a critically ill patient are minor compared with the possible consequence of cardiovascular collapse and death.

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Review Questions

1. What is the most common cause of secondary adrenal insufficiency?
- **a.** Infection
- **b.** Exogenous steroid administration
- **c.** Surgical adrenal gland removal
- **d.** Pituitary gland dysfunction

Answer: b. Secondary adrenal insufficiency is due to a decrease in adrenocorticotropic hormone (ACTH) production caused by either hypothalamic-pituitary disease or by suppression of the hypothalamic-pituitary-adrenal (HPA) axis as a result of glucocorticoid therapy. Worldwide, infectious disease is the most common cause of primary adrenal insufficiency (AI). Surgical adrenal gland removal is an exceedingly rare clinical occurrence and would result in primary AI. Although pituitary gland dysfunction results in secondary AI, exogenous steroid administration is the most common etiology for secondary AI. The correct answer is choice b. A thorough medication history and reconciliation should be performed for every intensive care unit (ICU) patient searching for past or present steroid exposure.

2. What is the primary mechanism of the shock syndrome associated with AI?
- **a.** Direct glucocorticoid action on vascular smooth muscle
- **b.** Permissive glucocorticoid effect on the vasopressor action of catecholamines
- **c.** Glucocorticoid alteration of prostaglandin levels
- **d.** Glucocorticoid up regulation of β-adrenergic receptors
- **e.** All of the above

Answer: e. The shock syndrome associated with AI is complex and multifactorial. The complete or relative deficiency of glucocorticoids affects the volume status, vascular tone, and cardiac contractility directly and indirectly. The cardiovascular effects of AI are related but not limited to the direct actions on the vascular smooth muscle, the permissive glucocorticoid effect on the vasopressor action of catecholamines, alteration of prostaglandin levels, and the upregulation of β-adrenergic receptors. Therefore choice e (all of the above) is the correct answer.

3. Which of the following patients would be most likely to have AI after a complex abdominal surgery?
- **a.** Patient with asthma receiving inhaled steroids
- **b.** Patient with seborrheic dermatitis receiving topical steroid cream
- **c.** Patient with chronic obstructive pulmonary disease that requires pulse-dose prednisone several times a year
- **d.** Patient with recurrent anaphylaxis requiring short-course steroids twice a year

Answer: c. Exposure to systemic steroids places patients at risk for adrenal insufficiency. This includes exposure via several routes, including dermal, inhaled, or enteral. All of the answers listed may place a critically ill or injured patient at risk for developing AI. Increased potency and duration of exposure to glucocorticoids likely increases the risk for CI. Therefore the patient described in choice c is most likely to develop AI.

4. What is the most appropriate sequence of care for a hemodynamically unstable patient with suspect adrenal insufficiency?
- **a.** Isotonic fluids, vasopressors, parenteral steroids, serum cortisol testing
- **b.** Vasopressors, isotonic fluids, serum cortisol testing, parenteral steroids
- **c.** Serum cortisol testing, parenteral steroids, isotonic fluids, vasopressors
- **d.** Parenteral steroids, isotonic fluids, vasopressors, serum cortisol testing

Answer: d. Of the sequences listed, choice d is the most appropriate sequence of care. The administration of parenteral steroids and isotonic fluids should be performed concomitantly. The decision regarding the administration of vasoactive medications will be dependent on the patient's response to parenteral steroids and fluids. Serum cortisol testing should never take priority over resuscitation of a patient with documented or suspected AI.

5. Which of the following medications has not been shown to cause adrenal insufficiency?
- **a.** Ketoconazole
- **b.** Propofol
- **c.** Etomidate
- **d.** Rifampin

Answer: b. Ketoconazle, etomidate, and rifampin have all been documented to cause AI. Propofol may interfere with the actual cortisol measurement. However, patients receiving propofol maintain the response to the cosyntropin stimulation test. Therefore the correct answer is choice b.

57
Thyroid Disorders

JAMES A. KRUSE

CHAPTER OUTLINE

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- Thyrotropin
- Thyroid Hormone Transport and Metabolism

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- T_3 and T_4 Measurement
- Resin Uptake Testing
- Discordance Between TSH and Thyroid Hormone
- Thyroid Antibody Testing
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Drug Effects and Thyroid Function
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Hypothyroidism and Myxedema Coma
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- Manifestations of Hypothyroidism
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Thyrotoxicosis and Thyroid Storm
- Etiologies of Thyrotoxicosis
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- Manifestations of Thyrotoxicosis
- Diagnosis of Thyroid Storm
- Emergency Treatment of Thyroid Storm
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In a Colorado screening study involving more than 25,000 participants, the prevalence of hypothyroidism and hyperthyroidism was 0.4% and 0.1%, respectively, after excluding subclinical cases.[1] Although patients receiving long-term thyroid hormone supplementation are seen frequently in the intensive care unit (ICU), patients with active or newly diagnosed thyroid disease are not commonly confronted in this setting. The extreme forms of decompensated thyroid disease are even less common in the ICU. Based on survey and administrative data obtained in Japan between 2004 and 2008 the annual incidence of thyroid storm was estimated at 0.20 per 100,000.[2] The annual incidence of myxedema coma has been estimate at 0.22 per million.[3,4] Survey data from Germany obtained between 1993 and 1995 uncovered only 12 cases of myxedema coma.[5] Although rare, both of these life-threatening thyroid conditions will likely be encountered by intensivists on multiple occasions during their career.

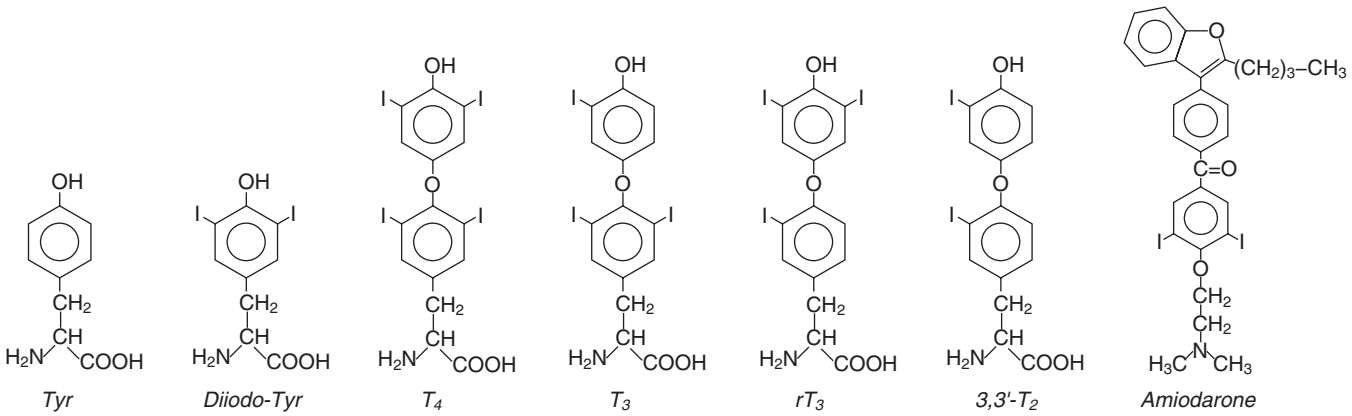
This chapter briefly reviews thyroid physiology, provides an overview of thyrotoxicosis and hypothyroidism, examines the nonthyroid illness (NTI) syndrome, and focuses on the emergency recognition and initial ICU management of patients with thyroid storm and myxedema coma.

Thyroid Physiology

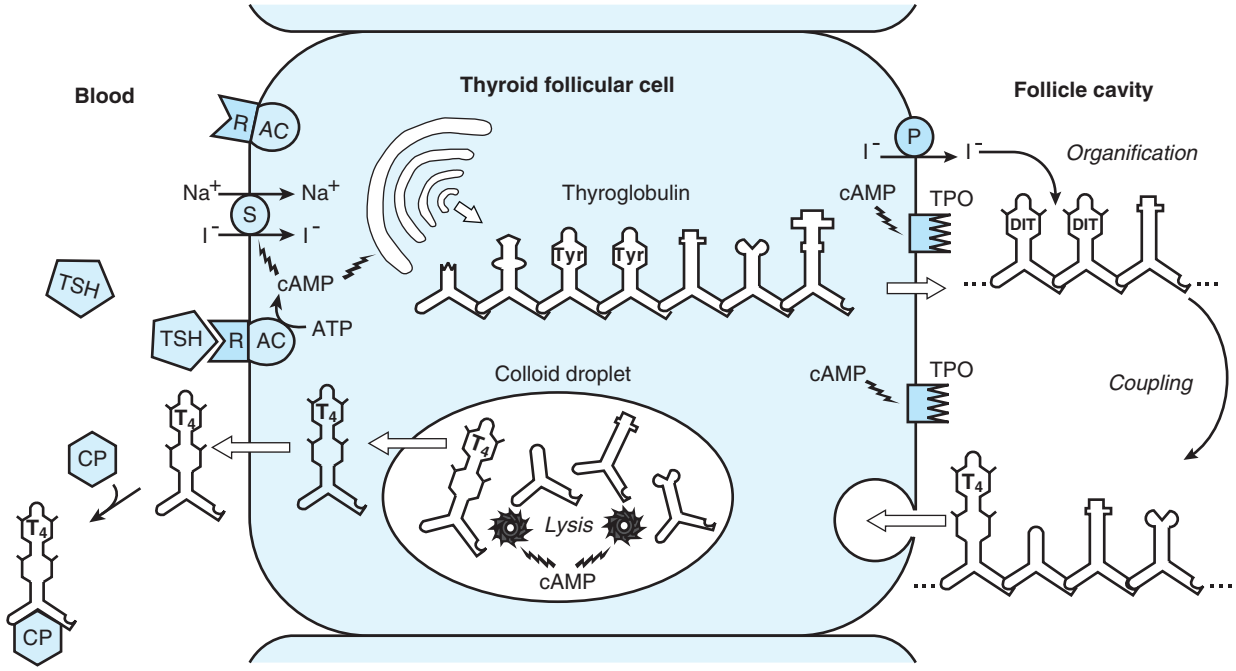
Thyroid Hormone Synthesis

Thyroid tissue consists of spherical cavities called follicles, each lined with epithelial cells (follicular cells or thyrocytes) that surround a cavity containing a colloidal suspension of a protein called thyroglobulin.[6] Two hormones are produced by the thyroid: thyroxine (tetraiodothyronine or T_4) and triiodothyronine (T_3), both of which are iodinated derivatives of the amino acid tyrosine (Fig. 57.1). Because T_4 can be converted in vivo into T_3, and because T_3 has substantially greater biological activity, T_4 can be considered a prohormone. Both T_3 and T_4 are amino acids, but they are not among the 20 amino acids included in the standard genetic code.

The synthesis of T_3 and T_4 begins with the production of thyroglobulin, a 660-kDa homodimeric glycoprotein synthesized and processed at the endoplasmic reticulum and Golgi apparatus of thyroid follicular cells and secreted by exocytosis into the follicle cavities (Fig. 57.2).[7] Among the 2768 amino acids that comprise each thyroglobulin monomer are 66 tyrosine units. The aromatic rings of a fraction of these tyrosine units are subsequently iodinated by the enzyme thyroperoxidase (or thyroid peroxidase, TPO) to form either monoiodotyrosyl or diiodotyrosyl residues, a process called *organification*.[8] Iodide ions enter the thyrocyte by way of sodium-iodide symporters located on the basolateral cell membrane. Iodide egress at the apical membrane has been ascribed to an anion transporter called pendrin.[9] TPO also catalyzes a coupling reaction that combines two iodotyrosyl residues to form either a triiodothyronyl or tetraiodothyronyl residue. At that point the inchoate



• **Fig. 57.1** Molecular structures for the amino acid l-tyrosine *(Tyr)*; diodo-l-tyrosine *(diiodo-Tyr)*; the (pro-) hormone l-thyroxine *(T_4)*; the active hormone triiodo-l-thyronine *(T_3)*; and the inactive deiodination products reverse triiodo-l-thyronine *(rT_3)* and 3,3′-diiodo-l-thyronine *(3,3′-T_2)*. The molecular structure for the drug amiodarone is also shown.



• **Fig. 57.2** Production of thyroxine by follicular cells of the thyroid. The pituitary hormone thyrotropin *(TSH)* interacts with TSH receptors *(R)* on the basolateral surface of follicular cells, activating adenylyl cyclase *(AC),* resulting in intracellular generation of cyclic adenosine monophosphate *(cAMP)* from adenosine triphosphate *(ATP).* cAMP stimulates (depicted by lightning bolt icons) activity of the sodium-iodide symporter (S), allowing uptake of circulating iodide by the cell; stimulates cytoplasmic synthesis of thyroglobulin; and stimulates activity of the enzyme thyroid peroxidase *(TPO),* which is located on the apical surface of the cell. Iodide is transported from the cytoplasm to the follicle cavity by the anion transporter pendrin *(P).* Among the 2768 amino acid residues comprising each monomer of the dimeric protein thyroglobulin are 66 tyrosine moieties, 2 of which are depicted in the thyroglobulin segment shown within the follicular cell. Ellipses represent the remainder of the thyroglobulin peptide backbone, which is not shown. Thyroglobulin is secreted into the cavity of the thyroid follicle where it undergoes organification (the covalent addition of iodine) by TPO, converting selected tyrosyl residues to either monoiodotyrosyl (not shown) or diiodotyrosyl *(DIT)* residues (shown at upper right). TPO also catalyzes oxidative coupling (i.e., joining an aromatic moiety of one iodinated tyrosyl residue to another, forming an ether linkage) of certain tyrosine residues to form thyroxyl residues. The iodinated thyroglobulin is then taken back up by the follicular cell via pinocytosis and subjected to digestion by proteolytic enzymes (depicted by *saw-toothed circular icons*) after merger of the colloid droplet with intracellular lysosomes. The thyroxine molecules *(T_4)* molecules thus derived from thyroglobulin then enter the blood stream where they are largely bound to plasma carrier proteins *(CPs)*—namely, thyroxine-binding globulin, transthyretin, and albumin. The thyroid also produces a proportionately smaller amount of triiodothyronine in a similar manner (not shown). *I^-,* Iodine ion; *Na^+,* sodium ion; *T_4,* tetraiodothyronine (thyroxine).

hormone is still covalently bound to the thyroglobulin molecule as a newly derived, posttranslational amino acid residue. The follicle thus serves as a reaction chamber for the developing thyroid hormones and also serves as a colloidal storage reservoir of hormone precursor. Each thyroglobulin molecule contains several T_4 residues, but typically either one or no T_3 residues. Via pinocytosis, follicular cells can then absorb the modified thyroglobulin protein molecules, forming intracellular vesicles (colloid droplets) that fuse with intracellular lysosomes, thereby subjecting thyroglobulin to proteolytic enzymes that hydrolyze the protein into its constituent amino acids, releasing finished T_3 and T_4 molecules in the process.[7] The T_3 and T_4 molecules are then secreted by the thyrocytes into surrounding capillaries. Iodide inhibits both this intrafollicular cell breakdown of thyroglobulin and the subsequent release of thyroid hormones into the blood.

Thyrotropin

T_3 and T_4 production and release by the thyroid are largely under control of thyrotropin, also known as thyroid-stimulating hormone (TSH), which is a heterodimeric glycoprotein synthesized and secreted by thyrotroph cells of the anterior pituitary and consisting of α- and β-subunits.[10] The α-subunits are common to luteinizing hormone, follicle-stimulating hormone, and human chorionic gonadotropin (hCG), but the β-subunit is unique to TSH. Pituitary secretion of TSH is stimulated by thyrotropin-releasing hormone (TRH), a tripeptide produced by neurons in the paraventricular nucleus of the hypothalamus, released into the hypophyseal portal circulation, and thereby delivered to the anterior pituitary where it serves as one of a number of determinants of the set point for thyroid hormone production.[11] Pituitary secretion of TSH is normally pulsatile with a diurnal variation.[12] Circulating TSH binds to transmembrane receptors expressed on the basolateral membrane of thyroid follicular cells, triggering a series of reactions that ultimately stimulate thyroglobulin synthesis and thyroid hormone release (see Fig. 57.2). hCG can also stimulate TSH receptors and is responsible for a transitory form of hyperthyroidism in early pregnancy called gestational transient thyrotoxicosis.

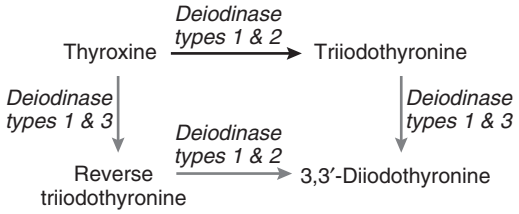
Follicular cell TSH receptors are coupled to a G protein that activates the enzyme adenylyl cyclase, which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP).[13] cAMP in turn stimulates intracellular synthesis of thyroglobulin and activates both TPO and the sodium-iodide symporter (see Fig. 57.2). TSH receptors normally have a minimal degree of constitutive activity—that is, the ability to catalyze the generation of intracellular cAMP even without TSH agonism at the TSH receptor. This constitutive secretion of hormones by thyroid tissue in the absence of TSH or TSH-receptor–stimulating antibodies is called *thyroid autonomy*. Inherited or sporadic mutations in the gene for TRH receptor can occur that alter this constitutive activity, and such mutations may not be expressed until later adulthood. These mutations promote thyroid autonomy, in which the thyroid constitutively secretes hormone even in the absence of TSH.[14] Normal feedback inhibition of pituitary TSH secretion by high levels of circulating T_3 and T_4 still occurs if there is autonomous thyroid tissue, but thyroid hormone production does not decrease as a result.

Thyroid Hormone Transport and Metabolism

Circulating T_3 and T_4 are largely protein bound, mostly (~70%) to thyroxine-binding globulin (TBG), but also to albumin (~15%) and transthyretin (~10%), with a small fraction (<5%) bound to circulating lipoproteins.[15,16] Transthyretin, so-called because it serves to transport both thyroid hormone and retinol, is also called thyroxine-binding pre-albumin. Approximately 0.3% of T_3 and 0.04% of T_4 circulate as unbound (free) molecules. The half-life of T_4 and T_3 are about 1 week and 2 days, respectively. Free T_3 and free T_4 are absorbed by most tissues throughout the body by way of monocarboxylate transporters located on the cell membranes.

After T_3 enters peripheral cells it binds to intracellular thyroid hormone receptors, which act in the nucleus to promote or inhibit transcription of genes that broadly control basal metabolic rate, affect carbohydrate and lipid metabolism, regulate heat production, and influence a host of other systemic and vital organ processes, including body temperature, ventilation, heart rate, cardiac output, and protein metabolism.[17] T_4 is converted by peripheral cells, mainly in the liver, to the active T_3 by a reductive deiodination reaction catalyzed by either of two isoforms of the selenium-containing enzyme iodothyronine monodeiodinase (Fig. 57.3).[18,19] These two activating isoforms are known as type I and type II deiodinase (or D1 and D2, respectively). Because D2 can remove only one iodine atom from the outer aromatic ring (specifically designated as the 5′-carbon position), this enzyme is also referred to as 5′-deiodinase. D1 shares this 5′-deiodination ability but can also remove one iodine atom from inner aromatic ring of T_3 or T_4. D1 is located on the plasma membrane of peripheral cells, whereas D2 (the major activating isoform) is intracellular and localized to the endoplasmic reticulum.[17] A third isoform, known as type 3 deiodinase (D3), is not expressed in the liver of healthy individuals, but hepatic induction of D3 occurs in critically ill patients, particularly those with perfusion failure.[20] The D3 isoform deactivates T_4 by removing one iodine atom from the inner aromatic ring of the molecule (5-deiodination), forming reverse T_3 (rT_3, see Fig. 57.1). D3 also deactivates T_3 by removing an inner ring iodine atom to form 3,3′-diiodothyronine (3,3′-T_2).

D1 and D2 can also convert rT_3 to 3,3′-T_2. Both rT_3 and 3,3′-T_2 are essentially devoid of known biological activity. The deiodinases thus serve to regulate peripheral production of T_3 from circulating T_4 and also regulate intracellular T_3 and T_4 concentrations by controlling the initial steps of their catabolism. Less than 20% of T_3 is produced by the thyroid, whereas 80% to 90% is produced in peripheral tissues by monodeiodination of T_4. Thyroid hormones and their deiodination products are also metabolized by nondeiodination reactions, including cleavage of the ether bond to form diiodotyrosine, glucuronidation or sulfation of the phenol moiety to form inactive conjugates, and oxidative deamination to form tetra- or triiodothyroacetate.[21,22]



• **Fig. 57.3** Activating and deactivating thyroid hormone reactions catalyzed by the three isoforms of selenodeiodinase. The horizontal *black arrow* represents activating reaction; the vertical *gray arrows* represent deactivating reactions.

Thyroid Function Tests

Although recommendations have varied regarding screening of both asymptomatic ambulatory subjects and unselected hospitalized patients for thyroid disease, routine or unselected screening of acutely ill hospitalized patients should not be recommended because the true positive yield is low and because the probability of a false positive result is relatively high.[23–25] Attia and colleagues showed that the positive likelihood associated with an abnormal sensitive TSH test is an order of magnitude lower in hospitalized patients compared with ambulatory patients.[26] Nevertheless, thyroid function testing can be of value in hospitalized patients with known thyroid disease and in cases where there is specific pretest suspicion of a possible thyroid disorder.

TSH Measurement

In primary hyperthyroidism, high levels of circulating thyroid hormone act by feedback inhibition to suppress TSH secretion at the pituitary. Historically, laboratory assays for TSH were insufficiently sensitive to differentiate these low TSH levels from normal levels found in healthy subjects. Thus the clinical utility of TSH measurement was limited to the diagnosis of primary hypothyroidism, where TSH levels are abnormally high and could be readily quantified by those first generation assays. Since that time, second- and then third-generation TSH assays have become widely available, with each generation essentially signifying an order of magnitude increase in sensitivity, allowing TSH measurements to serve as a first-line screening test for disorders of thyroid function. Third generation TSH assays have been defined as those with a functional sensitivity of less than 0.02 mIU/L.[27]

One such family of methods for sensitive TSH measurement is the immunometric assay.[28] One variant employs an enzyme-linked immunosorbent assay (ELISA) in which a sample of the patient's serum is added to a plastic surface to which prepared anti-TSH antibodies have been affixed. The TSH molecules are thus captured by the fixed antibodies and the excess serum can be rinsed away. A different anti-TSH antibody is then added; this one has a specific enzyme covalently linked to it. The reaction chamber is then rinsed again to remove the excess enzyme-linked antibody and a substrate reagent is then added. The remaining enzyme-linked antibody catalyzes the conversion of the added substrate to a reaction product that can be detected and quantified (e.g., by a change in color, fluorescence, or other means). The method is referred to as a *sandwich* ELISA assay because each TSH molecule is trapped between the two types of antibodies.

As with older TSH assays, results above the upper normal limit point to primary hypothyroidism, but the increased sensitivity of immunometric assays allows values well below the lower normal limit to be quantified, thus conferring the ability to detect primary hyperthyroidism as well. In secondary hypothyroidism or hyperthyroidism, however, the interpretation is reversed, with low circulating TSH levels observed in secondary hypothyroidism owing to lack of TSH production by the pituitary and high TSH levels seen in secondary hyperthyroidism owing to excessive TSH production.[4,29] However, these secondary forms of thyroid disease are considerably less common than the primary varieties, and the secondary forms are even more unlikely to lead to the extreme expressions of thyroid disease—namely, thyroid storm or myxedema coma.

TSH measurement and interpretation are not foolproof. Abnormal TSH results can occur in patients who are neither hypothyroid nor hyperthyroid (e.g., in patients with nonthyroidal illness syndrome as discussed in following text). Asymptomatic individuals with subclinical hypothyroidism or hyperthyroidism have abnormal TSH levels. but thyroid hormone measurements are within normal limits.[23,24] Therapeutic administration of dopamine or pharmacologic doses of glucocorticoids can acutely suppress TSH levels and thus spuriously suggest hyperthyroidism.[28] Another potential cause is TSH assay interference caused by circulating heterophile antibodies. These are antibodies produced by the body against nonhuman antigens, such as can occur after exposure to biological pharmaceutical products derived from animal proteins. A common example can occur after a patient is given a therapeutic monoclonal antibody derived from a murine cell line, to which the patient subsequently produces human anti-mouse antibodies. Some heterophilic antibodies, particularly human anti-mouse antibodies, may cross-react with the antibodies used in sandwich ELISA assays, forming a bridge between the capture antibody and the enzyme-linked antibody and thus competing with TSH molecules for anti–TSH-binding epitopes.[30] If the linked enzyme is not disabled in the process, a falsely high TSH value will result. If the active site of the linked enzyme is compromised by the bound heterophile antibody, a falsely low TSH value occurs.

T_3 and T_4 Measurement

Laboratory assessment of plasma T_4 can be accomplished by assessing either the total concentration or the free concentration. The free T_4 concentration (FT_4) represents only those T_4 molecules that are unbound to their plasma carrier proteins. The total T_4 concentration (TT_4) includes all T_4 molecules, bound and free, but because the proportion of free molecules is so low, the total and bound concentrations are essentially equal. Similarly, T_3 can be assayed as either total T_3 (TT_3) or free T_3 (FT_3). The bound molecules serve as a reservoir of thyroid hormone within the circulation, but those molecules are not directly available for uptake by the peripheral cells. Thus the free levels can be considered more physiologically relevant. If circulating carrier protein concentrations remain normal, and the number of hormone-binding sites remains normal, then TT_4 and FT_4 will remain proportional and either test could be used to assess whether T_4 concentration is physiologic or abnormal. However, the plasma concentrations of carrier proteins can be altered by various factors, including drugs, hormone levels, pregnancy, and various disease states, thereby altering the relationship between free and total hormone levels and confounding interpretation of total hormone values (Tables 57.1 and 57.2). In practice, there are two available methods of overcoming these common influences. The most common contemporary means of negotiating this problem is to focus on free hormone levels, if they are available.

Using free thyroid hormone levels as second-tier tests after assessing TSH generally works well but there are potential problems. First, some hospital laboratories may not perform free hormone assays on-site, necessitating sending serum specimens to a distant reference laboratory with the attendant delays involved. Some patients develop autoantibodies against thyroid hormones and these antibodies can interfere with certain free hormone assays to cause falsely elevated results.[31] This interference seems to affect hospitalized patients more so than ambulatory patients and also depends on the particular assay used.[32] Repeating the measurement with a different free hormone assay may show a markedly different result and suggest that this type of interference is occurring.

TABLE 57.1 Diseases Influencing Plasma Thyroxine-Binding Globulin Concentrations

Decrease Plasma TBG	Increase Plasma TBG
Hyperthyroidism	Hypothyroidism
Systemic illness	Pregnancy
Cirrhosis	Infectious hepatitis
Alcoholism	Primary biliary cirrhosis
Acromegaly	AIDS
Cushing disease	Adrenal insufficiency
Congenital TBG deficiency	Genetically determined
Diabetic ketoacidosis	Malnutrition
Nephrotic syndrome	Acute intermittent porphyria
Sepsis	Small cell lung cancer

TBG, Thyroxine-binding globulin.

TABLE 57.2 Drugs That Can Either Alter Plasma TBG Concentration or Interfere With Thyroid Hormone Binding to TBG

Decrease Plasma TBG	Increase Plasma TBG	Interfere With TBG Binding
Glucocorticoids	Oral contraceptives	Furosemide
Androgens	Estrogens	Heparin
Anabolic steroids	Tamoxifen	Sulfonylureas
Testosterone	Raloxifene	Salsalate
Danazol	Clofibrate	Salicylates
Phenytoin	Methadone	Phenytoin
Nicotinic acid	Heroin	Dinitrophenol
L-Asparaginase	Perphenazine	Phenylbutazone
Salicylates	Fluorouracil	Mefenamic acid
	Mitotane	Fenclofenac
		Thiocyanate
		Perchlorate

Resin Uptake Testing

An alternative to free hormone measurement is to use an older method that preceded the clinical availability of FT_3 and FT_4—namely, to assess plasma binding protein capacity and take it into account when interpreting the total hormone levels. To do this, a laboratory assay commonly referred to as either the T_3 resin uptake (T_3RU) or T_4 resin uptake (T_4RU) has been widely used to evaluate binding protein capacity.[16,33] Note that although the term *T_3* or *T_4* appears in the name of the assay and in commonly used abbreviations, these terms do not refer to the patient's thyroid hormone but rather signify exogenous thyroid hormone that is used solely as a reagent for performing the test. The term *T_3RU* was more commonly used historically because T_3 was the reagent in widespread past use to perform the test, although T_4 was later used in more modern versions of the assay. Whichever reagent hormone is used, the test yields a result that is inversely proportional to the available binding sites in the specimen, and that result can be used to correct the patient's TT_3 or TT_4 level for changes in binding protein levels using the following formulas:

$$FT_3I = TT_3 \times \frac{T_3RU_{patient}}{T_3RU_{control}} \quad \text{and} \quad FT_4I = TT_4 \times \frac{T_3RU_{patient}}{T_3RU_{control}},$$

where FT_3I is the free T_3 index and FT_4I is the free T_4 index. These indices serve as surrogate measures for more direct assay determinations for the free hormone levels. Because the T_3RU and total hormone assays have been widely available for many years, smaller clinical laboratories that do not perform FT_3 or FT_4 assays may be able to substitute the index measurements as a useful surrogate.

Discordance Between TSH and Thyroid Hormone

In straightforward cases of primary hyperthyroidism with thyrotoxicosis, serum TSH is low and measurements of T_3 or T_4, or both, are elevated, whereas in primary hypothyroidism, TSH is high and the thyroid hormone levels are low. However, discordant results can be seen in some cases.[34] Because plasma TSH levels can take time to respond to therapy,[35] patients with hypothyroidism who have recently started taking thyroid hormone supplementation may continue to have abnormally high TSH levels (sometimes markedly elevated) while their total and free T_4 levels more quickly normalize from the prescribed hormone supplement. Monitoring during this transitional phase can yield seemingly paradoxical discordance. Similarly, if a hypothyroid patient who is chronically noncompliant with prescribed levothyroxine decides to take a few doses just before undergoing phlebotomy for thyroid function testing, serum T_4 levels may be within normal limits while the TSH level remains substantially elevated. The opposite phenomenon can occur in patients who recently started thionamide therapy for hyperthyroidism, showing paradoxical analyte discordance owing to the relatively rapid normalization of thyroid hormone levels but persistently suppressed TSH levels.[28] Other factors that can lead to discordance include central hypothyroidism or hyperthyroidism, the nonthyroidal illness syndrome, drug effects, and assay interference.[30]

Normal thyroid hormone levels in the face of an abnormally low or abnormally high TSH value are termed subclinical hyperthyroidism or hypothyroidism, respectively. However, elevated T_4 levels can be seen in some euthyroid patients under a variety of circumstance (Box 57.1).

Thyroid Antibody Testing

Antithyroid antibody testing can help differentiate autoimmune-mediated thyroid disease from nonautoimmune causes of hyperthyroidism or hypothyroidism. The percentages indicated in the following text are approximate and may vary because thyroid antibody assays tend to be method dependent.

Autoantibodies directed against TSH receptors (TRAbs), specifically those types that are capable of activating the TSH receptor, are the cause of Graves disease and are present in most patients (~90%) with the disease. Testing for TRAbs is recommended in

• BOX 57.1 Causes of Euthyroid Hyperthyroxinemia

Increased thyroxine-binding globulin
Familial dysalbuminemic hyperthyroxinemia
Prealbumin-associated hyperthyroxinemia
Amiodarone
Amphetamine
Iodinated contrast agents
Nonthyroidal illness syndrome
Thyroid hormone resistance syndromes
Idiopathic

guidelines issued by the American Thyroid Association (ATA) to assist in the diagnosis of Graves disease, especially in thyrotoxic patients who do not have orbitopathy.[36] In addition to Graves disease, TRAbs are seen in some cases of autoimmune thyroiditis. Modern assay methods (e.g., ELISA) have high sensitivity and specificity[37]; false-positive results (positive test results in patients without autoimmune thyroid disease) are uncommon. False-negative TRAb assay results can occur in mild Graves disease, but are unlikely in patients with Graves disease who present with severe thyrotoxicosis or thyroid storm. Some patients have TRAbs that occupy the receptor but do not activate it. These blocking antibodies thus compete with TSH for TSH receptors, thereby causing circulating TSH levels to rise. TRAb assays do not differentiate stimulating from blocking antibodies; however, specific thyroid-stimulating immunoglobulin assays are available.[38]

Thyroperoxidase antibodies (TPOAbs) are autoantibodies directed against TPO. They were formerly known as antimicrosomal antibodies, a term that is sometimes still used. TPOAbs are detectable in nearly all patients with Hashimoto thyroiditis and in about 75% of patients with Graves disease. They are also seen in patients with postpartum thyroiditis. Positive TPOAb test results can be seen in patients with destructive autoimmune thyroid disorders; however, they are positive in some patients with nondestructive thyroid disease, in some patients with nonthyroidal autoimmune disorders, and even in individuals without apparent thyroid disease (~11%), especially among the elderly.[39] The presence of TPOAbs in a euthyroid patient may indicate that the patient is at future risk for thyroid disease.

Autoantibodies against thyroglobulin (TgAbs) are detectable in most patients with autoimmune thyroiditis (~85%), in most patients with Graves disease (~60%), and in about 10% of the general population.[39] Most patients with TgAbs present will also have positive results for TPOAbs, but measuring both may increase the diagnostic sensitivity. TgAb assays are also used in conjunction with thyroglobulin monitoring to follow patients with differentiated thyroid cancer.

Other Thyroid-Related Measurements

Thyroglobulin is normally produced only in the thyroid and therefore serves as a marker for functioning thyroid tissue. High levels of thyroglobulin are seen in patients with hyperthyroidism, goiter, thyroid trauma, and thyroid inflammation, as well as in pregnancy and in patients with differentiated (follicular cell) thyroid tumors. Low serum thyroglobulin levels, as well as decreased radioactive iodine uptake, are seen in patients with lack of functional thyroid tissue and in surreptitious chronic thyroid hormone ingestion[40]; however, thyroglobulin assay results can also be low in patients with TgAbs. TgAb testing should therefore be done in conjunction with thyroglobulin measurement. Sex hormone–binding globulin levels are increased in thyrotoxicosis but may take a matter of days to increase following a one-time overdose in otherwise healthy subjects.[41]

TBG can be directly measured by means of immunoassays. Abnormal TBG levels, whether the result of concomitant nonthyroidal conditions (see Table 57.1) or pharmacotherapy (see Table 57.2) alter the relationship between total and free thyroid hormone levels and can be used to interpret TT_4 measurement results. In conjunction with TT_4 measurement, the TBG result can serve as an alternative to resin uptake testing, allowing calculation of a form of FT_4I or hormone-binding ratio ($TT_4 \div TBG$).

Radioactive iodine uptake (RAIU) testing assesses the ability of the thyroid to actively absorb iodine from the blood, thereby allowing differentiation of hyperthyroidism from other forms of thyrotoxicosis.[42] For example, uptake is expected to be high in Graves disease and low in thyrotoxicosis owing to exogenous thyroid hormone ingestion. Although typically low, the results can be variable in patients with hypothyroidism. The patient is given an oral dose of ^{123}I and RAIU is determined at intervals using a stationary radiation detector. A related procedure is nuclear thyroid scanning, in which the radioactive iodine isotope is given intravenously (IV) and scintigraphic imaging is performed using a gamma camera to localize hypofunctioning and hyperfunctioning areas of the thyroid. RAIU and nuclear imaging are not performed in ICU patients but may be indicated after ICU discharge for further assessment of thyroid function.

Levels of rT_3 are elevated or normal in patients with severe illness and NTI syndrome and low in patients with hypothyroidism.[43] Although it is logical to assume that rT_3 measurement would allow distinction between NTI syndrome and actual thyroid disease in critically ill patients, the test appears to have limited ability to differentiate the two situations in practice. Elevated rT_3 levels have been described in patients taking propranolol, dexamethasone, or amiodarone and following the use of halothane. In addition, the test is not widely available. As a result, the test generally is not indicated or recommended in ICU patients.

Drug Effects and Thyroid Function

A number of drugs can interfere with thyroid function, and some drugs are capable of causing overt hypothyroidism or hyperthyroidism or aggravating existing thyroid disease.[30,44,45] Certain drugs can cause transient changes in thyroid hormone levels that later correct even when the drug is continued. Some drugs can cause systematically spurious thyroid test values as an analytical artifact, in which case in vivo hormone levels are actually normal and the patient remains euthyroid. Other drugs actually stimulate or inhibit release of TSH or thyroid hormone. Others increase or decrease metabolic degradation or inactivation of thyroid hormone. Others alter the concentrations of thyroid hormone–binding proteins, and still others displace T_3 or T_4 from these carrier proteins. This section elaborates on some of these effects for selected drugs relevant to the ICU setting.

Iodide

Exposure of a euthyroid subject to excessive iodide, including iodide derived from dietary sources (e.g., kelp or iodide-containing dietary supplements), iodinated radiocontrast media, or other pharmaceuticals containing inorganic iodide or iodine-containing organic compounds, results in decreased thyroid iodide uptake,

decreased thyroid hormone synthesis, and decreased release of hormones from the thyroid. These are all normal physiologic effects known as the Wolff-Chaikoff effect. FT_4 levels decrease as a result, and as a consequence the plasma TSH level increases. This effect, which can exacerbate hypothyroidism, is temporary, followed typically within 2 weeks by an escape phenomenon in which thyroid hormone synthesis renormalizes. However, in patients with even low-grade or latent preexisting thyroid autonomy (e.g., compensated Graves disease or multinodular goiter), excessive iodine may provoke overt thyrotoxicosis or thyroid storm by the Jod-Basedow effect.[30] In this situation plasma free T_4 will increase and TSH will be suppressed.

Amiodarone

The antiarrhythmic drug amiodarone is used frequently in the ICU setting. A portion of the amiodarone molecule bears a structural resemblance to T_4 (see Fig. 57.1) and has complex effects on thyroid hormone metabolism, potentially affecting thyroid function. More than 50% of patients taking amiodarone on a long-term basis have abnormal results on thyroid function testing, but the majority are actually euthyroid.[46] Amiodarone is 37.7% iodine by weight and when metabolized the iodine is released from the drug, usually resulting in a large increase in plasma iodide levels. As noted earlier, exposure to large amounts of iodide will decrease synthesis and release of thyroid hormones by the Wolff-Chaikoff effect. Amiodarone can also inhibit deiodination of T_4 and rT_3 by interfering with D1 activity. In the euthyroid patient this inhibition (see Fig. 57.3) itself leads to a rise in plasma FT_4 and TT_4 levels, with corresponding decreases in FT_3 and TT_3 levels (modestly decreased or to the low reference range), along with an increase in rT_3 levels. In response, TSH levels transiently rise, albeit to less than 20 mIU/L. Within a few months of continued amiodarone therapy, TSH levels usually renormalize. Although the FT_4 and TT_4 levels can remain above the upper normal limit, this by itself does not signify that the patient is hyperthyroid. However, amiodarone may also interfere with cellular uptake of T_3 and T_4 and noncompetitively inhibits the binding of T_3 to intracellular β_1-thyroid hormone receptors.[47]

The reported incidence of thyroid dysfunction in patients taking amiodarone varies from 2% to 50%. This wide range is in part due to how the thyroid dysfunction is defined—for example, by abnormal laboratory values alone versus by clinical assessment of thyroid disease—as well as the screening procedures used and variations owing to statistical sampling. There is also a prominent geographic variance that depends on the regional prevalence of iodine deficiency.[46,48–50] Both hypothyroidism and hyperthyroidism can occur, with high dietary iodine predisposing to hypothyroidism and low iodine intake predisposing to hyperthyroidism. There does not appear to be a clear relationship between the daily or cumulative amiodarone dose and the risk for developing either hypothyroidism or hyperthyroidism.[46] In view of the possibility of causing an actual thyroid disorder, baseline TSH, FT_4, T_3, and thyroid antibody assays should be obtained before initiating the long-term amiodarone therapy in stable patients. In the setting of critical illness, thyroid function test results may not represent baseline thyroid status if NTI syndrome is present. Periodic thyroid function test monitoring has been recommended (e.g., at 3- to 6-month intervals), for patients receiving long-term amiodarone to help identify development of hypothyroidism or hyperthyroidism.

It is important to note that mild TSH elevations (<10 mIU/L or so) can be seen in patients who are taking the drug but remain euthyroid. Nevertheless, actual hypothyroidism from amiodarone has been reported in 1% to 32% of patients taking the drug, most often in patients taking the drug for less than 2 years, and TSH is usually above 20 mIU/L in these cases.[44,46,48,49] The presence of anti-TPO, antithyroglobulin, or antithyrotropin receptor antibodies before receiving amiodarone is associated with an increased risk for amiodarone-induced hypothyroidism.[51] Elevated antibody titers can also develop after amiodarone use in patients who develop hypothyroidism.[52,53] The mechanism is likely related to an inability to escape from the Wolff-Chaikoff effect, often in patients with preexisting Hashimoto thyroiditis. The general approach to treating amiodarone-induced hypothyroidism is to either discontinue the drug, if feasible, or provide thyroid hormone supplementation, or both.

Overall, hyperthyroidism is less common and may develop rapidly or after several years of amiodarone treatment, with thyrotoxicosis reported in less than 1% to 23% of patients taking the drug.[48,54] Amiodarone-induced thyrotoxicosis can be divided into two types. Type 1 occurs in patients with previous autoimmune thyroid disease and thyroid autonomy (e.g., Graves disease or nodular goiter), may be iodine-induced (the Jod-Basedow phenomenon), and results in hyperthyroidism similar to Graves disease. Antithyroid antibodies are often present in patients with preexisting thyroid disease but are uncommon otherwise.[55] Type 2 amiodarone-induced thyroid dysfunction is a form of subacute thyroiditis that occurs in patients with previously normal thyroid function. This is a destructive, inflammatory process in which cytotoxicity causes release of preformed thyroid hormone. Type 2 amiodarone toxicity predominates in North America; type 1 is more often seen in iodine-deficient regions.

Treatment of both types includes stopping amiodarone, if possible. That decision involves a benefit-risk consideration taking into account the individual patient's underlying cardiac disease and potential alternatives to amiodarone therapy. In general, additional first-line treatment for type 1 is a thionamide drug, whereas a trial of glucocorticoid therapy is used in type 2. Perchlorate treatment, and in refractory cases, radioactive iodine ablation or thyroidectomy have also been used in selected cases.

Phenytoin and Carbamazepine

Phenytoin and carbamazepine displace thyroid hormones from their plasma carrier proteins, increasing FT_3 and FT_4 levels in patients who are euthyroid. This effect, however, is transient because the resulting elevation of the free hormone concentrations causes TSH to decrease by feedback inhibition. As a consequence, TT_3 and TT_4 decrease, resulting in normalization of FT_3 and FT_4. A new steady state subsequently ensues in which TSH renormalizes. At that point, in attempting to measure FT_4 using assays that require dilution of the serum sample, the presence of therapeutic levels of phenytoin or carbamazepine interferes with FT_4 determination and causes a falsely low result.[56] The low free hormone level in this case is an in vitro artifact resulting from the increased availability of hormone-binding sites as the anticonvulsant drug separates from the carrier proteins after dilution; the patient otherwise remains euthyroid.

Apart from their effects on thyroid hormone assays, phenytoin and carbamazepine use can also increase the metabolism of thyroid hormones such that patients who require chronic levothyroxine therapy may need to have their T_4 supplement dose increased after starting either anticonvulsant. This occurs because both T_3 and T_4 can undergo conjugation with glucuronic acid in reactions

catalyzed by the enzyme uridine 5′-diphosphate (UDP) glucuronosyl transferase acting at the phenolic hydroxyl group of the hormones to form T_3- and T_4-glucuronides. These glucuronides are inactive, water-soluble metabolites that are excreted in bile with a degree of enterohepatic recirculation.[21,22] Intestinal bacteria produce enzymes that cleave off the glucuronide, leaving some of the free thyroid hormones to be reabsorbed and thus constituting a form of enterohepatic thyroid hormone recirculation. UDP-glucuronosyltransferase also metabolizes and inactivates a number of drugs, including phenytoin, carbamazepine, phenobarbital, and rifampin. Treatment with these drugs induces synthesis of UDP-glucuronosyltransferase, augmenting glucuronide formation and thereby potentially lowering thyroid hormone levels in patients with hypothyroidism.

Other Drugs

Dopamine can suppress secretion of TSH by stimulating type 2 dopaminergic receptors on pituitary thyrotroph cells. However, the resulting low-TSH state is often transient and probably does not cause central hypothyroidism, at least in most cases.[30] Mild decreases in FT_4 may occur in some cases, but this may represent NTI syndrome given that dopamine use is commonly restricted to critically ill patients. Like dopamine, both the somatostatin analog octreotide and high-dose glucocorticoids also can suppress TSH secretion. Amphetamine use can result in increased endogenous dopamine release, thereby indirectly lowering plasma TSH levels. Metoclopramide at doses greater than 1 mg/kg can slightly raise TSH levels, usually no higher than 10 mIU/L.[44]

A number of drugs commonly used in the ICU setting can affect circulating thyroid hormone levels by interfering with hormone binding to plasma proteins (see Table 57.2). Unfractionated heparin and low–molecular-weight heparin increases the activity of lipoprotein lipase, causing an increase in plasma free fatty acid levels, which in turn displace T_4 from its plasma carrier proteins. The result is an increase in FT_4 levels, with the degree of the effect depending on the plasma heparin level, the plasma triglyceride level, and the preanalytical delay period. In one study, FT_4 levels increased by up to 171% in samples obtained 2 to 6 hours after enoxaparin administration.[57] In patients receiving intermittent subcutaneous injections of unfractionated or low–molecular weight heparin, blood sampling for FT_4 analysis should be deferred until the heparin administration is discontinued or the sample can be obtained during the heparin trough period (i.e., just before the next scheduled heparin dose). Specimens from patients who have received heparin should also be analyzed promptly because the length of preanalytical delay correlates with the magnitude of artifactual FT_4 elevation. Furosemide at doses greater than 80 mg, especially in the presence of renal dysfunction, can cause a transient fall in TT_3 and TT_4, with concomitant rises in FT_3 and FT_4, as the result of interference with hormone binding to TBG, albumin, and prealbumin.[58] Nonsteroidal antiinflammatory drugs, including salicylates, also displace T_3 and T_4 from TBG and transthyretin.[59] A variety of drugs may influence total circulating thyroid hormone levels by increasing or decreasing plasma TBG concentration (see Table 57.2).

Chronic treatment with lithium carbonate can lead to hyperthyroidism in 1% to 5% of patients and either subclinical or overt hypothyroidism in 5% to 50% of patients.[44,60] Lithium inhibits thyroid hormone synthesis and release, inhibits deiodinase activity and thereby decreases peripheral conversion of T_4 to T_3, and promotes thyroid autoimmunity by stimulating lymphocyte activity. Diffuse goiter can occur in some patients. Hyperthyroidism secondary to lithium use is less common than hypothyroidism but can occur. It usually manifests as painless thyroiditis that is self-limited. The mechanism may involve lithium-induced thyroid autoimmunity.

By inhibiting 5′-deiodinase, propranolol and dexamethasone can reduce circulating T_3 levels. Corticosteroids can also decrease T_4, TSH, and TBG levels by other mechanisms,[61,62] whereas propranolol can decrease FT_4 and TT_4 levels.[63] Thyroid dysfunction, including a pattern of autoimmune thyroiditis, has been noted in some patients after treatment with recombinant granulocyte-macrophage colony-stimulating factor, sargramostim.[64] Sucralfate, colestipol, and cholestyramine can cause malabsorption of levothyroxine.[65,66]

Nonthyroidal Illness Syndrome

Significance

Abnormal levels of circulating thyroid hormones are frequently observed in patients with acute and chronic systemic illness who otherwise have no manifestations suggesting thyroid disease. This state has been called NTI syndrome or the euthyroid sick syndrome, and it is particularly common in the ICU setting. Whether this condition represents a normal response to any underlying severe illness versus a maladaptive pathologic response has long been debated, but the prevailing view is that it is more likely a physiologic adaptation.[67] Other endocrine abnormalities are also commonly observed in conjunction with critical illness, such as alterations in prolactin and cortisol levels, high endogenous catecholamine concentrations, glucose intolerance, and increased protein catabolism, all of which could be considered elements of a generalized systemic endocrine response to critical illness or injury.[68] As an adaptive acute-phase response, these changes could have protective or beneficial effects, but substantiating data are lacking. The practical value to recognizing the syndrome in the ICU setting is that it can present serious difficulties in the interpretation of thyroid function test results, thus interfering with detection of actual hypothyroidism or hyperthyroidism.

Plasma Hormone Patterns

In a study analyzing autopsy samples obtained from 12 patients dying from NTI and 10 previously healthy individuals dying suddenly from trauma, mean serum T_3, T_4, and FTI values were lower by 79%, 71%, and 49%, respectively, in the NTI group compared with the comparison group, but serum TSH values did not differ significantly.[69] The earliest and most consistent change in plasma thyroid hormone levels that is commonly observed in patients with an acute critical illness or undergoing surgery is a decrease in plasma T_3 level.[70] This fall in T_3 is characteristic of the NTI syndrome, hence the synonym *low T_3 syndrom*e. This is sometimes paralleled by a rise in rT_3 levels. Plasma TT_4 concentrations may also decline early in critical illness. FT_4 levels are often maintained in the normal range during NTI, but they tend to decline if the patient's condition is protracted or worsens. Total and free T_4 levels sometimes transiently rise before this decline.[70] Thus a low plasma FT_4 concentration serves as a marker of disease severity and a prognostic sign for poor outcome. Circulating TSH levels typically remain normal but sometimes show an early transient rise, usually mild, at the onset of critical illness.[71] TSH levels then usually remain within normal limits despite progression of the

NTI. However, in some patients TSH declines, particularly with more severe and prolonged illnesses. In those patients who recover, a transient rebound overshoot in TSH may occur during their recovery phase, with plasma TSH levels commonly rising to slightly above the upper normal limit, but occasionally peaking to 20 mIU/L or so.[72] At this point, the elevated TSH level (potentially in conjunction with low T_4 levels, low T_3 levels, or both) can suggest hypothyroidism, but most of these patients have no signs of thyroid disease after recovery from their acute illness. Severe illness is also associated with a decrease in the pulsatile amplitude of TSH secretion by the pituitary. In addition, the usual relationship between the biological effect of TSH and immunogenic response can vary in some patients with critical illness, affecting accuracy of the assay.[33]

The previous hormone patterns present a challenge in differentiating ICU patients with NTI syndrome from those who actually have hypothyroidism or hyperthyroidism. Although there are no criterion standard biochemical tests that differentiate these conditions, there are some practical points that are helpful.[33] TSH levels assessed by a sensitive TSH assay remains the single best measurement for discriminating NTI syndrome from real thyroid disease. TSH levels above 20 mIU/L are more likely to represent actual (permanent) hypothyroidism. Using a third-generation TSH assay, TSH levels below 0.01 mIU/L in a critically ill patient most likely mean the patient has hyperthyroidism. On the other hand, a low but still detectable TSH in a severely ill ICU patient more likely indicates NTI syndrome.[73] Because T_3 levels are usually low in critically ill patients, the finding of elevated TT_3 or FT_3 in such patients suggests hyperthyroidism. Although rT_3 levels in principle should be increased in NTI syndrome and diminished in patients with hypothyroidism, this relationship has not proved to be helpful in practice. Although the test is available through some clinical reference laboratories, few hospital laboratories perform the test on-site. In addition, Burmeister showed that although rT_3 may be elevated in patients with NTI syndrome, rT_3 levels can also be low in euthyroid patients, and hypothyroid patients can have normal rT_3 levels.[74]

Pathophysiology

A putative mechanism that provides an explanation for the decrease in plasma T_3 and increase in plasma rT_3 levels in NTI is inhibition of deiodinase isoforms D1 and D2, induced either by a phenotypic change brought on by the systemic illness,[75,76] the presence of circulating endogenous inhibitors (e.g., oleic acid and other free fatty acids),[77–80] or the effects of pharmacotherapy used to treat the NTI (e.g., amiodarone, propranolol, or corticosteroids).[62] In support of this contention, low tissue activity levels of D1 and D2 have been observed in biopsy specimens from ICU patients succumbing to critical illness, whereas hepatic D3 activity is induced in patients with poor tissue perfusion.[20,81]

Peeters and colleagues examined deiodinase expression in tissue samples from 80 ICU patients.[20] TSH, T_4, and T_3 levels in these patients were significantly lower, and rT_3 higher, compared with normal subjects ($P < 0.0001$). Hepatic D1 activity was downregulated while liver and muscle D3 activity was induced. The ratio of serum T_3:rT_3 was directly correlated with liver D1 activity ($P < 0.001$). In another report Peeters et al. examined 451 patients receiving intensive care for longer than 5 days, assaying thyroid hormone levels on days 1, 5, 15, and their last day, and also obtaining liver and muscle biopsies from 50 of the 71 nonsurvivors.[81] rT_3 levels on day 1 were higher in nonsurvivors compared with survivors ($P = 0.001$), whereas TSH, T_4, and T_3 levels were all lower in nonsurvivors from day 6 until their last day ($P < 0.001$). TSH, T_4, and T_3 levels increased over time in survivors but decreased or did not change in nonsurvivors. Serum rT_3 and T_3:rT_3 correlated with postmortem tissue deiodinase activities.

Laboratory studies have shown that lipopolysaccharide (endotoxin) from gram-negative bacteria administered to rats induces D2 expression in the mediobasal hypothalamus.[82] The resulting increase in T_3 at the level of the hypothalamus could augment normal feedback suppression of TRH secretion. Extrapolation of these findings to critically ill patients could explain low circulating levels of TSH, T_4 and T_3 in critically ill patients with sepsis. In a murine model, Boelen and coworkers found that serum T_3 and T_4 levels declined 24 hours after administering endotoxin, but those changes were preceded by increased D2 expression at the level of the hypothalamus, decreased TSH production and pituitary D1 activity, and decreased D1 messenger RNA in liver. In the hypothalamus, D2 messenger RNA expression was strongly increased.[83]

In addition to changes in deiodinase activity and suppression of TRH release by the hypothalamus, other mechanisms have been postulated to explain NTI syndrome. Given that the deiodinases are selenium-containing enzymes, and D1 and D2 activity is required to convert T_4 to T_3, selenium deficiency has similarly been postulated as a mechanism for NTI. Alterations in thyroid hormone binding to plasma proteins, effects stemming from starvation, and various cytokine-mediated effects on thyroid hormone levels have also been implicated.[84–87] A study in healthy volunteers showed that fasting induced a decline in mean serum T_3 concentrations from 140 to 93 ng/dL with a concomitant rise in mean rT_3 from 51 to 106 ng/dL, but with no significant changes in TSH, TT_4, or FT_4.[88] That investigation also showed that the rate of conversion of T_4 to T_3 decreased by 50%, whereas T_4 to rT_3 conversion increased by 146% in fasting subjects compared with a control group. Stouthard and associates infused recombinant human interleukin 6 (IL-6) over 4 hours to patients with renal cell cancer and compared the patients hormone levels to those obtained after a saline solution control infusion given on another day.[84] No effects were seen on TT_4 or FT_4, but there was a significant decrease in plasma TSH and an increase in rT_3 compared with the saline solution placebo. When recombinant human IL-6 was given daily for 42 days, weekly assays showed a decrease in T_3 and a transient increase in rT_3 and FT_4. On the other hand, Michalaki et al. showed that serum T_3 declines within minutes of elective abdominal surgery and anesthesia, preceding the rise in endogenous IL-6 induced by operation.[70]

In a study by van der Poll and associates, tumor necrosis factor (TNF) was administered to six healthy men to examine the effects on circulating T_3, T_4, rT_3, and TSH.[86] T_3 and TSH fell significantly, rT_3 rose, and FT_4 was essentially unaffected (except for a small nonsignificant rise in a few subjects), changes that are commonly observed early in the NTI syndrome. Nagaya et al. showed that activation of nuclear factor κB (NF-κB) by TNF-α inhibits T_3-dependent induction of the D1 gene in a hepatic cell line, suggesting a possible molecular basis for euthyroid sick syndrome. The macrolide antibiotic clarithromycin, which blocks activation of NF-κB by TNF-α, was shown to restore hepatic D1 expression.[85]

Prognosis

Multiple investigations has demonstrated that the euthyroid sick state is associated with an increased fatality rate in critically ill

patients.[89–91] Slag et al. studied thyroid function tests in 86 ICU patients, excluding 2 who were determined to have hypothyroidism.[92] Of the 22% of patients that had hypothyroxinemia with normal TSH levels, the associated mortality rate was 84%. They also showed an inverse correlation between the serum T_4 level and mortality. In an observational study of 480 consecutive ICU patients without known thyroid disease, Wang and colleagues measured TT_4, FT_4, TT_3, FT_3, rT_3, and TSH and found that FT_3 levels had the strongest association with mortality, followed by TT_3, then TT_4, then FT_4, then TSH, and finally rT_3.[93] In another study, Chinga-Alayo and colleagues studied thyroid hormone patterns in 113 ICU patients.[94] After adjusting for severity of illness using Acute Physiology and Chronic Health Evaluation (APACHE) II scores and adjusting for TSH levels, they found a 49% rise in odds of dying in the ICU for every 10-ng/dL decrease in TT_3.

Alevizaki and associates found low TT_3 levels were present in 56% of 737 acute stroke patients, with low TT_3 levels proving to be an independent predictor of early and late mortality.[95] A study of 49 consecutive medical ICU patients receiving mechanical ventilation found that severely low TT_4 levels (<3 μg/dL) were associated with a 75% mortality compared with 19% mortality in patients with TT_4 levels of 3 μg/dL or higher. Low TT_4 levels had an 80.5% specificity for predicting death.[96] Tas et al. studied more than 400 patients and found that low FT_3 was a better predictor for mortality than either FT_4 or TSH, but they also showed that combined suppression of FT_3, FT_4, and TSH had higher predictive value than any individual measure.[97] In both of the preceding studies, however, the area under the receiver operating characteristic curve for FT_3 was less than that for the patients' APACHE II scores.

Plikat and coworkers reviewed thyroid hormone patterns in 227 ICU patients with complete thyroid hormone assay results available and who were not receiving either thyroid hormone supplementation or antithyroid drugs.[67] Ninety-seven patients (41%) had low FT_3 levels, consistent with NTI syndrome, 6 patients had hypothyroidism, and 1 had hyperthyroidism. Of the 97 patients with low FT_3, TSH levels were normal in 24% and reduced in 21%, whereas 23% had both low FT_3 and low FT_4 concentrations. NTI syndrome was significantly associated with APACHE II scores, mortality, length of stay, and use of mechanical ventilation. Patients with the combination of low FT_3 and low FT_4 levels had a significantly higher mortality rate compared with those with low FT_3 levels alone.

Treatment

There are limited studies examining whether therapeutic thyroid hormone supplementation influences outcome in patients with the euthyroid sick syndrome. A randomized, placebo-controlled trial testing IV levothyroxine supplementation (1.5 μg/kg per day for 2 weeks) failed to show any survival benefit in 23 medical ICU patients with NTI syndrome and TT_4 concentrations less than 5 μg/dL, despite significant increases in serum T_3 levels.[98] A randomized, double-blind study of 59 patients with acute renal failure treated with either levothyroxine (150 μg IV every 12 hours for 48 hours) or placebo showed significant suppression of TSH levels in the treatment group.[99] The levothyroxine-treated patients also had a significantly higher mortality rate (43% vs. 13%, $P = 0.01$).

In a placebo-controlled study of patients with thermal burn injury, treatment with T_3 did not affect survival.[100] Sirlak and associates studied 80 patients undergoing coronary artery bypass surgery with preoperative left ventricular ejection fractions below 30%, randomly assigning 40 patients to receive oral T_3 (125 μg/day for 7 days before surgery and from postoperative day 1 until discharge) and the other 40 patients to receive placebo.[101] Postoperative cardiac index was significantly higher in the treatment group ($P < 0.01$) and inotropic requirements lower ($P < 0.001$) compared with the placebo group, but the mortality rate was equal (three patients died in each group).[102–104]

In a prospective controlled study Spratt and colleagues studied patients undergoing coronary artery bypass surgery and found that serum T_3 fell from a mean value of just over 140 μg/L to less than 50 μg/L at the time of aortic cross-clamp removal.[105] At that point patients were randomly assigned to receive a 24-hour IV infusion of either placebo or T_3, using a dose previously shown to maintain preoperative T_3 levels. Over the next 36 hours, serum T_3 levels remained essentially unchanged from the value measured at cross-clamp removal in the placebo group. The T_3 group had only a transiently higher cardiac index at 6 hours after operation (3.0 vs. 2.5 L/min per m^2, $P < 0.002$), but there was no significant difference at 1, 12, or 18 hours.[105]

In NTI syndrome, the finding of normal values for TSH and either FT_4 or FT_4I are reassuring that thyroid function is likely normal. Markedly abnormal TSH (e.g., TSH values that are either >20 mIU/L or undetectable using a third-generation assay), even in critically ill patients, are suggestive of real thyroid disease because NTI syndrome usually causes only mild abnormalities in TSH.[28]

Hypothyroidism and Myxedema Coma

Hypothyroidism is the pathologic state that occurs when there is inadequate hormone secretion by the thyroid. Patients with this disorder span a spectrum of severity of illness ranging from a compensated state that is asymptomatic, clinically undetectable, and discernable only by specific laboratory testing to a severely decompensated state resulting in critical illness. The latter is known as myxedema coma, an uncommon, extreme degree of hypothyroidism that results in a characteristic syndrome associated with life-threatening organ dysfunction and requiring prompt recognition and urgent initiation of treatment.

Etiologies of Hypothyroidism

The two most common causes of hypothyroidism are Hashimoto thyroiditis and noncompliance with thyroid hormone replacement therapy. Hashimoto thyroiditis is an autoimmune disorder that can result in thyroid destruction by circulating antithyroid antibodies. If the destructive process is sufficiently severe, lifelong thyroid hormone supplementation is necessary to prevent hypothyroidism. Patients who have undergone thyroidectomy or radioactive iodine ablation are also treated with thyroid hormone replacement. Discontinuation of replacement therapy in these patients can lead to progressive hypothyroidism that can eventually lead to myxedema coma. Secondary hypothyroidism occurs when the thyroid is functional but lack of TSH owing to pituitary dysfunction results in inadequate thyroid hormone production. Secondary hypothyroidism is uncommon, probably occurring in about 5% or so of patients with hypothyroidism.[106] Secondary hypothyroidism has rarely led to myxedema coma.[4,107] The term *tertiary hypothyroidism* has been used to describe hypothyroidism resulting from hypothalamic dysfunction with inadequate TRH. Common causes of drug-induced hypothyroidism include amiodarone and lithium. Myxedema coma caused by amiodarone is not common, but multiple cases have been reported in the literature, including with a duration of use

• BOX 57.2 Etiologies of Hypothyroidism

Congenital Primary Hypothyroidism
- Endemic iodine deficiency
- Thyroid agenesis
- Thyroid dysplasia
- Iodine utilization defect
- Organification defect
- Thyroglobulin synthetic defect
- Iodine transport defect
- Iodotyrosine dehalogenase deficiency
- Thyrotropin receptor defect
- Idiopathic thyrotropin unresponsiveness
- Type 1a pseudohypoparathyroidism
- Excessive maternal iodine ingestion
- Maternal antithyroid drug ingestion

Drug-Induced Hypothyroidism
- Lithium
- Amiodarone
- Thionamides
- Iodine and iodides
- Sulfonamides
- Sunitinib
- Interferon alfa
- Phenylbutazone
- Aminoglutethimide
- Resorcinol
- Interleukin 2
- Thalidomide
- Perchlorate
- Sulfonylurea agents
- Ketoconazole

Acquired Primary Hypothyroidism
- Hashimoto disease
- Thyroidectomy
- Radioactive iodine (^{132}I) ablation therapy
- Neck or whole-body irradiation
- Endemic iodine deficiency
- Hemangioma, hemangioendothelioma
- *Transient hypothyroidism:*
  - Postsubacute thyroiditis
  - Painless thyroiditis
  - Postpartum thyroiditis
- *Infiltrative diseases:*
  - Amyloidosis
  - Sarcoidosis
  - Scleroderma
  - Lymphoma
  - Other neoplasms
  - Hemochromatosis
  - Cystinosis

Acquired Secondary Hypothyroidism
- Hypopituitarism
- Head trauma
- Infiltrative diseases (see earlier)
- Sheehan syndrome
- Bexarotene, dopamine, other drugs

Congenital Secondary Hypothyroidism
- Thyrotropin deficiency
- Thyrotropin structural defect

Tertiary Hypothyroidism
- Hypothalamic dysfunction

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• BOX 57.3 Precipitating Factors in Myxedema Coma

- Amiodarone
- Cold exposure
- Congestive heart failure
- Diabetic ketoacidosis
- Gastrointestinal hemorrhage
- Hypoglycemia
- Iatrogenic withdrawal of thyroid replacement therapy
- Infection or sepsis
- Noncompliance with thyroid replacement
- Opioid drugs
- Raw bok choy ingestion
- Sedative-hypnotic drugs
- Stroke
- Sunitinib
- Surgery
- Trauma

less than 6 months.[108,109] Other causes of hypothyroidism are listed in Box 57.2.

Precipitating Factors in Myxedema Coma

In addition to noncompliance with thyroid replacement therapy, a variety of intercurrent illnesses and circumstances can serve to trigger myxedema coma in patients with underlying compensated hypothyroidism (Box 57.3). Common precipitants include infection, stroke, surgery, trauma, and use of sedative, hypnotic, or opioid drugs.[110,111] As an example of a rare precipitating factor, myxedema coma has been described after ingestion of excessive amounts of raw bok choy (Chinese white cabbage, *Brassica rapa chinesis*), metabolites of which are apparently goiterogenic, inhibiting iodine uptake by the thyroid.[112]

Manifestations of Hypothyroidism

A wide variety of symptoms and physical findings can be seen in patients with hypothyroidism (Table 57.3). The sensitivity and specificity for the occurrence of various symptoms in association with hypothyroidism was examined in a cross-sectional survey involving more than 25,000 subjects participating in the Colorado Thyroid Disease Prevalence Study.[1] Among the 9.5% who were found to have elevated TSH levels, 26% of them had TSH levels higher than 10 mIU/L. Based on questionnaire data, symptoms with the highest sensitivity for hypothyroidism were dry skin (28%); memory difficulty (25%), slowed mentation (22%), weakness (22%), tiredness (18%), and muscle cramps (18%), whereas those with the highest specificity were deepening voice (98%), hoarseness (95%), constipation (95%), periorbital puffiness (90%), and feeling cold (88%).

Bradycardia is common, but not always present; tachycardia is much less common.[113] The electrocardiogram frequently shows abnormalities, most commonly sinus bradycardia and low QRS voltage, but various degrees of heart block, prolonged QT interval, and nonspecific ST-segment and T-wave abnormalities can also be seen. Imaging studies may reveal the presence of pericardial or pleural effusions.

In overt primary hypothyroidism, with or without myxedema coma, serum T_4 levels are low and TSH levels are high. There are no TSH or T_4 threshold values that distinguish those patients with myxedema coma. In secondary and tertiary hypothyroidism the TSH concentration is low or undetectable. In addition to these

TABLE 57.3 Manifestations of Hypothyroidism

System	Symptoms	Signs
Integument	Skin texture change Thinning hair Facial puffiness Brittle nails Swelling	Coarse, dry skin Coarse, dry, brittle hair Periorbital edema Transverse nail ridges Peripheral, nonpitting edema Pallor Alopecia Yellow skin Loss of sweating
Neurologic	Generalized weakness Poor concentration Daytime sleepiness Memory impairment Headache Insomnia Tinnitus Auditory impairment Dizziness Paresthesia	Mental slowness Apathetic affect Daytime somnolence Impaired intellectual function Lethargy Slow speech Hyporeflexia Dementia Psychosis, paranoia Hallucinations Neuropathy Ataxia Seizures
Cardiovascular	Dyspnea	Diastolic hypertension Distant heart sounds Hypotension Bradycardia Conduction disturbances Pericardial effusion Cardiac tamponade (rare)
Gastrointestinal	Constipation Anorexia Abdominal pain Nausea, vomiting Bloating Dysphagia	Weight gain Obesity Paralytic ileus Ascites Fecal impaction
Musculoskeletal	Myalgia Arthralgia	Myopathy Arthritis
Ocular	Blurry vision Diplopia	Blepharoptosis Cataracts
Miscellaneous	Menorrhagia Amenorrhea Decreased libido Nocturia Polyuria Fatigue Cold intolerance	Goiter Macroglossia Thick, slurred speech Pleural effusion Sleep-disordered breathing Respiratory distress Daytime somnolence Hoarseness Macroglossia Hypothermia

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specific thyroid function tests, a variety of nonspecific laboratory findings tend to be associated with hypothyroidism. Serum creatine kinase activity is commonly elevated in patients with untreated hypothyroidism owing to secondary myopathy.[114,115] Elevated serum transaminase activity may give the appearance of hepatic dysfunction when the enzymes are actually secondary to hypothyroidism-related myopathy.[114,116] Similarly, elevated plasma ammonia concentration and ascites have been reported in myxedema coma, giving the impression of hepatic coma.[117–120] A subset of untreated patients with hypothyroidism have been demonstrated to have a blunted ventilatory response to both hypercarbia and hypoxemia.[121] This impaired respiratory response was reversed within 1 week of initiating hormone replacement therapy. Macrocytic anemia, hypercholesterolemia, and both hypoglycemia and hyperglycemia have been described in hypothyroid patients.[1,110,113,122]

An association between hypothyroidism and hyponatremia has long been described, although it is not common and the validity of a relationship has been debated.[113,123–125] Reports have indicated findings consistent with a purely renal mechanism rather than inappropriate antidiuretic hormone secretion.[113,126–128] Hyponatremia has also been specifically reported in patients with myxedema coma.[124] Berndt and associates retrospectively reviewed emergency department and medical ICU admissions over a 44-month period at a university hospital in Germany and compared serum sodium levels in the 132 patients with overt hypothyroidism (TSH >10 mIU/L and FT_4 <2 pmol/L) to 1253 control patients with normal TSH.[129] Serum sodium in the hypothyroid patients averaged 137.8 compared with 137.4 mmol/L in the control group ($P = 0.2$), with no correlation between TSH and serum sodium in the hypothyroid group ($r = -0.07$, $P = 0.3$).

Diagnosis of Myxedema Coma

The term *myxedema coma* is somewhat of a misnomer. Although the term implies that all patients with this diagnosis are unresponsive, current usage of this nomenclature encompasses a broader range of acute alterations in sensorium and mental status, such as lethargy, somnolence, disorientation, psychosis, obtundation, and stupor.[4,110,130] Patients with this disorder tend to be older adults. They often, but not invariably, have a prior diagnosis of hypothyroidism or some other past history of a thyroid disorder.[130] Any of the symptoms or physical findings of hypothyroidism can occur in patients with myxedema coma. In addition to disturbances in sensorium, key clinical findings in myxedema coma include hypothermia, bradycardia, hypotension, periorbital edema, abdominal and bladder distention, delayed relaxation phase of deep tendon reflexes, and myxedematous skin changes.[110] The presence of a neck scar consistent with thyroidectomy can be an important physical finding.

Individually, the clinical manifestations of hypothyroidism and myxedema coma are for the most part nondiagnostic or nonspecific, particularly when encountered among patients with critical illness. Thus a constellation of findings from the patient history, physical examination, and routinely available test results is often critical to making a clinical diagnosis before obtaining specific thyroid function test results.[2] Even so, uncertainty in the clinical diagnosis is commonly present. A diagnostic scoring system has been devised to assist with the early identification of patients with myxedema coma.[113] The system assigns points for body temperature, heart rate and certain other cardiovascular findings, central nervous system (CNS) effects, gastrointestinal findings, any identified precipitating factor, and certain laboratory findings (but not thyroid function

test results) to arrive at a score that could range from zero to 230. In 21 patients retrospectively studied, the area under the receiver operating characteristic curve for the scoring instrument was 0.88. Sensitivity and specificity for myxedema coma were 100% and 43%, respectively, using a threshold score of 45. The authors concluded that a score or 60 or higher is potentially diagnostic in the appropriate clinical context, but that further validation is required. A simpler tool was developed by Chiong and colleagues, using the Glasgow Coma Scale score, TSH and FT_4 levels, and the presence or absence of hypothermia, bradycardia, and a precipitating event, with the score potentially ranging from zero to 10.[131]

Treatment of Hospitalized Patients With Hypothyroidism

Several points commonly arise regarding the treatment of hospitalized patients with previously diagnosed hypothyroidism who are not critically ill and do not have myxedema coma.[132] If TSH is measured and found to be elevated, consideration should be given to initiating or adjusting the dose of levothyroxine supplementation. Before initiating hormone supplementation in noncritically ill patients, the possibility of adrenal insufficiency should be considered and, if indicated, either excluded by laboratory testing or empirically treated by administering a corticosteroid.

The approach is more difficult in critically ill patients because the TSH abnormality may be a reflection of NTI syndrome. Chronic levothyroxine supplementation is generally continued in the ICU setting, although parenteral administration may be required. If used, IV dosing for levothyroxine is given at 75% of the established oral or enteral dose. Mild TSH elevations can be seen in critically ill patients during their recovery phase as a manifestation of NTI syndrome and do not require treatment. During the acute phase of critical illness, a significant TSH rise in a patient receiving chronic replacement could indicate inadequate supplementation and consideration should be given to increasing the patient's thyroid hormone dose.

Emergency Treatment of Myxedema Coma

Patients with myxedema coma should be treated in an ICU where their level of consciousness, airway control, gas exchange, and hemodynamic status can be closely monitored. Inadequate airway control owing to an altered sensorium can lead to acute respiratory failure. Respiratory failure can also develop, in some cases rapidly, because of impaired ventilatory responses to hypoxemia and hypercapnia.[121,133] Secure IV access is established and continuous electrocardiographic and pulse oximetry monitoring are used. Adequate systemic perfusion is ensured. Hypoglycemia should be excluded and periodic monitoring of blood glucose is instituted. Hypothermia is treated with passive rewarming, as active warming measures pose a risk of provoking or worsening hypotension by causing vasodilation. Any underlying precipitating factor, as well as any chronic or complicating comorbid conditions, should be identified and treated, as appropriate. Assessment and treatment of any concomitant fluid and electrolyte disorders are addressed. If not already available, plasma TSH and T_4 measurements are evaluated.

The specific treatment of myxedema coma is hormone supplementation (Table 57.4). Levothyroxine is the preferred hormone. The optimal initial dosing is unknown,[134] but typical initial doses recommended in the literature range from 200 to 500 μg, given IV and typically followed by daily doses of 50 to 200 μg.[4,106,135–137] The ATA recommends giving 200 to 400 μg IV of levothyroxine initially and then 1.2 μg/kg per day IV (or 1.6 μg/kg per day orally).[132] IV dosing is preferred for initial dosing because of the possibility of ileus or otherwise impaired gastrointestinal absorption. Whether concomitant liothyronine (pharmaceutical T_3) should be administered has long been debated. The theoretical rationale is that T_3 is the active hormone and unlike T_4 does not require endogenous conversion. If used as a supplement to levothyroxine in patients with myxedema coma, liothyronine can be given at a dose of 5 to 20 μg initially, and then 2.5 to 10 μg at 8-hour intervals.[132] If used, the lower ranges of liothyronine dosing are appropriate for smaller patients, older patients, and patients with cardiac dysrhythmias or coronary artery disease. Higher initial doses of liothyronine (75–100 μg) have been reported to be associated with lower survival in myxedema coma, although the data are very limited.[134,138]

TABLE 57.4 Initial Pharmacologic Treatment of Myxedema Coma

Drug	Dosage
Levothyroxine	Give a loading dose of 200–400 μg IV, followed by daily maintenance doses of 100 μg IV and later 50–200 μg orally.
Liothyronine	Give an initial dose of 5–20 mg IV followed by 2.5–10 mg IV every 8 hours until stabilized (optional adjunct to levothyroxine therapy).
Hydrocortisone	Give 100 mg IV before above and every 8 hours for possible adrenal insufficiency (see text).

IV, Intravenously.

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An association exists between adrenal insufficiency and hypothyroidism, both for the primary forms of both diseases as well as their secondary (central) forms. Type 2 polyglandular disease (Schmidt syndrome) is a reflection of this relationship. There is agreement that thyroid hormone supplementation given to patients with myxedema poses a risk for provoking adrenal crisis because some of these patients have underlying adrenal insufficiency.[106,132,139] To avoid precipitating an acute adrenal crisis with its attendant hemodynamic derangements, corticosteroid treatment should precede thyroid hormone administration in patients with myxedema coma. This can be accomplished by giving hydrocortisone (e.g., 100 mg IV every 8 hours). When individual circumstances are present in which the use of corticosteroids could pose significant risk, a potential alternative is to perform rapid cosyntropin testing to exclude adrenal insufficiency. Initial steroid dosing is still required (in this case using dexamethasone initially so as not to interfere with plasma cortisol assay), but dosing could be stopped if post-stimulation cortisol levels demonstrate adequate adrenal reserve. Testing also provides baseline information regarding the patient's adrenal function.

It is reasonable to follow serum hormone levels at intervals of 1 to 2 days in the ICU to ensure that TSH is declining and T_4 normalizing. If T_3 is measured and found to be elevated, consideration can be given to reducing the daily dose of thyroid hormone.[132,138]

Prognosis in Myxedema Coma

The mortality rate of untreated myxedema coma approaches 100%, but contemporary management has lowered the risk of fatal outcome to the range 20% to 50%.[4,106,110,111,140,141] Older age, persistently low heart rare or body temperature, and higher doses of thyroid hormone administration have been identified as possible factors predisposing to fatality. Common mechanisms of death include respiratory failure, myocardial infarction, gastrointestinal and cerebral hemorrhage, circulatory shock, and severe sepsis.[106,111,138]

Thyrotoxicosis and Thyroid Storm

Thyrotoxicosis is a syndrome caused by supraphysiologic levels of circulating thyroid hormones. Patients with this disorder span a spectrum of severity of illness ranging from a compensated state that is asymptomatic, clinically undetectable, and discernable only by specific laboratory testing to a severely decompensated state resulting in critical illness. The latter is known as thyroid storm, an uncommon, extreme degree of thyrotoxicosis that results in life-threatening organ dysfunction. In common with myxedema coma, prompt recognition and urgent initiation of treatment are vital.

Etiologies of Thyrotoxicosis

Of the various etiologies of thyrotoxicosis (Box 57.4), hyperthyroidism is the most common. Hyperthyroidism is a pathologic state of excessive thyroid hormone production by the thyroid. The most common cause of hyperthyroidism is Graves disease, an autoimmune disorder in which antibodies directed at TSH receptors are produced. These antibodies bind to and stimulate TSH receptors, mimicking the effects of TSH on the thyroid, and thereby stimulating production and release of T_4 and T_3 by the thyroid. Stimulatory TRAb can also result in thyroid nodules, lead to growth of existing nodules, and promote thyroid autonomy. In addition, TRAb is the mediator of some of the extrathyroidal manifestations of Graves disease, such as the characteristic orbitopathy.[142,143] Graves disease is the most common cause of thyrotoxicosis and is also the most common cause of thyroid storm. Another common etiology of thyrotoxicosis is nodular thyroid disease, which includes solitary toxic nodules and toxic multinodular goiter.[144,145] Toxic multinodular goiter is the second most common cause of thyroid storm,[106] but solitary toxic nodules may also cause thyroid storm.[146,147]

In patients with underlying thyroid disorders that confer abnormally high levels of thyroid autonomy, iodine administration can stimulate thyroid hormone synthesis and elaboration, and can precipitate thyrotoxicosis or thyroid storm (the Jod-Basedow phenomenon). This has occurred after administration of radioactive iodine for the treatment of hyperthyroidism and also after administration of iodinated contrast for radiographic procedures.[148–152]

All of the preceding etiologies are categorized as primary hyperthyroidism. Secondary (central) hyperthyroidism occurs when the thyroid produces excessive hormones owing to the stimulatory effects of pituitary TSH on thyrotropin receptors at the surface of thyroid follicular cells (see Fig. 57.2). Thus pituitary adenomas that secrete excessive TSH are therefore a potential, albeit uncommon, cause of thyrotoxicosis. Thyroid storm caused by pituitary adenomas have been reported, but the condition is exceedingly rare.[153]

Thyrotoxicosis, including thyroid storm, can occur in patients with embryonal cell carcinoma, choriocarcinoma, and hydatidiform moles[154–158] as the result of high circulating levels of hCG. The hCG molecule shares sufficient structural resemblance to TSH that it can stimulate TSH-receptors on the thyroid. Physiologic levels of hCG have little or no effect, but the high levels that can occur in trophoblastic disease or germ cell neoplasms can cause thyrotoxicosis. In this case the thyrotoxicosis can be considered a form of hyperthyroidism because the thyroid is being stimulated, albeit inappropriately, to a hyperfunctional state of hormone production.

Thyrotoxicosis existing without hyperthyroidism can occur in destructive forms of thyroiditis.[145,159] These include trauma- or radiation-induced thyroiditis, Hashimoto disease, which is an autoimmune disorder causing thyroiditis, Riedel thyroiditis, bacterial (also known as acute or suppurative) thyroiditis, and various forms of subacute thyroiditis. Included among the latter are viral (de Quervain), postpartum, silent, and painless thyroiditis. Iodine uptake studies in these disorders reveal that the thyroid is not hyperfunctional. Instead, the underlying mechanism involves release of stored hormone from the thyroid as a consequence of the attendant injury or inflammation. Depending on the amount of hormone released, the resulting thyrotoxicosis can range from asymptomatic to thyroid storm, but the latter is rare.[106,160] The inflammatory (thyrotoxic) phase of subacute, postpartum, and painless thyroiditis tends to be mild and self-limited. The patient may progress through a hypothyroid phase, which is usually transient but in some cases the destruction process is sufficient to render the patient permanently hypothyroid.

• BOX 57.4 Etiologies of Thyrotoxicosis

Graves disease
Toxic multinodular goiter
Toxic adenoma
Thyroiditis (early phase)
  Hashimoto disease (early autoimmune thyroiditis)
  de Quervain thyroiditis
  Reidel thyroiditis
  Silent thyroiditis
  Postpartum thyroiditis
  Painless or silent thyroiditis
  Inherited nonautoimmune hyperthyroidism
  Sporadic nonautoimmune hyperthyroidism
  Iodine-induced hyperthyroidism (Jod-Basedow disease)
  Drug-induced thyroiditis
Thyrotropin-secreting pituitary adenoma
Excessive hypothalamic thyrotropin-releasing hormone production
Excessive thyrotropin production due to pituitary thyrotropin resistance
Gestational hyperthyroidism
Trophoblastic disease
Hyperthyroid thyroid carcinoma
Metastatic thyroid neoplasm with ectopic thyroid hormone production
Struma ovarii and other teratomas
Thyrotoxicosis factitia (excessive exogenous thyroid hormone ingestion)
  Ingestion of ground beef with excessive bovine thyroid gland inclusion ("hamburger thyrotoxicosis")
  Administration of pharmaceutical thyroid hormone preparation
    Iatrogenic overdose
    Intentional or accidental self-ingestion

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Struma ovarii is a rare ovarian teratoma or dermoid that in some cases can contain functional thyroid tissue. The ectopic thyroid tissue operates autonomously and may elaborate sufficient amounts of hormone to cause thyrotoxicosis or even thyroid storm.[161] TSH secretion is thus suppressed and thyroid hormone elaboration by the thyroid gland itself essentially ceases. This neoplasm represents another potential cause of thyrotoxicosis that occurs in the absence of hyperthyroidism. Another is metastatic differentiated thyroid cancer, in which ectopic hormone production originates from the metastases.

Factitious thyrotoxicosis occurs when there are pathologically high levels of circulating thyroid hormone that are not produced by the body but instead represent exogenous hormone from either intentional or unintentional ingestion or administration.[162] Intentional overdose of pharmaceutical thyroid hormone can occur as a means of attempting suicide.[163–165] Intentional ingestion can also occur in patients who surreptitiously use thyroid hormones on a chronic basis either irrationally or owing to psychiatric disease, or as a misguided attempt at inducing weight loss.[166–168] Accidental overdoses are usually benign, particularly in pediatric patients, but thyroid storm can occur.[169–171] Thyroid storm has occurred from massive iatrogenic overdoses as a result of pharmacy compounding errors.[172–174] Dietary supplements or food products containing thyroid hormones or processed animal thyroid tissue have been reported.[175–177] Thyroid storm from thyrotoxicosis factitia is rare, but fatalities have occurred.

Precipitating Factors in Thyroid Storm

Thyrotoxic patients who do not receive treatment can develop progressive worsening and eventually develop a thyrotoxic crisis, a synonym for thyroid storm. More commonly, the disease may not appear progressive but transitions suddenly from an untreated, well-compensated state. This transition is usually triggered by some acute illness, injury, or other intervening physiologic stress that causes decompensation of the underlying thyroid disorder and rapidly leads to the development of thyroid storm. Either course can also be seen in patients who were previously diagnosed and pharmacologically treated for hyperthyroidism but later discontinued that treatment.[2] An uncommon precipitating cause of thyroid storm has occurred in some patients who were known to have hyperthyroidism and were prescribed radioactive iodine ablation therapy, but in whom the iodine administration caused worsening thyrotoxicosis by the Jod-Basedow effect.[151,152] Other examples of precipitating events that can trigger thyroid storm in susceptible patients are given in Box 57.5.[2,178–181]

• BOX 57.5 Precipitating Factors in Thyroid Storm

- Amiodarone
- Bowel infarction
- Cerebrovascular accident
- Congestive heart failure
- Cytotoxic chemotherapy
- Diabetic ketoacidosis
- Emotional stress
- Gastrointestinal hemorrhage
- Hypoglycemia
- Infection or sepsis
- Iodinated contrast administration
- Nonthyroidal surgery
- Organophosphate intoxication
- Pharmaceutical thyroid hormone overdose
- Preeclampsia
- Pregnancy or parturition
- Pulmonary thromboembolism
- Radioactive iodine (^{132}I) administration
- Salicylate overdose
- Thermal burn injury
- Thionamide withdrawal or noncompliance
- Thyroid surgery
- Trauma
- Vigorous thyroid palpation

Manifestations of Thyrotoxicosis

Thyroxicosis is a constellation of clinical manifestations that results from excess circulating thyroid hormone. Table 57.5 lists the wide variety of clinical manifestations that can be found in patients with thyroxicosis.[142,146,180,182] Among the most common complaints in patients with any degree of manifest thyrotoxicosis are heat intolerance, increased appetite, weight loss, increased frequency of defecation, generalized weakness, irritability, and emotional lability. Vital signs may reveal resting tachycardia and systolic hypertension with a widened pulse pressure. The skin tends to be warm and moist, the hair thin, and a fine tremor is often present. Goiter may be present or absent. Neuropsychiatric abnormalities may be evident.

Thyrotoxic patients may show characteristic ocular findings, acropachy, and cutaneous myxedema. However, these particular manifestations are ascribed to TRAbs, so they rarely occur in etiologies other than Graves disease, and even then are often not present.[142] Nevertheless, their appearance can facilitate clinical recognition of an underlying thyroid disorder in patients presenting without a prior diagnosis of hyperthyroidism. There can be a history of decreased visual acuity or diplopia, while the examination may show some of the characteristic findings of Graves orbitopathy, including thyroid stare with lid retraction or findings of lid lag, chemosis, corneal ulceration, proptosis, or extraocular muscle involvement. Myxedema occurs in a minority of patients with Graves disease, and may also occur in patients with Hashimoto thyroiditis. The term refers to bilateral, nonpitting, nodular induration, often with a yellow-brown, erythematous, or violaceous coloration. The most common distribution is pretibial, but the lesions may also be seen to involve the dorsal surfaces of the shoulders, elbows, knees, and feet.[183] Both the orbitopathy and the skin lesions are due to soft tissue accumulation of glycosaminoglycans generated by fibroblasts in response to stimulating TRAbs. Orbitopathy is seen in about 30% of patients with Graves disease, whereas 4% or less have dermopathy and less than 1% develop acropachy.[184]

Among the cardiovascular findings, sinus tachycardia and atrial fibrillation with rapid ventricular response occur commonly. Rarely, conduction disturbances may be seen, including third-degree heart block with bradycardia. A high-output form of congestive heart failure (CHF) can occur, which is in effect a potentially reversible form of cardiomyopathy.[185,186] Severe hypertension can occur, but hypotension is also possible. In some cases of thyroid storm the heart failure is sufficiently severe to lead to acute pulmonary edema or circulatory shock. Acute coronary syndrome can occur from the hypermetabolic effects of thyrotoxicosis in association with underlying coronary artery disease or from associated coronary artery spasm. Sudden cardiac death has also been reported, both in patients with hyperthyroidism and in patients abusing pharmaceutical thyroid hormone.[167,185]

Other than specific thyroid function tests, several nonspecific laboratory tests may reveal abnormalities. For example, associations between thyrotoxicosis and hypercalcemia, hyperglycemia, low cholesterol, abnormal liver function tests, and neutropenia have been reported.[1,114,117,151,187–193]

TABLE 57.5 Manifestations of Thyrotoxicosis

System	Symptoms	Signs
Integument	Excessive perspiration	Diaphoresis
	Skin texture change	Warm, moist, soft skin
	Hair texture change	Fine, friable hair
	Hair thinning	Alopecia
	Nail changes	Onycholysis (Plummer nails)
	Swelling	Vitiligo
		Pretibial myxedema[a]
		Hyperpigmentation[a]
		Digital clubbing[a]
		Thyroid acropachy[a]
		Palmar erythema[a]
Neurologic	Anxiety	Fine tremor
	Generalized weakness	Hyperreflexia
	Nervousness	Proximal myopathy
	Restlessness	Hyperkinesia
	Insomnia	Cognitive changes
		Decreased attention span
		Emotional lability
		Manic behavior
		Delirium
		Psychosis
		Obtundation
		Stupor, coma
Gastrointestinal	Increased appetite	Hyperphagia
	Anorexia	Splenomegaly[a]
	Diarrhea	Hepatomegaly[a]
	Nausea, vomiting	Gynecomastia[a]
	Abdominal pain	Jaundice
Cardiovascular	Palpitations	Sinus tachycardia
	Heart failure symptoms	Atrial fibrillation or flutter
		Other tachydysrhythmias
		Systolic hypertension
		Widened pulse pressure
		Signs of congestive heart failure
		Cardiac conduction disturbances
		Hypotension
		Systolic ejection murmur
		Hyperdynamic precordium
		Systolic thyroid bruit
		Supraclavicular venous hum
Ocular	Feeling of sand in eyes	Widened palpebral fissures
	Excessive tearing	Lid retraction (Dalrymple sign)
	Other eye complaints	Lid lag (von Graefe sign)
	Blurry vision[a]	Globe lag
	Diplopia[a]	Exophthalmos[a]
	Photophobia[a]	Ophthalmoplegia[a]
	Loss of color vision[a]	Chemosis[a]
		Palpebral xanthelasma
		Corneal ulceration[a]
		Impaired visual acuity[a]
Miscellaneous	Fatigue	Goiter
	Heat intolerance	Weight loss
	Dyspnea	Respiratory distress
	Amenorrhea	Muscle wasting
	Infertility	Fever
	Mild polyuria	

[a]Seen predominantly or exclusively in Graves disease.

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Diagnosis of Thyroid Storm

Thyroid storm is more common beyond the sixth decade and there is a female preponderance.[194] Essentially any of the symptoms or physical findings of thyrotoxicosis can potentially occur in the patient with thyroid storm, but qualifying for the designation of storm implies the presence of an acute, life-threatening condition with significant organ system dysfunction, particularly neurologic, cardiovascular, or both. A frequently cited triad of characteristic physical findings of thyroid storm that are indeed present in many cases includes hyperthermia, severe tachycardia, and CNS derangements, but many cases have deviated from this rule.[179] Either significant neurologic or cardiovascular dysfunction (or both) could be considered diagnostic requirements. The presence of CNS involvement appears to be of major importance in distinguishing patients with thyroid storm from patients with lesser degrees of thyrotoxicosis.[195] The neurologic findings commonly include restlessness, agitation, and delirium, but frank psychosis, coma, or seizures may be present. Apathetic thyroid storm—that is, cases in which neurologic hyperactivity is lacking—can occur and is more common in the elderly.[2,196]

The diagnosis of thyroid storm rests on an underlying diagnosis of thyrotoxicosis. In some cases information from the history and physical examination provides convincing evidence of thyrotoxicosis and specific laboratory testing of thyroid function serves as corroboration. In other cases the clinical diagnosis of underlying thyrotoxicosis (and therefore thyroid storm) is uncertain or only suggestive. For acutely ill, hospitalized patients in whom either thyroid storm or lesser degrees of thyrotoxicosis are considered, thyroid function testing is important. Minimum testing ideally should include serum TSH and FT_4 assays. Where FT_4 assays are not immediately available, FT_4I is substituted. The majority of patients with thyroid storm either have underlying Graves disease or multinodular goiter.

Given that thyrotoxicosis occurs as a result of excessive thyroid hormone, supraphysiologic levels of thyroid hormone are expected and are indeed present in most patients. Free and total thyroid hormone levels will often be elevated and the TSH level will be suppressed. Less commonly thyrotoxicosis can occur in which either T_3 alone (T_3 thyrotoxicosis) or T_4 alone (T_4 thyrotoxicosis) are elevated. Other patterns may be seen in certain of the more rare forms of thyrotoxicosis than can result in thyroid storm. For example, where thyroid crisis is due to acute ingestion of exogenous T_3, serum T_4 levels may not be elevated and TSH not suppressed. In rare cases of pituitary adenoma causing secondary hyperthyroidism and thyrotoxicosis or storm, the TSH level is elevated instead of suppressed. In the aggregate, patients with thyroid storm may have higher T_4 levels than thyrotoxic patients without storm. However, in an individual patient the two conditions cannot be distinguished from one another on the basis of the degree of T_4

TABLE 57.6 The Burch-Wartofsky Scoring System

Diagnostic Parameter	Scoring Points
Body Temperature	
<99.0°F (<37.2°C)	0
99.0°F–99.9°F (37.2°C–37.7°C)	5
100.0°F–100.9°F (37.8°C–38.3°C)	10
101.0°F–101.9°F (38.3°C–38.8°C)	15
102.0°F–102.9°F (38.9°C–39.4°C)	20
103.0°F–103.9°F (39.4°C–39.9°C)	25
≥104.0°F (≥40°C)	30
Central Nervous System Findings	
Absent	0
Mild: agitation	10
Moderate: extreme lethargy, delirium, psychosis	20
Severe: seizures, coma	30
Gastrointestinal and Hepatic Findings	
Absent	0
Moderate: nausea, vomiting, diarrhea, abdominal pain	10
Severe: unexplained jaundice	20
Heart Rate	
<90 beats/min	0
90–109 beats/min	5
110–119 beats/min	10
120–129 beats/min	15
130–139 beats/min	20
≥140 beats/min	25
Congestive Heart Failure Findings	
Absent	0
Mild: pedal edema	5
Moderate: bibasilar rales	10
Severe: pulmonary edema	20
Atrial Fibrillation	
Absent	0
Present	10
Precipitating Event	
Absent	0
Present	10

Modified from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am.* 1993;22:263–277.

of T_3 elevation.[2,197,198] Thus there are no threshold hormone levels that are diagnostic for thyroid storm. Although patients with storm tend to have higher thyroid hormone levels on average than thyrotoxic patients without storm, there is substantial overlap.

The Burch-Wartofsky (BW) scoring system[179] (Table 57.6) was proposed in 1993 and has been widely advocated. This severity scoring instrument uses readily available clinical information to derive an integer score that can range from zero to a maximum of 145 points. It was designed for evaluating patients with biochemical evidence of thyrotoxicosis to assess the likelihood of thyroid storm. A total score less than 25 is unlikely to represent thyroid storm, a score of 25 to 44 is suggestive of impending storm, and a score or 45 or higher is highly suggestive of thyroid storm. For patients with intermediate BW scores (25–44 points), the decision to use aggressive therapy is a clinical judgment.[36]

A newer scoring system was developed by the Japan Thyroid Association (JTA) that classifies patients into category 1 (definite) and category 2 (suspected).[2] In addition to requiring thyrotoxicosis, this system specifies requirements from among 5 criteria: (1) fever (≥38°C), (2) tachycardia (≥130 beats/min), (3) CHF (Killip class III or New York Heart Association class IV), (4) gastrointestinal or hepatic (nausea, vomiting, diarrhea, or serum total bilirubin >3 mg/dL), and (5) Glasgow Coma Scale score less than 15 (with lethargy, delirium, psychosis, seizures, or coma). Category 1 requires that the CNS criterion and at least 1 other criterion are met, or alternatively that at least 3 of the 4 non-CNS criteria are met. Category 2 requires 2 of the non-CNS criteria. Patients in whom FT_3 or FT_4 values are not available to confirm thyrotoxicosis are classified as category 2 if they meet category 1 criteria and there is preceding information that supports the diagnosis of thyrotoxicosis.

From a cohort study of 150 hospitalized patients with thyrotoxicosis, 25 of whom were deemed to have thyroid storm, retrospective application of the BW and JTA systems found that 20 of the patients with storm (80%) had BW scores higher than 44 and met category 1 or 2 JTA criteria.[195] The remaining 20% of patients with thyroid storm had intermediate (25–44) BW scores. However, accepting BW intermediate scores as indicative of thyroid storm would have resulted in 66% of the cohort cases being labeled as thyroid storm. These results suggest that including BW intermediate scores as indicative of storm yields greater diagnostic sensitivity than the JTA system, but with a large cost in terms of specificity.

The ATA recommends that severely thyrotoxic patients with systemic decompensation and BW thyroid storm scores or 45 higher or JTA category 1 or category 2 thyroid storm receive aggressive therapy.[36] For thyrotoxic patients with intermediate BW scores (25–44 points), the decision to use aggressive therapy is a clinical judgment.[36] These scoring instruments can be useful; however, the variables used are largely nonspecific and can be seen in many patients with critical illness unrelated to thyroidal illness. Thus thyroid storm ultimately remains a clinical diagnosis and blind application of scoring systems cannot supplant clinical judgment.[36,146,195,199]

Emergency Treatment of Thyroid Storm

Thyroid storm is an emergency that necessitates ICU monitoring and prompt treatment Because of attendant risks, thyroidectomy and radioactive ablation have little place in the emergency management of thyroid storm, although surgery has been used in highly selected cases. Specific treatment begins with a thionamide drug to inhibit hormone synthesis. The mechanism of action of thionamide drugs involves interference with TPO-mediated iodination of tyrosyl residues on thyroglobulin.[200] Of the two thionamides available in the United States, methimazole (MMI) and propylthiouracil (PTU), both are effective (Table 57.7). MMI is preferred for most cases of hyperthyroidism treated with a thionamide because it has a better side effect profile. However, there are several situations in which PTU is preferentially advocated, at least in adults, and one of these is thyroid storm. A rationale is that PTU not only inhibits hormone synthesis in the thyroid, but it also inhibits peripheral conversion of T_3 to T_4, an effect that MMI lacks. The 2016 ATA guidelines recommend PTU over MMI for most patients with thyroid storm.[36] PTU and MMI are available in the United States only as oral formulations. A parenteral formulation is marketed in Japan and some other countries.[201] There are reports

TABLE 57.7 Initial Specific Pharmacologic Treatment of Thyroid Storm

Agent	Dosage
1. Give One Thionamide Agent to Inhibit Thyroid Hormone Synthesis	
Propylthiouracil	Give 400–1000 mg oral or rectal loading dose followed by 200 mg q4h to 400 mg q6h.
Methimazole	Give 20 mg orally or per rectum q4h
2. Give One Agent to Inhibit Thyroid Hormone Release (Starting 1 to 2 h After Above)	
Lugol solution	Give 1 mL orally q8h
Sodium ipodate[a]	Give 0.5 g orally q12h.
Iopanoic acid[a]	Give 0.5 g orally q12h
Potassium iodide	Give 5 drops of saturated solution orally q6h
Sodium iodide	Give 250 mg IV every 6 h to 1 g IV q8h
Lithium carbonate	Give 300–450 mg orally q8h (see text).
3. Give One β-Adrenergic Receptor Blocker to Blunt End-Organ Effects	
Propranolol	Give 2–10 mg or more IV in incremental doses, then give 40–120 mg orally q6h titrated to effect
Metoprolol	Give 5–15 mg or more IV in incremental doses, then give 5–15 mg IV q4–6 h
Esmolol	Give 500 μg/kg IV over 1 min, followed by 50–200 μg/kg per minute by continuous IV infusion, titrated to effect
4. Give One or More Agents to Inhibit Peripheral Conversion of T_4 to T_3	
Dexamethasone	Give 2 mg IV q6h
Propranolol	Give 40–60 mg orally q6h
Sodium ipodate[a]	Give 0.5 g orally q12h
5. If Not Already Given as Above, Give a Corticosteroid	
Dexamethasone	Give 2 mg IV q6h
Hydrocortisone	Give 100 mg IV q8h
6. Augment Clearance by Administering a Bile Acid Sequestrant	
Cholestyramine	Give 5 g orally q6h
Colestipol	Give 5 g orally q6h

[a]Currently off market in the United States.

IV, Intravenously; T_4, thyroxine; T_3, triiodothyronine.

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of reformulating oral preparations of PTU and MMI and administering the drugs both rectally (as retention enemas or suppositories)[202–205] and IV.[206,207]

The most common side effects of thionamides are rash, usually macular or urticarial, and arthralgias. Agranulocytosis is a potential complication of either thionamide, and the appearance while taking one thionamide contraindicates use of the other agent. Hepatotoxicity can occur with either drug. With PTU, this toxicity takes the form of a rare allergic hepatitis with hepatocellular necrosis, often with high levels of serum transaminase activity.[208] The hepatic dysfunction can potentially progress despite discontinuation of PTU, and fatal cases of hepatic failure or requirement for liver transplantation have been reported.[209] Fatalities have occurred in all age groups but may be more common in children (1 in ~2000) than adults (1 in ~10,000).[208,210] These adverse reactions led the U.S. Food and Drug Administration to issue a boxed warning in 2010 advising physicians on the risk of liver failure and death from PTU.[208,210] With MMI the hepatic effects are more likely cholestatic. Rarely, an antineutrophil cytoplasmic antibody–positive vasculitis can occur, particularly with PTU use, and can be associated with a drug-induced lupus-like picture, exfoliative dermatitis, hemoptysis, and rapidly progressive glomerulonephritis.

Both PTU and MMI have been labeled as class D drugs by the U.S. Food and Drug Administration, carrying risk to the developing fetus, but when necessary PTU has been recommended as the thionamide of choice.[200] PTU is preferred over MMI in the first trimester of pregnancy because the latter drug appears to be teratogenic.[208] MMI, on the other hand, has been advised over PTU in the second and third trimesters to avoid the risk of PTU-induced hepatotoxicity. PTU is also avoided in patients who have previously had prior adverse reactions to it.

Colloid stored in the thyroid follicles serves as a reservoir of hormone that can continue to be released from the thyroid even after thyroglobulin synthesis is completely inhibited by administered thionamide. This process of thyroglobulin degradation and thyroid hormone release can potentially continue for weeks after blocking synthesis. By a process defined as the Wolff-Chaikoff effect, supraphysiologic doses of iodine can temporarily halt this release process for a variable period, typically 10 to 14 days.[211] Iodine should therefore be administered routinely to patients with thyroid storm. Various forms of iodine have been available clinically for this purpose. Off-label use of the radiocontrast agents sodium ipodate and iopanoic acid, formerly in common use as oral cholecystographic agents, has been used as a highly effective means of providing this effect.[212,213] However, marketing of these agents was curtailed around the year 2000 in the United States, making them widely unavailable, but they may still be available from some compounding sources.[213–216]

Lugol solution, which contains potassium iodide (KI) (100 mg/mL or 0.6 mEq/mL) and iodine (50 mg/mL), has been widely available and used for decades to treat hyperthyroidism and prepare patients for thyroidectomy. It has also been used to treat thyroid storm. A safety concern with this preparation has been raised because of reports of dosing errors stemming from incorrectly ordering the drug or misconstruing administration orders. The drug is only to be administered orally, and it is frequently ordered as a number of drops to be given per dose. In the hospital setting multidose bottles have often been dispensed along with a bulb pipet (eyedropper). Lethal doses have been accidentally administered when the pharmacy dispensed a multidose bottle of the drug, which was then assumed to be a single dose and the entire bottle administered.[217] In at least one case Lugol solution was mistakenly instilled topically into a patient's eye. Hospitals should have a protocol for handling this solution to ensure that only safe doses are dispensed and that clear instructions are included. Another available formulation is KI oral solution, USP, a saturated solution of KI that contains 1 g (6 mEq) of KI per milliliter of solution and has been used as an expectorant. This solution has also been administered sublingually.[204] For patients who cannot take oral or enteral iodine, parenteral formulations of KI can be given as an IV infusion.

Regardless of the form of iodine administration, its timing is important. The iodine formulation should be administered 1 to 2 hours after the thionamide is given. If given before thionamide, the administered iodine will further stimulate thyroid hormone synthesis (the Jod-Basedow effect) and thereby potentially exacerbate the thyroid storm.

For patients who cannot tolerate a thionamide, lithium has been used therapeutically.[218] The element both interferes with thyroid hormone synthesis and inhibits hormone release from the thyroid. Its use to treat thyroid storm is infrequent because of its narrow therapeutic index. To help prevent lithium toxicity, serial plasma lithium levels should be obtained aiming for a therapeutic concentration of 0.6 to 1.0 mmol/L. Potassium perchlorate competitively inhibits iodide uptake by follicular cells and has also been used when thionamides cannot be given.[219] However, perchlorate can cause agranulocytosis and nephrotic syndrome.[220–222]

Thyroid hormones and their hepatic metabolic products are excreted in bile as sulfate and glucuronide conjugates. The conjugates can undergo hydrolytic deconjugation within the intestinal lumen, and both the secreted and hydrolyzed free hormone can be reabsorbed through the intestinal mucosa. Cholestyramine, an anion exchange resin, strongly binds thyroxine and thereby interferes with this physiologic enterohepatic recirculation of thyroid hormone.[66] Cholestyramine, as well as colestipol, another bile acid sequestrant, have been shown to significantly lower circulating T_3 and T_4 levels in patients with Graves disease.[147,216,223–226] They have been used off-label in the general treatment of thyrotoxicosis and thyroid storm, and specifically in cases of thyroid hormone overdose.

Although thyroid hormones and the endogenous catecholamines superficially would appear to have similar physiologic properties, thyroid hormones are not catecholamines and do not activate adrenergic receptors. Coulombe and colleagues examined norepinephrine secretion rate in normal, hypothyroid, and hyperthyroid subjects.[227] They found no difference between the healthy subjects and the patients with hyperthyroidism. Norepinephrine secretion rates were slightly, but statistically significantly, higher in the patients with hypothyroidism. Holt and associates studied the effects of thyroid hormone on cardiac β-adrenergic responsiveness in conscious baboons, showing that thyroid hormones produce inotropic and lusitropic effects, and the mechanism appears to be up-regulation of both β_1- and β_2-adrenergic receptors, with the latter predominating.[228] Several of the clinical manifestations of thyrotoxicosis can be ameliorated by therapeutic β-blockade, including tremor, tachycardia, hypertension, palpitations, diaphoresis, and eyelid retraction. β-Blockers are therefore used to treat thyrotoxicosis and thyroid storm. The ability of these drugs to lower the heart rate in severe sinus tachycardia and other supraventricular dysrhythmias, as well as to control the ventricular response to atrial fibrillation, positions them as an essential component of treatment in most cases of thyroid storm. Nevertheless, caution is indicated in their use because some patients in thyroid storm progress to severe heart failure, hypotension, and circulatory collapse.

Both propranolol and metoprolol have been shown to be about equally effective at accomplishing the above cardiac and systemic improvements.[229] However, the conventional agent of choice for this purpose has been propranolol, in part because it is one of the oldest available agents in this class and most of the clinical experience in thyroid storm has been with this drug. Another reason is that propranolol, unlike other tested β-blockers, is known to be a strong inhibitor of 5′-deiodinase. Shulkin and coworkers tested the ability of various β-blockers to inhibit T_3 production in rat liver homogenates and showed that propranolol is much more potent than pindolol, timolol, atenolol, metoprolol, and nadolol.[230] They also showed that this effect does not appear to be related to β-adrenergic antagonism but correlates with lipid solubility. Thus an additional effect of propranolol may be an ability to lower T_3 levels through a membrane-stabilizing effect in addition to its β-blocker and deiodinase inhibiting effects. From a Japanese inpatient administrative database containing *International Statistical Classification of Diseases and Health-Related Problems,* 10th revision (ICD-10) diagnostic codes, medications, outcome, and other information, patients spanning a 3-year period with the diagnosis of thyroid storm who received β-blockers were compared to those who did not.[231] Of the 65% of patients listed as receiving β-blockers, their mortality rate was 7.5%, compared with 15.1% in those not given β-blockers ($P < 0.001$).

For patients with reactive airway disease, a relative contraindication to propranolol, a cardioselective β-blocker such as metoprolol can be considered. In patients with a more concerning relative contraindication, consideration can be given to using esmolol, an ultrashort acting β-adrenergic antagonist. Esmolol is given by continuous IV infusion, which can be discontinued if adverse effects are noted, and has been used to treat patients with thyroid storm.[232–234] With a half-life of about 9 minutes, its effects can be expected to dissipate within 30 minutes or so.[235] For patients with an absolute contraindication to β-blockade, the options are more limited. The nondihydropyradine calcium channel–blocking drug diltiazem can be given IV, including by continuous IV infusion, and is commonly used to control the ventricular response in critically ill patients with atrial fibrillation. However, it has no adrenergic blocking effects and it has vasodilator properties that can pose a risk in hemodynamically unstable patients. The antihypertensive agents reserpine and guanethidine, which also have vasodilatory effects, have been used off-label in the past in thyroid storm.[199,236–241] Although they are not β-adrenergic receptor blockers, they both possess sympatholytic effects; however, they have troublesome side effects and the drugs are unlikely to be available.

In addition to propranolol, a number of other drugs have been shown to inhibit 5′-deiodination and thereby decrease peripheral T_3 production from T_4, including PTU (at doses ≥400 mg/day),

sodium ipodate, and dexamethasone. Other corticosteroids have been shown to share this effect, but dexamethasone has been the most extensively studied. Corticosteroids have also been recommended in the treatment of thyroid storm to cover for the possibility of concomitant adrenal insufficiency. Coexisting adrenal insufficiency has been observed in a small subset of patients with Graves disease.[242] The possibility of a more pervasive but subtle effect of thyroid storm on adrenal function was investigated by Tsatsoulis and associates.[243] Using overnight dexamethasone suppression and low-dose cosyntropin stimulation testing, they investigated the adrenocortical reserve before and after treatment in 10 patients with severe thyrotoxicosis and demonstrated an attenuated response to cortisol production in the thyrotoxic state compared with the subsequent euthyroid state. On the other hand, because cortisol-binding globulin (transcortin) levels are decreased in hyperthyroidism, plasma cortisol levels may be decreased sufficiently to interfere with the interpretation of total cortisol assays.[244] Thus low total cortisol levels in response to rapid cosyntropin stimulation testing may represent a false-positive indicator for adrenal insufficiency. Assaying free cortisol levels or transcortin level may avoid this interference, but these tests are not widely available. Of the 1324 patients with an ICD-10 diagnosis of thyroid storm in the Japanese retrospective study cited previously, mortality was 12.2% in the 62% of patients given steroids compared with 6.6% in those patients not given steroids ($P = 0.001$).[231] However, multiple regression analysis pointed to an underlying correlation between steroids and illness severity rather than outcome. Evidence-based treatment guidelines from the JTA and the Japan Endocrine Society recommend that patients with thyroid storm be given 300 mg of hydrocortisone or 8 mg of dexamethasone per day.[201] Hydrocortisone (or alternatively, dexamethasone) is also recommended for patients with thyroid storm by the 2016 ATA guidelines as prophylaxis against relative adrenal insufficiency.[36] For patients with individual circumstances that point to a specific disadvantage to the use of corticosteroids, consideration could be given to performing the rapid cosyntropin stimulation test to assess adrenal reserve.

Hyperthermia can occur in thyroid storm, sometimes with body temperatures exceeding 40°C. Temperature control measures may be necessary, including external cooling in some cases. Acetaminophen is the pharmacologic antipyretic of choice. Aspirin has the disadvantage of displacing thyroid hormones from plasma proteins, which conceivably could worsen the thyrotoxicosis.[59] Precipitation of thyroid storm ascribed to aspirin intoxication has been reported.[245] On the other hand, an individual benefit-risk analysis may favor using aspirin in the patient in whom acute coronary syndrome is either the precipitating factor or a secondary complication of thyroid storm. In all cases, there should be a diligent search for an underlying precipitating factor that may have provoked the thyrotoxic crisis. Usual supportive measures for critically ill ICU patients should be provided, including continuous electrocardiographic and pulse oximetry monitoring; general hemodynamic and respiratory support; appropriate correction of fluid, electrolyte and acid-base derangements; venous thromboembolism and stress ulcer prophylaxis; glycemic monitoring and control; nutritional support; and monitoring for signs of sepsis, delirium, and adverse drug effects.

In the case of serious overdose involving thyroid hormones, activated charcoal may be administered to patients who can protect their airway or have an endotracheal tube in place, if the ingestion occurred within the prior 1 hour.[246] Cholestyramine (or colestipol) can also be given to bind thyroid hormone in the gut. Because thyroid hormone suppresses hormone synthesis by the thyroid, thionamide therapy is not indicated in these cases. PTU could be used, however, to inhibit endogenous conversion of exogenous T_4 to T_3, but alternative pharmacotherapies are available (e.g., propranolol and corticosteroids). Charcoal hemoperfusion and plasmapheresis have been used to treat overdoses of thyroid hormone.[172,174] Conventional hemodialysis has little effect because only the unbound thyroid hormones are removed, which constitute less than 1% of the circulating hormone pool. Plasmapheresis, on the other hand, effectively removes the circulating plasma carrier proteins to which thyroid hormones are bound.

Plasma exchange and plasmapheresis have also been used outside the setting of overdose to treat thyroid storm owing to underlying hyperthyroidism, with numerous supporting case reports and case series.[173,174,236,247–249] It has been postulated that plasmapheresis exerts benefit not only by removing hormone, but also by removing autoantibodies, cytokines, and catecholamines.[247] The 2016 ATA guidelines acknowledge that plasmapheresis has been used to treat thyroid storm that responds poorly to conventional methods, but makes no recommendations regarding its use.[36] The 2016 JTA guidelines for treatment of thyroid storm recommend that therapeutic plasmapheresis should be considered if clinical improvement (e.g., fever, tachycardia, and sensorium) is not seen after 24 to 48 hours of initial treatment with appropriate pharmacotherapy; however, the recommendation is rated weak and the underlying evidence of low quality.[201]

Prognosis in Thyroid Storm

In the early 20th century, survival from thyroid storm was nil.[179,250] In three large series published in the 1930s, together reporting on a total of 176 patients with thyroid storm, the mortality rate was 100%.[251–253] In contemporary series the overall mortality ranges from 8% to 30%.[2,36,147,179,195,254] Mechanisms and causes of death in thyroid storm commonly involve single and multiple organ system failure, including CHF, cardiac dysrhythmias, circulatory shock, respiratory failure, and renal dysfunction.[2] Hyperthermia, pulmonary embolism, coagulopathy, and sepsis have also been reported.[2,255,256] For survivors, thyroidectomy is usually recommended. The use of therapeutic iodine during the acute phase precludes the use of radioactive iodine ablation unless thionamide treatment is continued until the thyroid recovers from the iodine exposure.[106]

Key Points

- A variety of drugs used commonly in the ICU setting, including glucocorticoids, amiodarone, dopamine, and heparin, can either affect thyroid function test results or affect actual thyroid function.
- Nonthyroidal illness syndrome, the finding of abnormal thyroid function test results in acutely ill patients who do not have thyroid disease, occurs frequently among ICU patients.

- The most common thyroid function test findings in NTI syndrome are low TT_3 and low FT_3 levels, with low FT_4 levels observed in the sickest patients.
- Critically ill patients with elevated TSH in conjunction with low FT_4 levels or FT_4I likely have primary hypothyroidism, particularly when the TSH level exceeds 20 mIU/L.
- Critically ill patients with elevated FT_4, FT_4I, TT_3, or FT_3 levels, in conjunction with an undetectable TSH level, likely have primary hyperthyroidism.
- Currently available evidence does not support thyroid hormone administration to patients with nonthyroidal illness syndrome.
- Patients with myxedema coma have an impaired ventilator response to both hypercapnia and hypoxemia and frequently develop acute respiratory failure.
- Thyroid storm is a medical emergency that requires specific multimodal pharmacotherapy, usually including a thionamide, some form of iodine, β-adrenergic blockade, and a glucocorticoid.

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Review Questions

1. A 42-year-old woman with unknown past medical history was brought to the emergency department by ambulance after she was found crawling on a city sidewalk outside a grocery store. She was unable to give a meaningful history because of mental confusion. Physical examination findings included body temperature 38.7°C, heart rate 149 beats/min, respirations 34 breaths/min, blood pressure 180/54 mm Hg, disorientation, and agitation. Serum ethanol was undetectable and a urine drug screen result was negative. Other initial laboratory findings included serum sodium 145, potassium 4.5, chloride 104, total carbon dioxide content 27 mmol/L; serum glucose 128, urea nitrogen 24, creatinine 1.3 mg/dL; serum thyrotropin less than 0.006 (reference range 0.3–3.0) mIU/L, and free thyroxine level 4.9 (reference range 0.6–1.6) ng/dL. The intensivist concluded that she had thyroid storm. An immediate plan for pharmacotherapy was formulated to include administration of a β-adrenergic blocker, a thionamide, sodium iodide, and dexamethasone. Which of the following caveats is most important regarding the order of administering the initial dose of these therapeutic agents?

a. Administer the sodium iodide before the β-adrenergic blocker
b. Administer dexamethasone before sodium iodide
c. Administer the thionamide before sodium iodide
d. Administer the β-adrenergic blocker before the thionamide
e. Administer sodium iodide before the thionamide

Answer: c. All of the listed drugs have a potential role in the emergency treatment of the patient with thyroid storm. The purpose of a β-adrenergic antagonist drug is to blunt certain end-organ effects resulting from the thyrotoxic crisis. Dexamethasone inhibits peripheral conversion of circulating thyroxine to the more active triiodothyronine. Thionamide drugs, such as methimazole and propylthiouracil, inhibit synthesis of thyroid hormones by the thyroid. The purpose of sodium iodide (or other acceptable forms of iodine) in the treatment of thyroid storm is to prevent release of already synthesized thyroxine and triiodothyronine from the thyroid gland. However, by serving as added substrate, administration of iodine or iodide can stimulate additional thyroid hormone synthesis within the thyroid. To avoid worsening the thyrotoxic state, the initial dose of thionamide should be given 1 to 2 hours before administration of sodium iodide.

2. A 74-year-old woman was found at home on the floor by a neighbor. No other history was obtainable. In the emergency department her initial vital signs included a rectal temperature of 35.2°C, heart rate of 46 beats/min, respirations 10 breaths/min, and blood pressure of 145/83 mm Hg. Physical examination showed periorbital edema, a healed surgical scar on her anterior neck, clear lungs, benign abdomen, and nonpitting pretibial edema. She responded to strong tactile stimulation by localizing the stimuli and occasionally making some incomprehensible verbalizations. Arterial blood gas analysis performed while receiving supplemental oxygen by nasal cannula showed pH 7.10, partial pressure of arterial carbon dioxide 78 torr, and partial pressure of arterial oxygen 144 torr. After endotracheal intubation and initiation of mechanical ventilation, the serum thyrotropin assay result became available and was 122 mIU/L. Shortly thereafter the patient's free thyroxine assay result returned as undetectable. A plan was formulated for emergency treatment of myxedema coma. In addition to administering intravenous levothyroxine, which of the following pharmacologic agents should be urgently administered?

a. Hydrocortisone
b. Lugol iodine solution
c. Enteral levothyroxine
d. Iopanoic acid
e. Intravenous dextrose and insulin

Answer: a. Myxedema coma is an extreme form of hypothyroidism that is treated with thyroid hormone replacement, usually consisting of levothyroxine. Hypothyroidism can, in some cases, be associated with adrenal insufficiency. In those cases, the adrenal insufficiency may be compensated by the general decrease in basal metabolism caused by the underlying hypothyroidism. Administration of levothyroxine would be expected to restore the metabolic rate and could thereby increase corticosteroid requirements and lead to the development of acute adrenal insufficiency. Empiric administration of hydrocortisone is advocated as a means of preventing the potential complication of adrenal crisis.

3. Which of the following thyroid hormone patterns is most likely to be observed in a critically ill patient with nonthyroidal illness (sick euthyroid) syndrome?

a. Low total triiodothyronine, high total thyroxine, high free thyroxine, high thyrotropin
b. High total triiodothyronine, low total thyroxine, low free thyroxine, low thyrotropin
c. Normal total triiodothyronine low total thyroxine, low free thyroxine, normal thyrotropin
d. Normal free triiodothyronine, high total thyroxine, normal free thyroxine, high thyrotropin
e. Low free triiodothyronine, low total thyroxine, low free thyroxine, normal thyrotropin

Answer: e. Patients with no history of prior thyroidal illness and no physical findings or symptoms pointing to thyroid dysfunction but who develop a critical nonthyroidal illness frequently are found to have one or more abnormal thyroid function tests. The frequency of this condition, known as the euthyroid sick syndrome or the nonthyroidal illness syndrome, correlates with the severity of the acute illness. The most common thyroid function test abnormality is depression of total or free triiodothyronine (T_3). The most severely ill patients often progress to having low values for T_3, thyroxine (T_4), and thyrotropin (TSH). Free T_4 levels are less likely to be low compared with total T_4 levels in these patients. T_4 levels can sometimes transiently elevate slightly during the early phase of critical illness. TSH levels can similarly be slightly elevated during the early phase, and also transiently elevate during the recovery phase. Reverse T_3 levels are often elevated in critically ill patients with nonthyroidal illness. Other factors, such as concomitant use of certain drugs, can affect thyroid hormone levels in critically ill patients without thyroid disease.

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Coma

HSUAN LU, JENNIFER ROSS, AND AXEL ROSENGART

CHAPTER OUTLINE

Consciousness and Its Clinical Spectrum

Neurobiology of Consciousness
Pathophysiology of Impaired Consciousness

Assessment and Acute Management of Coma
Initial Assessment and Emergency Treatment

Assigning a Neurologic Profile
Standardized Neurobehavioral Assessment
Neuroimaging

Electrophysiology
Cerebral Blood Flow Monitoring

Initiating Target Treatments Based on Etiology of Coma
General Treatment Approach

Ethical Considerations
Advanced Care Planning Documentation
Surrogate Decision Makers
Prognostications
Underrepresented Patients

Consciousness and Its Clinical Spectrum

Consciousness is defined as an individual's state of awareness of self and environment and his or her responses to internal and external stimulation.[1] The two basic components of consciousness—arousal and awareness—are regulated by different neuroanatomic domains within the central nervous system.

Arousal and ensuing wakefulness are tightly dependent on the network function of the ascending reticular activating system (ARAS), consisting of the midbrain reticular formation, mesencephalic nucleus and tegmentum, thalamic intralaminar (centromedian) nucleus, and dorsal hypothalamus. Self-awareness and the spectrum of cognitive interactions with the environment are the purview of the hemispheres. Simplistically, the hemispheres are composed of three functional systems: units that receive, process, and store sensory information; units that generate and regulate motor activity; and units that are responsible for programming, regulating, and verifying actions. These three functional systems operate as an intercortical network and relate to the experience of awareness and allow cognitive performance.

The partition of the arousal network and the intercortical (cognitive) network implies that the level of self-awareness and cognitive performance cannot be examined in a patient with lack of arousal. In other words, in a person with a quantitatively reduced state of consciousness, the qualitative assessment of the content of consciousness is not possible. The assessment of content (i.e., testing a patient's cognitive abilities and thinking) should be done after the best level of arousal has been achieved (i.e., during or shortly after stimulation). An individual with complete arousal can express completely normal or deficient awareness and cognitive performance. Conversely, failure of arousal renders it impossible to test awareness and cognition.

Alteration of consciousness secondary to brain insult is a frequent admission diagnosis to critical care services and should be regarded as a medical emergency. Immediate and often extensive diagnostic workup is required as both times to diagnosis and treatment initiation are decisive factors for further injury prevention and brain recovery. Accurate diagnosis and subsequent prognosis may be challenging, as disorders of consciousness exist on a continuum and subtle differences distinguish the degree of disordered consciousness (Table 58.1). Indeed, it is estimated that 30% to 40% of patients with disorders of consciousness are erroneously assigned a diagnosis of vegetative state.[2] Therefore defining each disordered state of consciousness in a succinct and operational manner will provide a deeper understanding of the depth of brain injury and avoid miscommunications and unrealistic prognostication.

Coma (from Greek κῶμα koma, or deep sleep) typically results from diffuse injury to the cerebral cortex, bilateral thalami, or the paramedian tegmentum of the midbrain and pons. Coma is best characterized as a continuous state of unresponsiveness identified by inability to arouse to vigorous (noxious) external stimuli and lack of spontaneous waking. In addition to a lack of speech or purposeful motor activity, clinical features of coma include persistently closed eyes accompanied by no diurnal electroencephalographic (EEG) activity. Coma most commonly lasts only a few weeks, in which time the patient's condition either deteriorates or transitions to another neurologic state, such as a vegetative state or even a minimally conscious state.

A stuporous patient (from Latin *stupure*, meaning insensible) requires repeated, stronger stimuli to show some arousal and these patients may or may not open their eyes. Full arousal and alertness is not achieved and with continuing external stimulation, restlessness and stereotypic motor responses are observed, but without appropriate cognitive interactions. A deep stuporous state closer to coma is differentiated by European clinicians and is referred to as sopor (from Latin *sopor*, meaning deep sleep).

The *vegetative state* is characterized by the complete absence of behavioral evidence for self or environmental awareness; however, brainstem and thalamic activity is present to a degree that clinical

TABLE 58.1 Characteristic Clinical Features of Disorders of Consciousness and Locked-In Syndrome

Disorder	Consciousness	Cognition	Receptive Language	Expressive Language	Visual Perception	Motor Function	Structure Injured
Coma	No sleep-wake cycles	None	None	None	None	Primitive reflexes only	RAS *OR* Diffuse brain damage
Vegetative state	Intermittent periods of wakefulness	None	None	None	Variable visual startle responses	Involuntary movements only	Cerebral cortex Thalamocortical pathway ± RAS
Minimally conscious state	Intermittent periods of wakefulness	Inconsistent but clear behavioral signs of self or environmental awareness	Inconsistently one-step command following	Aspontaneous and ranging from single words or short phrases	Visual pursuit Object recognition	Localize to noxious stimuli Object manipulation Automatic movement sequences	Normal to variable lesion in RAS
Akinetic mutism Abulia	Normal or depressed	Normal or depressed	Normal or depressed	Normal or depressed	Normal	Delayed, slow responses	Hypothalamic Basal forebrain
Acute confusional state	Extended period of wakefulness	Confusion and disorientation	Consistent one-step command following	Yes-no responses Perseverative Short sentences Confused	Object recognition	No functional deficit	Normal to variable lesions in RAS
Brain death	Absent	Absent	None	None	None	Preserved postural and motor reflex	Global brain damage
Locked-in syndrome	Normal sleep-wake cycles	Normal to near-normal	Normal	Aphonic	Normal	Quadriplegia	Bilateral ventral pons

RAS, Reticular activating system.

signs of spontaneous or stimulus-induced arousal and sleep-wake cycles are observed. Patients often show blink responses to light, intermittent eye movements (sometimes erroneously interpreted as following objects or looking at family members); stimulus-sensitive automatisms, such as swallowing, bruxism, and moaning; or primitive motor responses. If this state lasts longer than 30 days, it is referred to as *persistent vegetative state* and is used as a descriptive clinical syndrome rather than a disease-specific entity.

The *minimally conscious state* (MCS) is characterized by limited albeit inconsistent behavioral evidence of awareness of the environment. MCS has recently been further divided into a lower boundary (MCS–), which is defined by a patient's ability to visually track and an upper boundary (MCS+), which is reflected by recovery of command following.[3] The condition of MCS includes a particular subtype known as akinetic mutism, which is portrayed as a silent, alert-appearing immobility of a patient with injury to the hypothalamus or basal forebrain. It manifests as apparent depressed levels of consciousness in a patient with well-formed sleep-wake cycles and little or no evidence of awareness or spontaneous motor activity. However, high-intensity sensory or personally relevant stimuli may elicit appropriate behavioral responses in patients with akinetic mutism, indicating that it is a lack of motivation rather than a true perturbation of arousal.

The term *locked-in syndrome* was introduced by Plum and Posner to describe the quadriplegia and anarthria resulting from the disruption of corticospinal and corticobulbar pathways, respectively. The extent of the deficits in patients with locked-in syndromes can vary, but these patients are aware of the environment and can hear and understand what is discussed around them. They are able to retain some ability of oculomotoric (i.e., ability to open eyelids) or other residual cranial nerve (CN) or motor functions. These patients are also anarthric or severely dysarthric with varying degrees of motor deficits ranging from quadriparesis to complete quadriplegia. As consciousness is preserved, communication is possible using preserved vertical or lateral eye movements or blinking of the eyelid to signal yes/no responses. The majority of cases are caused by basilar artery occlusion leading to brainstem infarction in the ventral pons, yet numerous other etiologies have been described.

Drowsiness, sleepiness, and lethargy resemble reduced spontaneous physical and mental activities in a person who cannot sustain wakefulness without repeated external stimulation. These states are somewhat comparable to the experience of lighter sleep. However, drowsy patients almost always have reduced attention and concentration and some degree of associated mild confusion. Although sleep and pathologic states of consciousness share common features such

that sleeping individuals are unaware that their condition resembles unconsciousness, quick reversal to full consciousness is a classic feature of sleep.

Abulia (from the Greek word for lack of will) is an apathetic state in which the patient is awake, has normal sleep wake cycle, and is very slow to respond to stimuli. Mental function is usually normal when tested with sufficient stimulation. Abulia is secondary to bilateral frontal lobe disease and in severe instances may mimic or progress to akinetic mutism.

An *acute confusional state* is distinguished from MCS by the reestablished ability of the patient to engage in rudimentary communication or use common objects appropriately. The condition is referred to as a confusional state because patients commonly exhibit signs of confusion, including diminished focus and attention, anterograde amnesia, disinhibition, agitation, and sleep disturbances.[4,5]

Delirium involves a fluctuating level of consciousness and pervasive impairment in mental, behavioral, and emotional functioning. It is commonly acute in onset and short in duration and is frequently correlated to a specific etiology, such as medications, anesthesia, or sleep deprivation. The *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition criteria for delirium include a disturbance of consciousness with reduced ability to sustain or shift attention and focus. In our experience, attention and concentration deficits are always present in delirious patients and accompanied by a variable degree of cognitive dysfunction unattributed to preexisting dementia. The dysfunctions of this acute syndrome include memory deficits, disorientation, disturbance of language and situational perception, and disorganized behavior. Other delirium markers are its acute onset and tendency to fluctuate along a spectrum of hyperactivity (i.e., agitation, restlessness, emotional labiality), hypoactivity (withdrawal, flat affect, apathy, decreased responsiveness), or mixed presentations.

Neurobiology of Consciousness

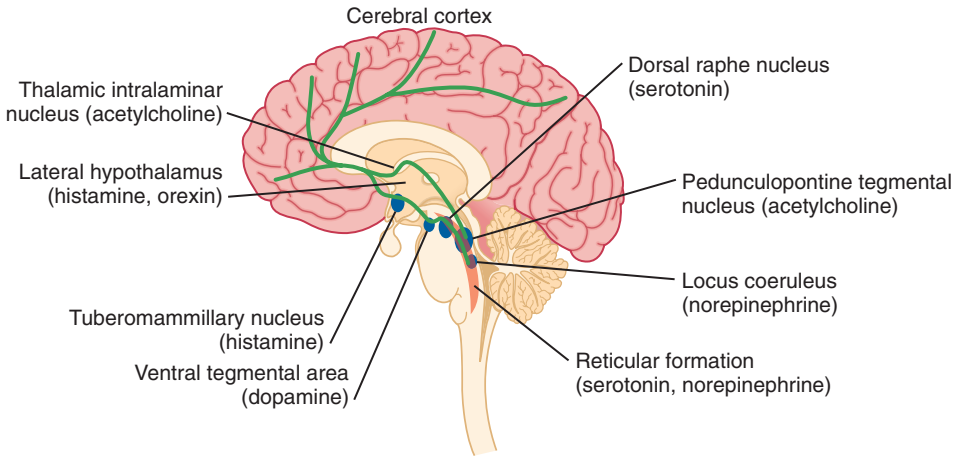
Neuroscientists have established a basic understanding of the neuroanatomic underpinnings of the two components of consciousness: arousal and awareness. The basic neuroanatomic relay stations underlying consciousness are depicted in Fig. 58.1.

The foundation of arousal is the ARAS, which consists of sets of brainstem nuclei extending from the medulla to the midbrain and including the midbrain reticular formation, mesencephalic nuclei (dorsal raphe nucleus, pedunculopontine tegmental nucleus, locus coeruleus), and ventral tegmental area. Various human actions are activated by processes that occur preconsciously (strategic arousal)—for example, gamma-band oscillations within the ARAS excite the rostral thalami, tuberomamillary nucleus, lateral hypothalamus, and basal forebrain.[6,7] In turn, the interlaminar and midline thalamic nuclei have a rich cortical interconnection allowing subsequent cognitive determination of the content of consciousness, or awareness.[8]

Different neurotransmitter systems are responsible for facilitating communication between the aforementioned brain areas, including excitatory effects from cholinergic, orexinergic, noradrenergic, and glutamatergic systems and inhibitor effects from gamma-aminobutyric acid (GABA)ergic pathways, all of which are illustrated in Fig. 58.1.[9] Neurons in the key brain regions associated with arousal and awareness may shift their firing patterns or cease transmission altogether. The hallmark of the awake state is the occurrence of high-frequency firing patterns across these brain regions, resulting in synchronous depolarization of larger cortical networks. Hyperpolarization of these neurons, on the other hand, is associated with progressive loss of consciousness, as seen with deepening stages of sleep.[10–17]

Pathophysiology of Impaired Consciousness

Indeed, just as a properly functioning ARAS gives rise to arousal and maintains wakefulness, injury to the ARAS results in reduced levels of alertness, if not complete failure to arouse. Lesions that result in impaired consciousness can therefore be thought of as supratentorial, such as damage to cortical projections in the cerebral hemispheres; infratentorial, such as brainstem injury; or both. Of note, currently used descriptors of disorders of consciousness (i.e., coma, stupor) are based on assessment of a patient's behavioral features, not on neuroanatomic or imaging data. To date, diagnostic categorizations based on root pathology do not exist. Nevertheless, a variety of pathophysiologic mechanisms causing impairment of consciousness can be described and loosely grouped into the



• **Fig. 58.1** The foundation of arousal is the ascending reticular activating system. It includes sets of brainstem nuclei extending from the medulla to the midbrain, as well as the midbrain reticular formation, mesencephalic nuclei (dorsal raphe nucleus, pedunculopontine tegmental nucleus, locus coeruleus), and ventral tegmental area.

TABLE 58.2 Etiologies and Clinical Features of Different Causes of Impaired Consciousness

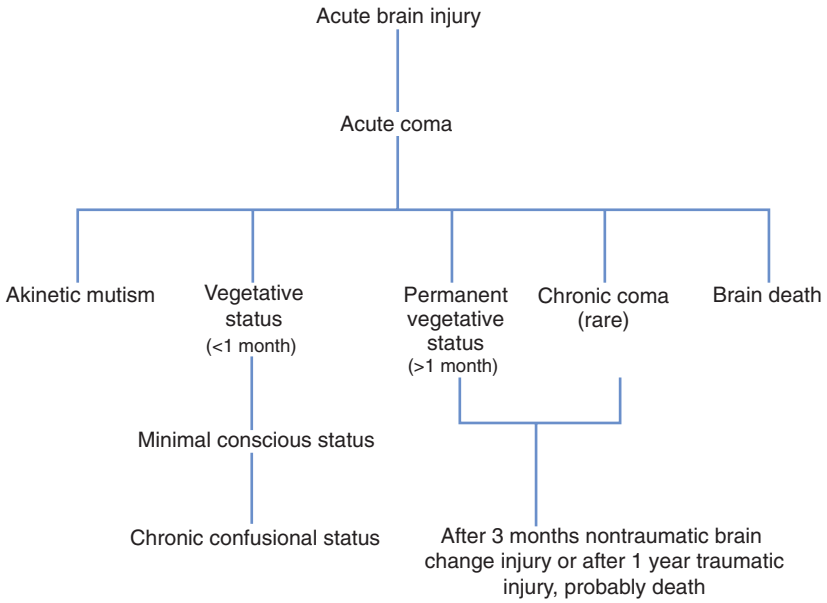
	Etiology	Clinical Features for Differential Diagnosis
Supratentorial lesion	• Destructive—ischemic infarct, hemorrhage (SAH, SDH, ICH) • Compressive lesion—ischemic infarct, hemorrhage, aneurysm, vascular malformation, tumor, venous thrombosis, abscess • Head injury, concussion	• Initial focal cerebral dysfunction • Dysfunction progresses rostral to caudal • Signs reflect cortical dysfunction, often multifocal • Often asymmetric cortical involvement and presentation
Infratentorial lesion	• Destructive—ischemic infarct, hemorrhage (SAH, ICH) • Compressive lesion—ischemic infarct, hemorrhage, aneurysm, vascular malformation, tumor, venous thrombosis	• Symptoms of brainstem dysfunction or sudden onset coma (posturing) • Brainstem signs precede/accompany coma • Cranial nerve and oculovestibular dysfunction—ocular bobbing, vertical pendular oscillation (pons), monocular movement (midbrain) • Early onset of abnormal respiratory pattern
Diffuse brain lesion	• Traumatic brain injury • Anoxic injury • Toxic encephalopathy • Seizure, nonconvulsive, postictal • Primary neuronal disorder • Infectious encephalitis (prion disease, progressive leukoencephalopathy) • Inflammatory encephalitis (ADEM) • Vasculitis	• Often asymmetric in presentation • Focal signs depending on main brain lesion
Metabolic coma	• Hypoglycemia • Nutritional (thiamine, niacin, pyridoxine, cyanocobalamin, folic acid), Wernicke encephalopathy • Hepatic encephalopathy • Uremia and dialysis • CO_2 narcosis • Exocrine pancreatic encephalopathy • Endocrine—Addison disease, pheochromocytoma, diabetes • Paraneoplastic • Drug poisoning • Thermal injury • Electrolyte/acid-base imbalance	• Confusion/stupor precede motor signs • Motor signs usually symmetric • Pupil responses generally preserved • Myoclonus, asterixis, tremulousness and generalized seizures common • Acid-based imbalance common with compensatory ventilator changes • Periodic alternating gaze deviation • Systemic—altered mental state with normal brainstem function (especially normal pupils). Possible triphasic waves on EEG • Stimulant-induced coma (cocaine, amphetamine, phencyclidine, tricyclic antidepressant) • Fever, mydriasis (except miosis with phencyclidine), and seizure • Sedatives (alcohol, benzodiazepine, barbiturates, antiepileptics) • Ataxia, impaired eye movements but normal pupils • Opiate-induced miosis
Psychiatric	• Conversion disorder • Depression • Psychosis—catatonia	• Forced eye closure • Pupils reactive or dilated, nonreactive • Unpredictable oculocephalic reflex: nystagmus on caloric test • Normal or inconsistent motor tone • No pathologic reflexes • Awake-pattern EEG

ADEM, Acute disseminated encephalomyelitis; *CO_2,* carbon dioxide; *EEG,* electroencephalogram; *ICH,* intracranial hematoma; *SAH,* subarachnoid hemorrhage; *SDH,* subdural hematoma.

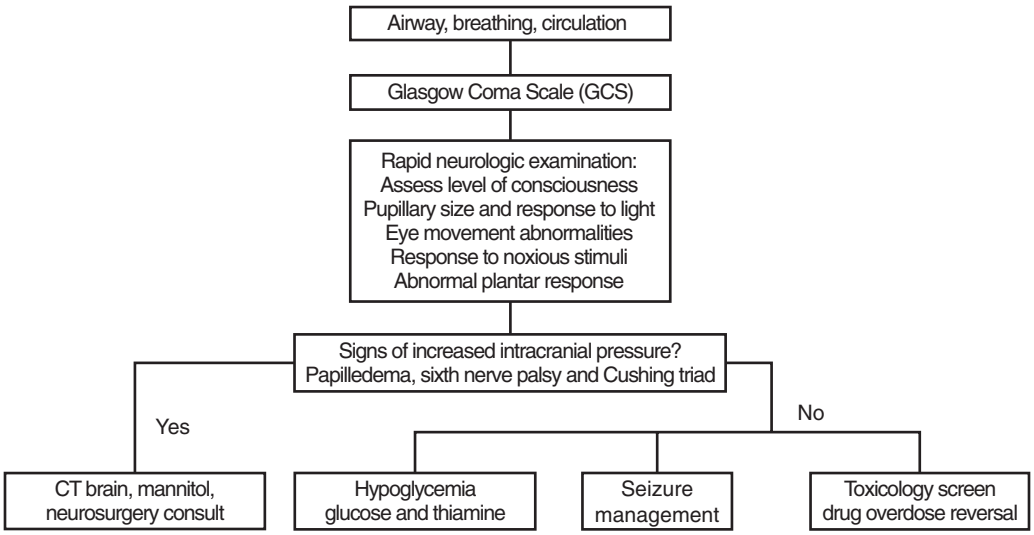
following categories: mass lesions, trauma, hypoxia/ischemia, encephalitis, and metabolic derangements. Each category is characterized by unique findings, as summarized in Table 58.2 and discussed further in later text. A neuronal-level mechanism has been proposed that outlines the transitions that occur from coma to less severe forms of disordered consciousness. This mesocircuit model illustrates the downregulation that occurs in the anterior forebrain secondary to widespread neuronal injury.[18,19]

Assessment and Acute Management of Coma

The initial approach to stupor and coma is based on the principle that all alterations in arousal are acute, life-threatening emergencies (Fig. 58.2). Interventions must be performed urgently in order to prevent or minimize permanent brain damage from reversible



• **Fig. 58.2** Natural course of acute coma.



• **Fig. 58.3** Management of acute coma.

causes. Patient evaluation and treatment must occur simultaneously (Fig. 58.3). Serial examinations with accurate documentation are necessary to determine a change in the patient's status. Accordingly, therapeutic management decisions must be made. The clinical approach to an unconscious patient entails the following steps:

1. Performing an initial assessment and providing appropriate emergency treatment
2. Obtaining a history from relatives, friends, and emergency medical personnel
3. Performing a thorough physical examination
4. Assigning a neurologic profile as this is the key to categorizing the nature of coma
5. Initiating specific therapeutic management relevant to the underlying cause of the patient's coma

Initial Assessment and Emergency Treatment

Initial assessment must focus on vital signs to determine appropriate resuscitation measures; in-depth diagnostic evaluation can occur later. Urgent and sometimes empiric therapy must be administered to avoid additional brain insult. While obtaining venous access, blood samples should be collected for anticipated tests (see Fig. 58.3).

Initial Assessment

A brief neurologic examination is mandatory. Signs of arousal include dilated and reactive pupils, copious tears, diaphoresis, tachycardia, and systemic hypertension. Although originally developed for assessment of patients with head trauma, the Glasgow Coma Scale (GCS) score can be derived by rapid bedside assessment and is useful for expedited assessment of level of consciousness (Fig. 58.4). Key points of a rapid neurologic examination are as follows:

- Assessment of level of arousal and level of consciousness (i.e., coma, stupor, lethargy)
- Checking pupillary size and response to light
- Assessing for abnormalities of eye movements (i.e., dysconjugate, unilateral paralysis, reflexive only, no movements)

Eye response (E)	Open spontaneously	4
	Open to verbal command	3
	Open in response to pain	2
	No response	1
Verbal response (V)	Talking and oriented	5
	Confused speech/disoriented	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Motor response (M)	Obeys commands	6
	Localizes to pain	5
	Flexion/withdrawal	4
	Abnormal flexion	3
	Extension	2
	No response	1
	TOTAL	3–15

Mild TBI	14–15
Moderate TBI	9–13
Severe TBI	3–8

• **Fig. 58.4** The Glasgow Coma Scale. *TBI,* Traumatic brain injury.

- Detecting grimacing and motor responses to noxious stimulation
- Observing an abnormal plantar response (Babinski sign)

Oxygenation and Intubation

Oxygenation must be ensured by establishing an airway for ventilation of the lungs. However, only after a brief neurologic examination has been performed should any sedative or paralytic for intubation be administered. The threshold for intubation should be low in a patient with altered mental status, even if respiratory function is sufficient for proper ventilation and oxygenation. The patient's level of consciousness may deteriorate or already be at a point at which airway reflexes are compromised. The patient's respiratory status may therefore decompensate suddenly and unexpectedly. A patent airway must be secured and protected from aspiration of gastric contents and blood. A nasogastric tube should be placed at the time of intubation to facilitate gastric lavage and decompression and to provide a route for administering oral medications. Indeed, a recent study found that early placement of a nasogastric tube does not increase risk of pneumonia, mortality, or poor functional outcomes in patients with stroke.[20]

If severe neck injury has not been excluded, intubation should be performed by the most skilled practitioner using in-line stabilization to avoid extension of the patient's neck, which may result in exacerbation of a cervical spine injury such as paralysis. Until the airway is secure with an endotracheal tube, bag-valve-mask ventilation should continue during the examination if necessary.

The preferred route of emergency intubation is orotracheal. Because laryngoscopy and placement of a tracheal tube is very stimulating, the patient may exhibit an intense, reflexive sympathetic nervous system response. In addition to hypertension and tachycardia, there is risk of a deleterious elevation of intracranial pressure (ICP). Therefore the patient should be adequately sedated. Etomidate (0.3 mg/kg intravenous [IV] push over 30–60 seconds) is the preferred sedative in patients with suspected ICP elevation as it reliably facilitates induction in less than 1 minute with a duration of action of 4 to 6 minutes. Propofol (1 mg/kg up to 2.5 mg/kg IV push every 10 seconds until induction onset) is another anesthetic agent that does not increase ICP. However, the use of propofol is often limited by its hypotensive effects, which can ultimately decrease cerebral perfusion pressure. Both medications result in a dose-dependent decrease of cerebral metabolic rate that reduces cerebral blood flow (CBF) and ICP. Ketamine (1.5–2 mg/kg slow IV) has a fast onset but may elevate ICP and cause paralysis, which should generally be avoided. Midazolam can alter the patient's mental status and may preclude a postintubation examination.

Respiration/PEEP

Generally, to rapidly decrease ICP, one should hyperventilate the patients (to reduce CBF), elevate the head of the bed (to facilitate cerebral venous return), and administer mannitol (0.25–1 g/kg as a 20%–25% solution bolus or in a pressure bag with filter over 30 minutes) or 23.4% sodium chloride (NaCl; 30 mL IV push over 2 minutes or IV piggyback over 10 minutes). However, in the setting of continuous cerebral spinal fluid (CSF) drainage, investigators have shown that transient hypercapnia and subsequent increases in CBF may be beneficial for patients with cerebral ischemia secondary to aneurysmal subarachnoid hemorrhage.[21]

The effect of positive end-expiratory pressure (PEEP) on ICP is only partly predictable for a number of reasons. Lung and pleural pressures are transmitted to the CSF column through intervertebral spaces and the vertebral venous plexus, and to the jugular venous

system through the superior vena cava. The effect of PEEP on ICP depends on both intracranial and pulmonary compliance and changes over time. ICP responses are not limited to PEEP but also relate to mean airway pressure, which can be elevated by many factors other than PEEP, including peak airway pressure and inspiratory time. Furthermore, the position of the patient's head and upper body can significantly affect ICP.

Circulation

Circulation must be maintained at a level that ensures adequate cerebral perfusion pressure (CPP). An arterial line may be placed in the radial artery for continuous blood pressure management and so that infusions administered for blood pressure control may be titrated to goal. An initial systemic mean arterial pressure (MAP) of approximately 100 mm Hg is adequate and safe for most patients (unless intracranial bleeding is suspected). Because CPP equals the difference between MAP and ICP, CPP-matching ICP therapy targets a CPP from 60 to 70 mm Hg in most instances. Invasive ICP monitoring is mandatory if ICP elevations are suspected. Hypotension may be treated by replacing blood and volume losses, and vasoactive agents may be used (if volume and cardiac status is adequate) to maintain target MAP and systolic blood pressures. In any patient with suspected brain injury, resuscitation fluids include isotonic solutions such as Normasol (Pfizer, Groton, Connecticut) or Plasma-Lyte (Baxter International, Deerfield, Illinois). Note that 0.9% sodium chloride solutions are slightly hypertonic (308 mOsm/L), and lactated Ringer solution is slightly hypotonic (273 mOsm/L). Norepinephrine infusions (1–40 μg/min IV infusion; titrate to effect) are often used as initial, first-line blood pressure–supporting agent. Hypertension should be aggressively managed with IV antihypertensive agents that do not elevate ICP by their vasodilatory effects. Thus labetalol and nicardipine are generally preferred and commonly used for managing uncontrolled hypertension. In most cases, including in patients with intracranial hemorrhage, systolic and diastolic blood pressures of less than 160 and 90 mm Hg, respectively, are tolerated and maintained. Urine output should be carefully observed as a surrogate of organ perfusion, with a goal of at least 0.5 mL/kg per hour. Accurate measurement of urine output requires bladder catheterization.

Glucose and Thiamine

Hypoglycemia is a frequent cause of altered consciousness and also leads to secondary brain injury if uncorrected. Glucose (25 g as a 50% dextrose solution) should be administered intravenously and immediately after blood is drawn for baseline values, as the benefits of empiric glucose in preventing possible hypoglycemic brain damage outweigh the risk of hyperglycemia. Thiamine (100 mg) may be given with the glucose infusion to prevent precipitation of Wernicke encephalopathy as seen in malnourished, thiamine-depleted patients receiving glucose infusions. In rare circumstances, an established thiamine deficiency can cause coma.

Seizures

Repeated generalized seizures invariably lead to secondary brain injury and should be treated aggressively with an IV benzodiazepine. Lorazepam (4-mg doses administered at 2 mg/min) has become the preferred agent owing to its longer duration of action; however, diazepam and midazolam are effective alternatives. Subsequent seizure control is maintained with an IV antiepileptic. Although there is no proven drug of choice, first-line agents generally include phenytoin (15–20 mg/kg IV bolus at a maximum rate of 50 mg/min), fosphenytoin (15–20 mg phenytoin sodium equivalents [PE]/kg IV bolus at a maximum rate of 150 mg/min), levetiracetam (1g IVP), or valproic acid (20–40 mg/kg IV bolus).[22] Fosphenytoin is often selected because of its faster rate of administration and lower risk of hypotension (as it is not formulated with propylene glycol). Phenobarbital (15–20 mg/kg IV bolus at a maximum rate of 100 mg/min) often requires intubation. Blood samples for drug levels of these agents should be drawn after the loading dose and maintenance dosing should be initiated. Corrected total target levels for phenytoin (and fosphenytoin) are 15 to 20 μg/mL; free levels can be drawn in patients who are critically ill or have low protein stores with a target of 1.5 2 μg/mL. Valproic acid target levels are 50 to 100 μg/mL, and phenobarbital target levels are 10 to 40 μg/mL. Seizure breakthrough requires immediate administration of benzodiazepines and loading of a second anticonvulsant. Continuous video EEG monitoring is frequently used to detect nonconvulsive seizures.

Sedation and Paralysis

Sedation is often required to facilitate comfort with respiratory support, to counteract agitation, or to treat elevated ICP. Short-acting medications administered as continuous infusions such as propofol or dexmedetomidine are preferred. However, deeper sedation, especially in patients with seizures, may require a midazolam infusion. Owing to accumulation of its active metabolite in patients with renal dysfunction, extended durations of midazolam should be avoided or interrupted if possible. Sedation should be titrated to a predefined goal using a validated sedation scale. The Richmond Agitation Sedation Scale is commonly used and a goal range of 0 (alert and calm) to −2 (light sedation, briefly awakens with eye contact to voice) is appropriate for most patients. Hourly interruption of sedation is needed to obtain serial neurologic examinations, except in paralyzed patients or those in whom awakening leads to deterioration of ICP. Additional analgesia (i.e., IV intermittent morphine [2–4 mg every 3–4 hours]) or a fentanyl infusion is often needed in postoperative patients or patients with traumatic injuries. Patients with critically high ICP should be paralyzed as part of the treatment regimen for increased intracranial hypertension; however, this should be done only after initiation of both a sedative and analgesic.

Reversal of Drug Overdose

Drug overdose is the largest single cause (30%) of coma in the emergency department.[23] Most drug overdoses are treated by supportive measures alone. Certain antagonists, however, specifically reverse the effects of coma-producing drugs. The μ-receptor antagonist naloxone (0.4–2 mg) is used as "test" antidote for opiate-induced coma and may be administered intravenously, intramuscularly, or subcutaneously. Caution is needed as the reversal of opioid effect may precipitate acute withdrawal in an opiate addict. In suspected opioid coma, the minimum naloxone dose (not complete reversal) should be given to establish the diagnosis by pupillary dilation and to reverse depressed breathing and consciousness. Because of its short half-life, patients who respond to naloxone reversal may require additional doses or a continuous infusion to avoid rebound sedation and respiratory depression.

IV flumazenil antagonizes benzodiazepine-induced coma and can be administered in 0.2-mg doses every minute for a maximum of 1 mg. In patients who initially respond to flumazenil reversal but experience recurrent sedation, flumazenil 1 mg may be redosed every 20 minutes with a maximum of 3 mg/h. Careful consideration should be given before administration of flumazenil as patients may experience benzodiazepine-withdrawal seizures. Thus, although

naloxone is commonly used with minimal serious adverse effects, the use of flumazenil should be restricted to select, low-risk cases.

The sedative effects of drugs with anticholinergic properties, particularly tricyclic antidepressants, can be reversed with 1 to 2 mg IV physostigmine (duration of action ~45–60 minutes). Pretreatment with 0.5 mg atropine will reduce the risk for symptomatic bradycardia. Of note, only full awakening is characteristic of an anticholinergic drug overdose because physostigmine has nonspecific arousal properties.

Body Temperature

Hyperthermia increases brain metabolic demands and may exacerbate brain injury.[24] Elevated temperature greater than 104°F (40°C) requires immediate, life-saving cooling measures, even before the underlying cause is determined and treated. In 2002, two research groups independently published that lowering the body temperature to 33°C for 12 or 24 hours in comatose survivors of cardiac arrest resulted in nearly doubling the number of patients who were discharged home or to rehabilitation. Modern technology provides a variety of noninvasive and invasive cooling equipments suitable to maintain any target core temperature desired. Core temperatures of less than 93°F (34°C) on admission should be slowly elevated to above 35°C to reduce the risks of unwanted side effects from uncontrolled, persistent hypothermia.

Patient History

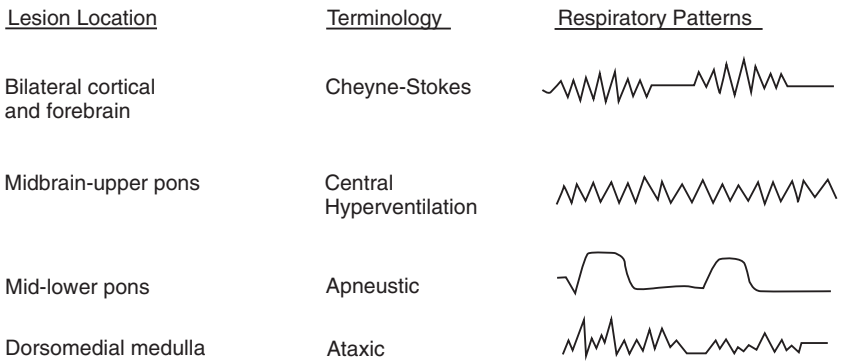
Once the patient's condition and vital signs have been stabilized, clues to the cause of coma should be sought by interviewing relatives, friends, bystanders, or medical personnel who may have observed the patient before or during the decline in consciousness. The history should address witnessed events, evolution of coma, recent medical and surgical histories, and medication/drug intake.

Thorough Physical Examination

A systematic, detailed examination is necessary when approaching a comatose patient. An in-depth physical and neurologic examination followed by serial neurologic evaluations (i.e., hourly) is the most important, indispensable, and most readily available method of assessing a comatose patient. However, in comatose patients the examination remains limited in detecting changes in brain function. Nevertheless, the astute clinician will carefully evaluate for changes in findings—that is, appearance of new asymmetry in examination or focal deficits, progressive loss of brainstem reflexes, or loss of reflex motor responses. Finding progression of impairment is of immense clinical value as it indicates a new or worsening "intracranial emergency" demanding immediate clarification and stabilization. Performing a skilled neurologic examination is challenging and provides a limited surveillance window of brain tissue at risk. Intracranial monitoring and, if needed, repeated head imaging have become the standard of care in neurocritical care units.

The differential diagnosis of a comatose patient is supported by the patient's risk factor profile, activity at symptom onset, and disease progression. For example, acute, devastating headaches with nausea and vomiting quickly followed by impaired consciousness in a hypertensive patient with a history of smoking should prompt a rapid workup for subarachnoid or intracerebral hemorrhage. Deterioration of consciousness hours after head injury necessitates immediate exclusion of newly emerging, delayed intracranial hematoma with ICP pressure crisis. In contrast, the slow progression of a focal neurologic deficit evolving to generalized depressed consciousness in an elderly individual directs diagnosis toward an intracranial metastasis with secondary seizures. Increased ICP is a common symptom seen in many acute and subacute central nervous system (CNS) injuries. Typical manifestations include headaches from the dural stretch of trigeminal (CN V) sensory fibers; intractable nausea and recurrent vomiting often associated with visual disturbances; some neurologic deficits on detailed examination; and in later stages, reduction in level of alertness.

When the neurologic examination is performed, vital signs should be considered as part of the autonomic nervous system evaluation. For example, the appearance of systolic hypertension, vagal bradycardia, and respiratory irregularity is known as the Cushing triad and indicates increased ICP. In addition, changes in the pattern of respiration in a spontaneously breathing patient can help localize the level of injury (Fig. 58.5). Abnormalities of respiration can range from apnea to hyperpnea with undulating crescendo-decrescendo patterns as well as complete irregularity of breathing with erratic pauses, which finally terminate in complete apnea. This "autonomic survey" is followed by the assessment of a patient's level of arousal. The reduction in response to external stimulations provides the basis for commonly used classification schemes such as the GCS (see Fig. 58.4). If the patient's level of alertness permits, then orientation, attention, concentration span, and intactness of cognitive functions are examined next. This is followed by a detailed assessment of CN, motor, and peripheral reflex status. Optic nerve (CN II) head edema (papilledema) is an important and, if present, reliable manifestation of raised ICP. Additional findings of increased ICP on fundoscopy include venous engorgement, loss of venous pulsation, optic disc hemorrhage with increased disc diameter, and blurring of disc margins. Compression of the oculomotor nerve (CN III) may result from a variety of intracranial processes, including uncal herniation and aneurysms



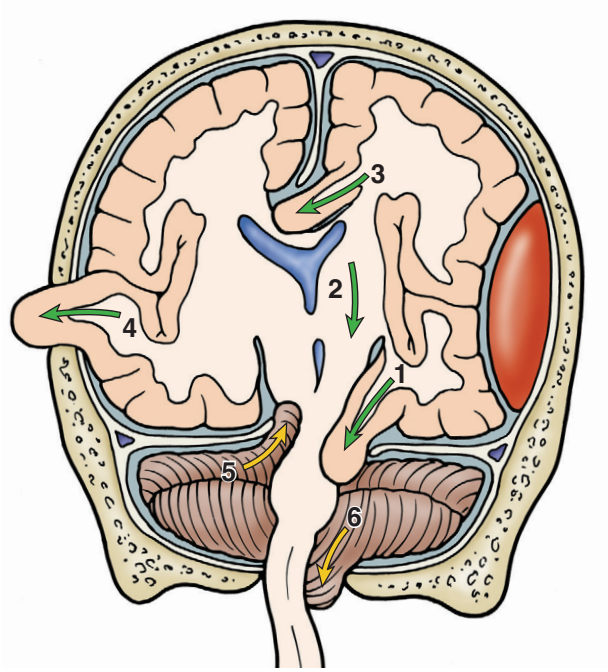
• **Fig. 58.5** Locations of lesions and patterns of respiration.

of the posterior communicating artery. It is identified by pupillary dilatation, ptosis, and various degrees of ophthalmoparesis except for abduction and intorsion-depression. A sixth nerve (abducens nerve) palsy, typically a nonlocalizing sign, is identified by abduction deficit and is seen in patients with elevated ICP or hydrocephalus and stretching of the nerve, but it is also present in patients with intrinsic brainstem injury (i.e., strokes).

Patients with acute intracranial mass lesions and increased ICP commonly develop herniation syndromes—that is, shifting of brain tissue from areas with higher regional ICP toward areas with normal ICP. If the mass lesion is predominantly located within one hemisphere, the main force vector will shift the brain primarily laterally across the midline and toward the opposite hemisphere as it impresses on the upper brainstem and thalamic structures during lateral displacement. More centrally located mass lesions—that is, acute, obstructive hydrocephalus, or global brain swelling as seen in fulminant encephalitis or hepatic encephalopathy—will instead lead primarily to downward herniation with the main force vector impressing on the brainstem. Different herniation syndromes have different clinical presentations and therapeutic approaches (Fig. 58.6). Readers are referred to Table 58.3 for further details. When intracranial hypertension remains uncontrolled and escalates, uniformly central, downward herniation occurs, increasing involving more brainstem structures in a rostrocaudal fashion. The terminal event is complete brainstem destruction resulting invariably in brain death. During this course, progressive loss of brainstem reflexes can be determined on examination and at this stage, the patient is deeply comatose. Injury to the trigeminal nerve nucleus within the pons results in loss of the corneal reflex. A vestibulocochlear (CN VIII) nerve nucleus compromise results in loss of the oculocephalic reflex and manifests as "doll's eyes" or the inability to maintain eye position as the head moves. Medullary injury with damage to the ninth and tenth nerves results in loss of lower CN reflexes, including absence of gag and cough reflexes.

Ipsilateral hemiparesis indicates the possibility of uncal herniation causing compression of the contralateral cerebral peduncle as temporal lobe tissue herniates into the space between the tentorium and brainstem. For example, a left-sided subdural hematoma causing temporal herniation pushes the opposite cerebral peduncle and its motor fibers against the right tentorial edge (right-sided Kernohan notch) leading to a hemiparesis on the same side as the hemispheric lesion (see Fig. 58.6).

Posturing is involuntary flexion or extension of the arms or legs spontaneously or elicited by stimulation, and it is included in the GCS as a measure of the severity of brain injury. Three types of posturing can be observed depending on the level of brain injury: decorticate (flexor), decerebrate (extensor), and opisthotonos (body arching along the craniospinal axis) posturing. Injury involving the brainstem above or below the red nucleus in the midbrain leads to decorticate and decerebrate posturing, respectively. Of note, flexion or extension can be witnessed either unilaterally or bilaterally, sometimes seen only intermittently and can involve one or all extremities. Decorticate posturing commonly indicates damage of the cerebral hemispheres, the internal capsule, and the thalamus, possibly also involving the uppermost brainstem. Decerebrate posturing is involuntary extension of both upper (elbow) and lower extremities indicating brainstem damage below the midbrain. Progression from decorticate to decerebrate posturing is indicative of progressive transtentorial herniation. Opisthotonic posturing is an infrequently encountered sign seen with severe brainstem injury or extrapyramidal lesions involving the axial muscles. Importantly, increasing downward pressure leads to dysfunction first at the level of the diencephalon (i.e., thalami), next affecting the upper and middle sections of the brainstem (midbrain and pons), and ultimately impeding medullary function, leading to deep coma without any reflexes or motor responses (flaccidity). Once complete rostrocaudal herniation has occurred the patient is brain dead.



• **Fig. 58.6** Herniation syndromes.

Assigning a Neurologic Profile

Correctly characterizing disorders of consciousness continues to pose interesting clinical questions and diagnostic challenges with important ethical consequences. Not only may an individual patient acutely fluctuate in his or her examination findings, but recovery may also take place over prolonged time periods necessitating frequent reassessments. To address this uncertainty, standardized neurobehavioral assessments have become the best tool in categorizing coma and its transitional stages. Predicting long-term outcome has significantly improved when standardized assessments are used. Generally speaking, clinical and electrophysiologic markers of coma and its transitional states remain unsatisfactory. Readers are reminded that larger observational studies identified a high rate of misdiagnoses (>40%), especially in patients in vegetative state, when assessment is made on clinical grounds only.[25]

Standardized Neurobehavioral Assessment

The behavioral diagnosis of the level of consciousness in severely brain-damaged patients remains challenging. To improve differential diagnostic evaluations, evidence-based recommendations endorse neurobehavioral characteristics using standardized tools.[25] The Coma

TABLE 58.3 Types of Brain Herniation Syndromes

Syndrome	Mechanism	Imaging Findings	Clinical Presentation
Uncal	• Downward displacement of medial temporal lobe into the posterior fossa through the incisural opening • Seen in patients with unilateral hemispheric mass lesions	• Contralateral temporal horn widening • Ipsilateral ambient and prepontine cistern widening • Uncus extending into the suprasellar cistern	• Ipsilateral pupil dilation and ophthalmoplegia • Contralateral or ipsilateral hemiparesis • Decerebrate posturing
Central (transtentorial)	• Downward displacement of cerebral hemispheres and basal nuclei compressing and displacing diencephalon and midbrain rostrocaudally through the tentorial notch	• Effacement of the sulci • Obliteration of the suprasellar cistern • Compression and posterior displacement of the quadrigeminal cistern	• Medium-sized, fixed pupils • Early coma • Decorticate posturing • Cheyne-Stokes respiration • Diabetes insipidus
Cingulate (subfalcine)	• Lateral displacement of the cingulate gyrus under the anterior falx	• Attenuation of ipsilateral aspect of frontal horn • Asymmetric anterior falx • Obliteration of ipsilateral atrium of lateral ventricle • Septum pellucidum shift	• Small reactive pupils • Headache • Contralateral leg paralysis
Ascending	• Infratentorial mass effect protruding through the tentorial opening compressing the midbrain and cerebellar structures at the tentorial edges	• Spinning top appearance of midbrain • Narrowing of bilateral ambient and quadrigeminal cisterns	• Progressive stupor • Nausea and vomiting
Tonsillar	• Cerebellar tonsils protruding into the foramen magnum compressing adjacent medulla and upper cervical cord	• Cerebellar tonsils at the level of the dens on axial view and 5 mm below foramen magnum on sagittal view (7 mm in children)	• Cushing triad • Coma • Bilateral arm dysesthesia

Recovery Scale-Revised (CRS-R) has excellent content validity and is a solid tool addressing all established differential diagnostic criteria. To differentiate vegetative MCS from emerging MCS, several other tools have demonstrated good validity, including the Sensory Modality Assessment and Rehabilitation Technique (SMART), Sensory Stimulation Assessment Measure (SSAM), Wessex Head Injury Matrix (WHIM), and Western Neuro Sensory Stimulation Profile (WNSSP). The Full Outline of UnResponsiveness (FOUR) and CRS-R tools showed substantial evidence of good interpreter reliability. Our recommendations are to use the CRS-R as a valid and reliable tool in most situations for differential diagnostic assessments. With reservations, the SMART, WNSSP, SSAM, WHIM, and Disorders of Consciousness Scale can be used.[26] The lack of evidence with respect to content validity, standardization, and reliability make the FOUR, Innsbruck Coma Scale, GCS, Swedish Reaction Level Scale-1985, Loewenstein Communication Scale, and Comprehensive Level of Consciousness Scale undesirable.[26]

Neuroimaging

Improvements in neuroimaging have rendered these studies more useful in determining an accurate diagnosis and prognosis for patients in a coma. Indeed, combining structural and functional imaging with a thorough standardized coma assessment seems to provide the best estimates for long-term outcome. Advanced neuroimaging studies have provided considerable evidence for the existence of major functional differences between the vegetative state and the minimally conscious state (Table 58.4). For example, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies delineated more extended cerebral processing in response to various external stimuli in patients with MCS. Resting-state fMRI studies identified that MCS patients have preservations of functional connectivity to higher-order associative cortices, such as default networks.[27–29] Complementary to these results, brain tissue integrity, as assessed by diffusion-weighted imaging and gray matter volumetry, is more preserved in MCS compared with a vegetative state.[29,30] These findings correlate to the relative improved long-term prognosis in MCS.[31]

MRI remains the procedure of choice for structural and functional imaging of the brain. Further experience with MR tractography, estimating the extent of brain connectivity, and MR spectroscopy, evaluating regional neuronal chemistry, will continue to enhance outcome predictions in patients with severe brain injury. In addition, passive, active-response, and resting-state functional MRI paradigms are currently being validated to help in differentiating impaired states of consciousness.

Conventional MRI

Commonly available morphologic MRI acquisitions include non–contrast-enhanced sagittal T1, axial diffusion, axial fluid-attenuated inversion recovery (FLAIR), axial T2 spin echo (SE), and coronal T2* (or gradient echo) sequences as well as three-dimensional (3D) T1-weighted volume acquisitions. FLAIR and T2-SE sequences are commonly used to delineate, measure, and monitor the extent and impact of acute brain injury. Common

TABLE 58.4 Neuroimaging and Electrophysiologic Techniques and Findings in Disorders of Consciousness

Technique	Measurement	Strengths	Limitations	Vegetative State	Minimally Conscious State	Comatose
FDG-PET	Metabolic	Relatively direct measure of neuronal energy use (glucose uptake)	Ionizing (limited repeated measures)	Voxel-based: Hypometabolism in lateral and medial frontoparietal cortices	Metabolic dysfunction in left hemisphere	
Functional MRI	CBF	High-resolution structural imaging of grey-white matter (DTI) and functional imaging (spectroscopy, resting, passive, and active CBF paradigms)	Sensitive to movement artifacts requiring sedation/anesthesia Incompatible with ferromagnetic material (deprivation, pumps, electrodes)	Activation fMRI: Low-level cortical activation DMN—partially preserved	Activation fMRI: Near-normal high-level cortical activation	
EEG/ERPs	Electrical	Repeatable, portable, and inexpensive	Muscle, eye, and dysautonomia artifacts Challenging source reconstruction		EEG: slow-wave activity through night and periods of REM sleep	ERP-poor outcome with absence of a cortical response to electrical stimulation of median nerves
EEG-TMS	Electrical	Stereotaxic stimulation connectivity studies	Stimulation areas are limited by muscle artifacts	TMS triggers a simple, local EEG response similar to deep sleep/anesthesia	Complex activations in distant cortical areas	

CBF, Cerebral blood flow; *DMN,* default model network; *DTI,* diffuse tensor imaging; *EEG,* electroencephalogram; *ERPs,* event-related potentials; *FDG,* ^{18}F-fluorodeoxyglucose; *fMRI,* functional magnetic resonance imaging; *REM,* rapid eye movement; *TMS,* transcranial magnetic stimulation.

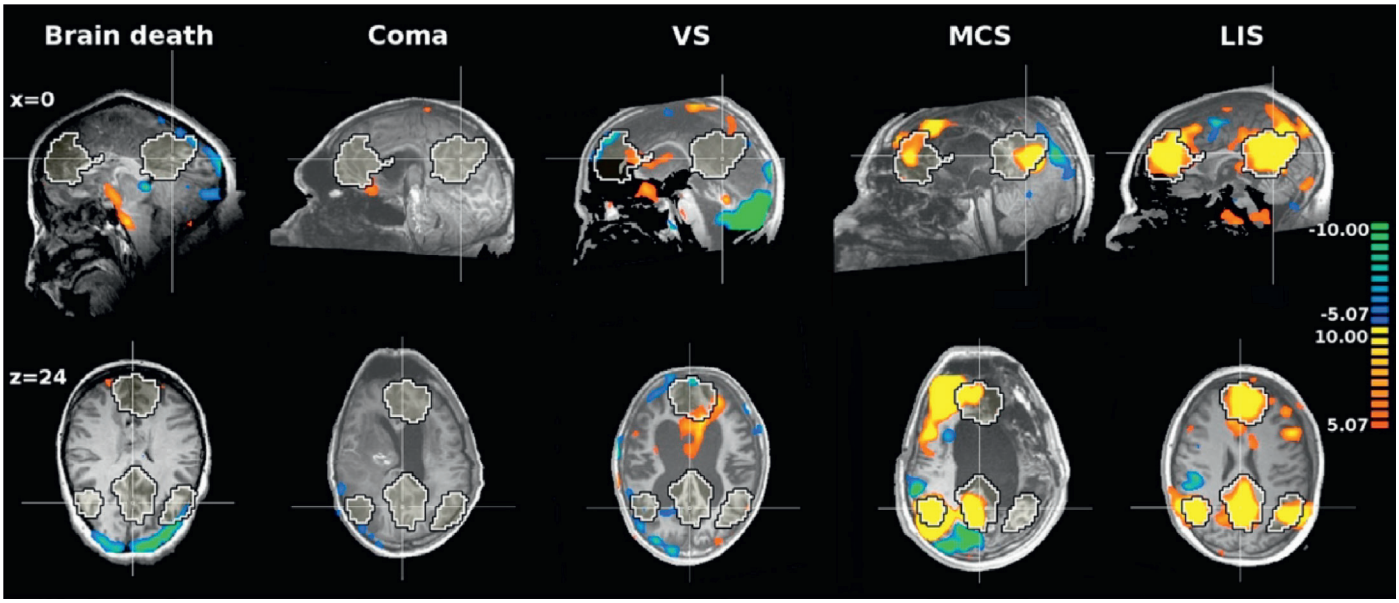
pathologies detected include brain edema, contusions, intracerebral, dural or subarachnoid blood, herniation syndromes, and hydrocephalus. T2* and susceptibility-weighted imaging are useful in detecting blood and hemorrhagic diffuse axonal injuries (DAI). Diffusion tensor imaging (DTI) can be viewed as an extension of diffusion-weighted imaging where diffusion-restricted water molecule movement (i.e., water trapped in ischemic cells or, in DTI, confined to axonal spaces) is preferentially visualized. As with most conventional MRI techniques, obtaining results with DTI is independent of the coma or sedation status of a patient.[33] Serial changes in white matter DTI metrics can be used as surrogate markers to evaluate treatment responses even when clinical scores cannot be obtained.[30] Whole brain white matter and regional DTI measures have become sensitive markers of traumatic body injury (TBI) impact correlating with acute and discharge injury severity, especially when adjusted for age, gender, and admission GCS score.[32,33] Three-dimensional rendering allows evaluating and quantifying brain atrophy after injury.[34]

Proton Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) reveals metabolic information of targeted brain regions, which correlates with the functional neuronal state of the examined sample region. To assess brain function, comprehensive MRS protocols using axial chemical shift imaging at the level of the cortical white matter,[35,36] splenium,[37] basal ganglia,[38] insular cortex, and pons[39] have been used. This approach enables detection of posttraumatic neurochemical damage and neuronal dysfunction in brain areas where conventional MR imaging techniques show no abnormalities.[40] In a TBI case-control study, the *N*-acetyl-aspartate (NAA)/creatinine (Cr) ratio correlated as a good neuronal marker with the overall recovery (and therefore lack as reliable index of unfavorable outcome after TBI), whereas less consistency was found using the choline (Cho)/Cr[41] or NAA/Cho ratios.[42] Moreover, early posttraumatic spectroscopic assessment of axonal damage is clinically relevant for prognostication and significant increases in brain lactate levels seem to be a dependable index of injury severity and outcome in TBI.[43]

Positron Emission Tomography

PET is a nuclear medicine, functional imaging technique that produces a 3D image of functional processes in the body. Using a radiopharmaceutical agent such as 18-fluorodeoxyglucose (FDG), glucose utilization may be evaluated, providing insights in neuronal metabolism that correlate with regional functional performance. For example, in acute vegetative state, overall glucose utilization was significantly reduced to 50% to 70% compared with age-matched healthy controls.[44] As expected, patients with locked-in syndrome (i.e., pontine lesions) showed normal cortical metabolism. Patients with TBI who had diffuse axonal injury had neuronal hyperglycolysis and metabolic depression.[45] Carbon 1 (^{1}C)-flumazenil-PET measures the density of benzodiazepine receptors, providing an estimate of neuronal integrity. Oxygen-15 H_2O (^{15}O-H_2O) PET imaging delineates activation-induced changes in regional CBF in response to passive external (auditory,



• **Fig. 58.7** Functional magnetic resonance imaging studies on the default/internal network of patients with brain death, coma, vegetative state *(VS)*, minimally conscious state *(MCS)*, and locked-in syndrome *(LIS)*. The black-and-white contour represents a template of the internal network extracted from 11 awake, healthy subjects. *Yellow* and *orange* areas represent activities that positively correlate with the time course of the internal network. There is decreased corticocortical connectivity in patients with disorder of consciousness and an absence of connectivity in brain death. Precuneus connectivity was significantly stronger in patients with MCS compared with patients in a VS. Patients with LIS were not significantly different from healthy control subjects. (From Noirhomme Q, Soddu A, Lehembre R, et al. Brain connectivity in pathological and pharmacological coma. *Front Syst Neurosci.* 2010;4:160.)

somatosensory or visual) stimulation. The combination of preserved activation of primary cortices (i.e., visual) but lack of coactivation of secondary processing areas provides evidence that "higher-order" associative cortical networks are disconnected from the primary sensory cortex.[46–51] Thalamocortical disconnections have also been reported using this technique.[52]

Functional MRI

fMRI imaging provides activity measures of brain regions at rest and after both passive (internal, thought-induced) and active (external, command-induced) stimulation (Fig. 58.7).[52] Such acquisitions can obtain estimates of average metabolic activity in relatively short time periods (i.e., 10 minutes) compared with PET (~30 minutes).[53] fMRI has been shown to be a good predictor of outcome in patients with impaired consciousness.[54–59] Evidence from PET studies of preserved but isolated (disconnected) cortical activation areas in patients in a vegetative state (discussed earlier) was corroborated by fMRI.[60–65]

Electrophysiology

Although a single EEG study can be a helpful diagnostic tool (i.e., to identify seizures), diagnostic certainty improves with continuous or serial EEG monitoring. Reactivity—the increase in brain wave frequencies with patient stimulation—has been used to assess thalamocortical function. For example, a patient with renal or hepatic dysfunction may have slowed background rhythms with triphasic waves and rather preserved or absent reactivity. Cerebral hypoxia, drug intoxications, sedative medications, and other CNS depressants produce abnormal EEG patterns, including burst suppression, alpha coma, and spindle coma. Focal EEG slowing with or without evidence of abnormal excitability (i.e., focal spikes) can be found in comatose patients with structural lesions, either focal cortical, focal deep-seated diencephalic or mesencephalic reticular formation, or diffuse bihemispheric. Furthermore, EEG is the primary diagnostic tool to identify patients with impaired consciousness caused by nonconvulsive seizures or status epilepticus.

Interpreting EEG can be challenging for anyone not trained in neurophysiology. However, despite the numerous etiologies leading to coma, EEG in coma patients is dominated by a few stereotypic patterns generally providing good indicators of the depth of the coma. Separating three common themes of interpretations will aid the nonexpert in using EEG for diagnosis and prognosis in patients with disorders of consciousness. EEG findings can be categorized into responsiveness (reactivity to acoustic, painful and photic stimuli), brain wave frequency abnormalities (focal or global), and specific EEG patterns (i.e., seizure discharges). The common EEG findings are discussed next.

In patients with alpha coma, the underlying brain wave activity is predominantly in the (normal) alpha range, from 8 to 12 Hz. In contrast to the normal EEG in a healthy, awake person, the EEG pattern found in comatose patients lacks alpha reactivity, implying a significant disturbance of thalamocortical pathways. Three major brain injury categories have been observed in alpha coma: status postcardiorespiratory arrest (anoxic encephalopathy), toxic encephalopathies, and de-efferentiated (locked-in) state (i.e., pontine hemorrhage).[66,67]

Patients with theta coma and alpha-theta coma show slower brain wave activities in the theta 4- to 7-Hz range (theta coma), which in some is superseded by a predominance of alpha activity (alpha-theta coma).[66] In many comatose patients, the alpha and

theta activities change after about 5 days to a more permanent pattern, at which time the EEG may be uniformly slow and depressed. EEG reactivity may emerge in subsequent studies as a relatively favorable sign; however, resolution into a burst-suppression pattern without reactivity signifies unfavorable outcome after anoxic encephalopathy.[68]

Beta coma consists of fast activities in the 12- to 16-Hz range, usually with frontal predominance. Interspersed alpha, theta, delta, and spindle (sleep)-like activities can be found. The most frequent cause for beta coma is sedative-hypnotic overdose, such as benzodiazepines and barbiturates.[69]

Intermittent rhythmic delta activity consists of low-amplitude, slow 2- to 3-Hz sinusoidal waves. These waves can appear intermittently during early stages of impairment of consciousness and soon after loss of alpha rhythm.[66] This nonspecific pattern can be seen in many metabolic and toxic encephalopathies, hemispheric lesions, acute brain injuries, and other conditions affecting cortical and subcortical structures diffusely. The prognosis of intermittent rhythmic delta activity depends on the underlying etiology.

Continuous high-voltage delta activity consists of arrhythmic, high-amplitude, polymorphic 1- to 2-Hz delta activity. This pattern is seen in later stages of coma and may evolve out of theta coma. This contrasts with the slow, nonreactive theta and delta coma EEG of low amplitude (<20 μV) and without reactivity.

Spindle coma consists of an EEG pattern predominated by 11- to 14-Hz spindle discharges, which are generally symmetric and synchronous, that appear as sleep-like oscillations on a background rhythm dominated by theta and delta activities. It resembles the EEG of a sleeping person and additional findings include anterior, low-voltage rhythmic bursts, K-complexes, vertex waves, and delta slowing. However, in these patients, wakefulness is not regained after stimulation and depth of consciousness does not fluctuate in spindle coma. These patterns indicate dysfunction at the brainstem level. TBI, anoxic encephalopathy, infectious encephalitis, drug-induced and metabolic encephalopathy, as well as postictal states can lead to this EEG finding.[70–72]

Periodic lateralized epileptiform discharges (PLEDs) occur asymmetrically (lateralized) and are episodic in nature. Morphologically, variations include sharp waves, spikes, slow waves, or a combination of these followed by a slow wave with a periodicity ranging from 0.3 to several seconds.[73] PLEDs are nonspecific and can be seen in a wide variety of brain injuries such as after cortical ischemia and with brain tumors. They are also associated with recent seizures, herpes simplex virus encephalitis, alcohol withdrawal and toxic-metabolic encephalopathy.[74] In contrast, generalized periodic epileptiform discharges are seen bilaterally and typically occur at a frequency below 1 Hz. Subclassifications define the interval between discharges and include periodic short-interval diffuse discharges, periodic long-interval diffuse discharges, and suppression-burst patterns.[75] GPEDs are seen after global brain injury—for example, after hypoxic or hepatic encephalopathy, drug intoxication, but also with various degenerative disorders.[75]

Bilateral independent periodic lateralized epileptiform discharges are slow (<1 Hz), bilateral independent epileptiform activity[76] seen in coma as the result of bihemispheric lesions. For example, after anoxic encephalopathy and infections, they are associated with a poorer prognosis[77] about two times higher overall mortality than patients with PLEDS.[76,78]

The burst-suppression pattern identifies an EEG demonstrating generalized, synchronous bursting of slow but mixed-frequency waves of high-voltage alternating periodically interspersing within longer periods of isoelectric (flat) EEG. It identifies abnormal cortical excitability,[77] and with deepening coma, the isoelectric periods become longer. The main etiologies include anoxic encephalopathy, severe intoxication, or sedative/anesthesia-induced coma states. The overall prognosis is determined by the underlying etiology.[79]

Triphasic waves are distinct, blunt delta waves (~2–3 Hz) consisting of a high-voltage positive wave preceded and followed by lower-amplitude negative waves. This nonspecific EEG can be seen in various brain injuries, among them serotoninergic syndrome, Creutzfeldt-Jakob disease, lithium and baclofen toxicity, hepatic and renal insufficiency, and neuroleptic malignant syndrome.[80]

Event-Related Potentials

Event-related potentials (ERPs) are EEG potentials identifiable after signal-averaging EEG-derived potentials evoked by a specific sensory, cognitive, or motor stimulus. Under normal circumstances, the brain generates event-related, neuronal (electrical) responses to stimulation. This neuronal activation can be detected by surface EEG; however, it requires specific mathematical processing of the EEG signal to identify brain oscillations that are time- and phase-locked to particular events (stimuli). Detection of such ERPs in patients with impaired consciousness has been interpreted as the brain's ability to process stimulus information and for cortical movement preparation. Advantages of this approach include detected signals that have an excellent time-stimulus correlation (within the millisecond range) helpful to relate a particular stimulus to certain cortical processing. The method is low-cost, noninvasive, and it can be used to monitor the brain function. Recently fast processors have allowed the development of brain-computer interfaces based on event-related signal responses that assist communication with brain-injured patients. Several ERP paradigms have been developed, allowing identification of specific response signals. The N1-P2 complex has been identified in visual ERPs and its presence interpreted as negative correlation to repressiveness.[81] The P300 (or P3) is an average, positive potential with a latency of about 300 msec. It is generated when a patient mentally reacts to a defined cognitive stimulus and is related to positive outcomes in coma.[82] Cognitive responses to command have been verified in patients with complete locked-in syndrome after basilar artery thrombosis.[83]

Brainstem auditory evoked responses (BAERs) are a series of seven potentials recorded at specific time intervals at the skull after defined auditory stimulation using headphones. Based on the redundancy and interconnections of the auditory pathways, BAERs are very robust and can be obtained in many patients with depressed level of consciousness, including patients under anesthesia or deep sedation. This implies that the absence of BAERs, or the lemniscal complexes III-IV reflecting the integrity of the upper brainstem, uniformly infers a poorer prognosis in coma (i.e., 3 to 6 days after head injury.[84] In addition, BAERs have been used as a "brainstem monitoring" tool to identify progressive downward brain herniation. Frequently, in clinical settings, BAER monitoring is combined with somatosensory evoked potential (SEP) and EEG monitoring. Somatosensory evoked potentials (SSEPs) are a series of peaks recorded over the neck and scalp in response to electrical stimulation of a peripheral nerve, usually the median nerve. The N13 wave is a negative peak at 13 msec, reflecting activity at the cervical cord, whereas the N20 wave is a negative peak at 20 msec, reflecting the earliest cortical activity. Longer latency responses are also seen at 25, 35, 45, 70, and 95 msec, reflecting higher cortical processing. Multimodality evoked potentials combine simultaneous brainstem auditory, somatosensory, and visual evoked potential monitoring[85]

to enhance the predictive value of evoked potential monitoring—for example, in TBI patients[86] or during induced barbiturate coma when examinations cannot be obtained.[87]

Cerebral Blood Flow Monitoring

Transcranial Doppler (TCD) records the velocity and pulsatility of CBF, allowing hemodynamic analysis, despite the use of sedatives or moderate hypothermia. TCD has been used for serial examinations in comatose patients after initial recovery from cardiac arrest to detect and treat early cerebral hemodynamic changes. If a patient has an appropriate temporal ultrasound window, TCD can determine cerebral perfusion arrest, and hence can be used as an ancillary study to determine brain death.[88] Further, velocity and pulsatility indices correlate as a noninvasive measure with ICP elevations and also identify delayed presence of a hyperemic flow pattern—that is, high velocities with low pulsatility as seen in patients with intracranial hypertension from hyperemia.[89]

Xenon computed tomography (CT) uses the diffusion of xenon into the CNS to determine CBF—for example, to assess perfusion deficits after a TBI.[90] Using hyperventilation, xenon CT can be used to estimate cerebral vasoreactivity, a marker correlating with outcome in comatose patients with TBI.[90]

Near-infrared spectroscopy is used to derive the levels of oxygen saturation by estimating deoxygenated and oxygenated hemoglobin in the brain. In TBI, near-infrared spectroscopy can be used to monitor the trend of deviation from the baseline cerebral oxygen saturation levels.[91]

Initiating Target Treatments Based on Etiology of Coma

General Treatment Approach

As discussed earlier, the immediate goals in a comatose patient are stabilization of vital signs, rapid diagnosis, immediate treatment to reverse the primary injury (i.e., recanalization of CBF) and minimization of further nervous system damage from secondary injury (i.e., brain swelling). These general goals are greatly facilitated by a team approach of medical and nursing staff with expertise in acute brain injuries. To improve outcome, subsequent management of a patient in a coma should be guided by the underlying etiology of the patient's brain injury, which is not always readily known.

It is important to keep in mind that *coma* is a descriptive term based on examination findings and it may result from a range of heterogeneous etiologies. Therefore first dividing coma into traumatic and nontraumatic etiologies can be useful, as each group is predominated by different demographics and disease prognoses.

Traumatic Etiologies of Coma

TBI, which is defined as physical injury to the head resulting in disruption of normal brain functioning, can manifest in severity from "mild" (i.e., transient alteration of mental status) to "severe" (i.e., coma). The leading causes of TBI include falls, being struck by or against an object, motor vehicle accidents, and assault.[92]

Therapeutic interventions after severe TBI should focus on blocking the primary injury process and preventing or reducing secondary brain injury. Primary injury in severe TBI includes hematoma formation, diffuse axonal injury after high-velocity injury (i.e., vehicle collisions, falls from a great height), and ischemic brain injury owing to traumatic vascular lesions (i.e., arterial dissection in the neck). Immediate arrest of the ongoing primary injury (i.e., by acute recanalization of a dissected arterial occlusion, reversing anticoagulation during ongoing intracerebral bleeding or hypoxia/hypotension) should be attempted whenever possible. Unfortunately, little can be done to treat or reverse the primary injury in TBI.

Secondary brain injuries after TBI are common and include brain edema with subsequent brain tissue shifts and reduction in cerebral perfusion pressure, formation of new hematoma, prolonged seizures, hypoxia, neurogenic/hypovolemic hypotension, uncontrolled hyperventilation, hypoglycemia, thromboembolism from venous thrombosis, and so on Therefore early TBI management strategies should focus on prevention and early recognition of such complications. A combination of intracranial (i.e., ICP, brain temperature, brain oxygen tension, and perfusion) and systemic monitoring as well as repeated neuroimaging is indicated in these patients.

Noncontrast CT is the most common imaging evaluation tool in patients with TBI. A cervical spine CT with reconstructed views and head and neck CT angiogram are often added during initial evaluation, if injury to the neck and arteries, respectively, is suspected. An experienced neuroradiologist should review bone and brain windows separately. Imaging has a good sensitivity for the presence of pathologic air, skull fractures, hemorrhagic lesions, abnormalities of the brain parenchyma (i.e., shift), and obstruction of CSF spaces (hydrocephalus). Injury to the neuroanatomic structures of consciousness or the presence of additional etiologies for coma (i.e., alcohol) should be considered when disparities between CT findings and examination exist.

Compared with CT, MRI has a higher sensitivity to detect DAI; however, this advantage has not translated into improved clinical outcomes as there is currently no treatment for this condition. However, both the detection of DAI and delineating injury of major motor (i.e., corticospinal) tracts on DTI can be used together with the clinical course to prognosticate TBI.[93] MRS provides additional "chemical" information, especially of the white matter injury process.[94]

The presence and severity of secondary brain injury should constantly be assessed and managed throughout the acute phase of TBI. Although the time course of secondary injury can be variable, it is somewhat predictable. For example, the development of a new hematoma may occur in the first several hours, whereas brain edema is usually seen within 1 to 3 days. Vasospasm, which may cause delayed brain ischemia, typically occurs even a week after injury secondary to irritation from subarachnoid blood.

There is only limited evidence to support the use of ICP monitoring. ICP monitoring has evolved as an essential tool and also as one of the earliest monitoring tools in clinical practice; thus many believe clinical trials cannot ethically be justified. The ongoing debate of ICP monitoring stemmed from the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP) trial, a randomized clinical trial that demonstrated that care focused on maintaining ICP at 20 mm Hg or less was not superior to a treatment protocol guided by CT imaging and examination without ICP monitoring.[95] Several criticisms include the primary impact of the study is that the trial is research based and should not alter clinical study, accumulating evidence demonstrates there are several mechanisms of secondary brain injury (SBI) that cannot be detected using an ICP monitor, and a need for multimodal monitoring should be adapted to improve outcome. Therefore current Brain Trauma Foundation management

guidelines recommend its use in severe TBI. Of note, head imaging cannot predict ICP. Furthermore, treating for elevated ICP (other than empirically in the emergency setting) and not monitoring ICP can be deleterious and results in a poor outcome.[96] In addition to ICP, other brain monitoring techniques used in modern TBI management include jugular venous and transcranial oxygen saturations (near-infrared spectroscopy); brain tissue oxygen tension; brain tissue metabolism (microdialysis) and temperature; direct brain perfusion; and TCD, sonography, and electrophysiologic studies such as EEG and evoked potentials. A discussion of these techniques is beyond the scope of this chapter, and readers are referred to recent reviews.

The management of severe TBI includes emergent decompressive craniectomy in controlling intractable ICP, especially if deterioration is associated and there is some evidence that there will be positive outcomes in surviving patients.[97–102] Although the timing of decompressive craniectomy remains controversial, early referral seems most intuitive. IV mannitol and hypertonic saline solutions are main building blocks in the management of increased ICP.[103–108] The superiority of one agent over the other is uncertain, and both approaches are routinely used in the management of severe TBI.[109]

Therapeutic hypothermia is postulated to exert neuroprotective effects by several mechanisms, including reducing cerebral metabolic rate/requirement, modulating apoptosis or programmed cell death, reducing intracellular calcium/toxic excitatory neurotransmitters/inflammation, and preserving protein synthesis.[110–115] However, the reported impact on neurologic outcome in severe TBI remains inconsistent and a meta-analysis of randomized controlled trials suggests its lack of benefit in severe TBI.[115] Therapeutic hypothermia is used as last-resort therapy and commonly, together with pentobarbital therapy and ICP-matching, CPP elevation to protect the brain from otherwise intractable ICP elevations. Studies have shown a specific group of patients, such as those with focal hematomas that can be surgically removed or patients treated in Asian centers, may benefit from moderate (32°C–35°C) hypothermia, if such treatment is implemented early and maintained for at least 48 hours.[116] Until well-designed, randomized controlled trials are available, temperature control should be determined with the intent to avoid hyperthermia while limiting hypothermia unless ICP is exceedingly difficult to control.

The initial GCS seems to be a reasonable marker to predict mortality from severe TBI. To further improve prediction, models include a combination of clinical data, imaging results, GCS score, and patient demographics.[117] In a large, traumatic coma databank study,[118] patients with severe injury (GCS scores 3–8) had approximately 36% mortality. In one study of 170 patients, the GCS score 5 hours after injury was compared with the Glasgow Outcome Scale (GOS) score at 1 month, and positive recovery was seen in 99% of patients with mild TBI (GCS scores 13–15), 71% of patients with moderate TBI (GCS scores 9–12), and in only 35% of patients with severe TBI. In contrast, only 2% to 3% of patients with mild TBI (GCS scores 13–15) died. Generally speaking, clinical outcome after TBI is more variable than in nontraumatic coma (i.e., after hypoxia).[119] Furthermore, outcome predictions for patients with intermediate GCS scores identify that midline shift of less than 4.1 mm on initial CT scanning had a significantly higher favorable outcome rate compared with patients with a larger shift.[120]

Biomarkers after TBI, such as cellular glial fibrillary acidic protein (GFAP) and S100B released with astrocyte injury, may offer diagnostic and prognostic tools in addition to clinical indices. In 79 patients with TBI (GSC score ≤12), identified intracranial mass lesion, pupillary reactivity, GFAP, and S100B were the strongest predictors of death and unfavorable outcome with S100B as the strongest single predictor of unfavorable outcome with 100% discrimination.[121] SEPs in 58 patients with TBI who were unconscious for more than 30 days were compared with outcome at 12 months,[122] showing excellent prediction for outcome (persistent coma or MCS, 92% and 86%, respectively) at 12 months when combined with age, sex, and GCS score.[123] Furthermore, among electrophysiologic tests SEPs and brainstem auditory evoked potentials are more sensitive indicators than EEG (i.e., 45%–60% sensitive vs. 35%); and if EEG and SEPs show opposing results, generally speaking, prognosis is linked to the better test result.[124] The results of multimodality evoked potentials can be used as a reliable prognostic indicator (91% accuracy) in patients with TBI.[85]

The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) is a prognostic model predicting 6-month functional outcome (GOS) and mortality in 587 patients with severe TBI (mean age 38 ± 17 years). At the sixth month, the median GOS was 3 (interquartile range 3) and 6-month mortality was 41%; age, motor score, pupillary reactivity, head CT findings, secondary insults, and laboratory values displayed good prediction ability for unfavorable outcome and mortality.[123]

Nontraumatic Etiologies of Coma

Determining the cause of nontraumatic coma can be challenging given the lack of clear external signs of injury. Brain imaging by CT scan may aid diagnoses by allowing the practitioner to distinguish between structural (i.e., cerebral infarction, intracranial hemorrhage, intracranial malignancy, or infection) and nonstructural (i.e., toxins, epilepsy, sepsis, metabolic disturbances, or anoxic injury caused by circulatory shock, respiratory failure, or cardiac arrest) causes of nontraumatic coma. Indeed the most common causes of nontraumatic coma are post–cardiac arrest anoxic brain injury, stroke, toxins, and metabolic disturbances.[124]

Coma After Cardiac Arrest (Anoxic Brain Injury)

Cardiac arrest remains one of the leading causes of mortality, affecting more than 300,000 people each year in the Unites States alone. In those who are successfully resuscitated, survival rates are low, ranging from 10% to 30%,[125] with morbidity and mortality attributable to the anoxic-ischemic encephalopathy that occurs after arrest.

The American Academy of Neurology recently published guidelines to address three major points in the management of patients who are comatose after successful cardiopulmonary resuscitation: (1) the utility of therapeutic hypothermia (TH) or targeted temperature management (TTM), (2) the role of neuroprotective drugs, and (3) additional medical interventions that may improve outcomes.

For patients who are comatose in whom the initial cardiac rhythm is ventricular tachycardia (VT) or ventricular fibrillation (VF), TH (32°C–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with patients without TH. For patients who are comatose in whom the initial cardiac rhythm is either VT/VF or asystole/pulseless electrical activity after out-of-hospital cardiac arrest, targeted temperature management—which includes 36°C for 24 hours, followed by 8 hours of rewarming to 37°C, and temperature maintenance below 37.5°C until 72 hours—is likely as effective as TH. Lastly, for patients who are comatose with an initial rhythm of pulseless electrical activity/asystole, TH possibly improves survival and functional neurologic outcome at discharge compared with standard of care. In regard to neuroprotective drugs, none has been shown

to be effective in improving survival or neurologic outcome in patients who are comatose after cardiac arrest to date.[126]

Certainly, TH has improved outcomes for patients in a coma after out-of-hospital ventricular fibrillation arrest. Hypothermia has multiple actions not only within the CNS but also systemically. Among them are depression of neuronal activity, amelioration of intracellular postischemic reactions mitigating secondary cell injury, cardiac arrhythmias, hypocoagulability, decrease in immune defense, and reduction in drug metabolism and clearance. Notably, the latter can lead to misinterpretation of the prolonged effects of sedatives and paralytics. Therefore interpretation of the neurologic examination and prognostication in patients undergoing hypothermia or rewarming is complex and challenging. Generally speaking and without the use of hypothermia, the absence of brainstem reflexes implies that the cortex is severely affected as the brainstem neurons are more resistant to hypoxia-ischemia than cortical neurons. Absence of pupillary reflexes at 72 hours predicts poor outcome with high specificity; however, the opposite—reflexive pupils—predicts good outcome in about only 21% of cases. Studies performed after the introduction of hypothermia delineate predictive findings for absent papillary responses but indicate that the corneal reflex seems to be more vulnerable to prolonged sedative and hypothermic effects.[127–130] With respect to motor responses, studies performed before hypothermia identify a high predictive value for poor outcome for the absence of motor responses at 72 hours, a clinical finding that outperformed even SSEP prediction.[131] On the contrary, recent studies suggest that the lack of motor responses does not invariably predict poor outcome in patients treated with hypothermia (i.e., positive predictive values of 92% and negative predictive values of 85%) and exceptions have been reported.[127,129,130,132]

EEG is used in post–cardiac arrest patients not only to determine outcome but also to differentiate myoclonus from shivering and detect seizures. Generalized EEG suppression, burst suppression with or without epileptiform activity, and a flat background with intermittent generalized periodic complexes are indicators of poorer prognosis. The opposite is true for finding reactivity and variability of the EEG pattern in both patients treated with or without cooling. Larger prospective studies are currently lacking; however, some recent reports identify some hypothermia-treated patients with postanoxic status epilepticus who can achieve good outcome,[133] especially when the status evolves from a continuous EEG pattern and not from burst suppression.[134] As seizures and status epilepticus are seen in up to 65% of patients with less severe cortical damage, continuous EEG is indicated to guide management and prognostication in many postarrest patients.

Another frequently seen pattern after cardiac arrest is myoclonic status epilepticus. These are generalized, multifocal, repetitive muscle jerks involving some or all parts of the body. They are seen within 24 hours after arrest and EEG often shows burst suppression or bursts of generalized spikes. Whether myoclonic discharges actually represent seizures remains controversial and as patients may have severe cortical damage and clinical myoclonic at the same time, it is postulated that myoclonus status epilepticus is subcortical in origin.[133] In contrast, postanoxic status epilepticus is cortical in origin (but some overlap to myoclonic status may exist), whereas the posthypoxic myoclonus (Lance-Adams syndrome) is generally seen after primary respiratory failure. It is triggered by startle, often subsides over time, and the patient may be aware and distressed by it. Myoclonic status epilepticus has been associated with poor prognosis and remains poor even in the setting of hypothermia.[127,130,133]

According to current practice parameter from 2006, the absence of the N20 (primary cortical somatosensory) wave on SSEPs in the first 3 days after cardiac arrest identifies a high likelihood for poor outcome. In contrast, only about 41% of patients with a present N20 wave will recover. Prognosticating based on SSEP findings in patients treated with hypothermia has only been reported in a few smaller studies with uncertain overall results[135,136]; however, SSEP likely remains useful as evoked potentials are relatively resistant to metabolic and temperature derangements. Also, neuron-specific enolase (NSE) is a frequently administered and validated biochemical marker used for prognostication. Levels above 33 μg/L at 72 hours or earlier were found to have a zero false predictive rate in patients not treated with hypothermia. However, hypothermia decreases NSE levels. Some recent studies have shown that a similar cutoff also holds true for the populations of hypothermia-treated patients,[137–140] whereas other authors found unacceptable false-positive rates for the cutoff value 33 μg/L.[141,142]

Certain MRI findings such as severe cortical abnormalities on diffusion-weighted imaging have been shown to correlate to poor outcome, but imaging studies often report on smaller patient numbers and are performed unblended, thereby reducing their value for prediction.[143] Some recent studies identify that most patients who regained consciousness had normal cortical structures, some of them having involvement of the deep gray nuclei.[144,145] Further prospective studies are needed; however, clinicians should be cognizant of the following points to maximize the benefits of neuroimaging for prognostication[146]:

1. Neuroimaging should not be used in isolation to determine prognosis.
2. It may be reasonable to repeat imaging if the initial imaging is not consistent with the patient's clinical status.
3. It is reasonable to procure a CT immediately after arrest to evaluate for possible intracerebral hemorrhage or if the cardiac cause is unclear. However, using CT for prognostication purposes may be misleading and premature.
4. The optimal timing for prognostication may be 2 to 3 weeks after arrest, especially in a cooled patient.
5. It is reasonable to obtain an MRI if CT results are unrevealing. The optimal timing to visualize ischemic changes may be 3 to 5 days after arrest, or longer if the patient undergoes targeted temperature management.
6. Neuroimaging does not exclude poor prognosis.

In the past, recommendations suggested that assessment of the postarrest patient treated with hypothermia take place 72 hours after arrest. However, it is now known that delayed awakening (up to 96 hours after arrest) may be associated with good neurologic outcome after TH in patients recovering from cardiac arrest.[147–150]

Still, examination should take place at least 12 hours after termination of all sedatives and later if concomitant renal and liver damage are confounding factors. Prognostic variables associated with but not invariably predictive of poor outcomes are as follows:

1. Absence of brainstem reflexes
2. Absence of motor responses or extensor posturing
3. EEG abnormalities, including generalized suppressions or periodic complexes on suppressed background, and burst-suppression pattern with generalized epileptiform activity
4. Myoclonic status epilepticus
5. MRI with widespread cortical injury on diffusion-weighted imaging or CT with loss of gray-white matter differentiation and sulcal effacement
6. High nonspecific enolase levels
7. Absence of N20 on SSEPs

Ethical Considerations

Advanced Care Planning Documentation

Patients with brain injuries severe enough to necessitate a stay in the neuroscience intensive care unit often lack the capacity to make treatment decisions for themselves. Advance care planning documentation based on previous conversations with other health care providers may exist. However, many times limitations and variability inherent in these advance care planning documents render them outdated. The only exception is physician orders for life-sustaining treatment (POLST), which provides legal protection to patients who explicitly expressed their wishes before hospitalization.

Surrogate Decision Makers

For patients with no living will who lack capacity, a surrogate decision maker is often appointed with the sole purpose of directing care in accordance with the patient's previously declared or presumed wishes. A surrogate designated by the patient has precedence over other potential decision makers and is delineated by an advanced directive, also known as health care proxy, health care agent, or durable power of attorney for health care. If there is not a readily obvious person to serve as surrogate, a court-appointed surrogate or a legal guardian may be necessary. Most states have an outlined hierarchy of those who may serve as a surrogate, with highest priority typically given to the spouse, followed by adult children or extended family members, although the order of surrogacy and the power granted to surrogates chosen by default vary from state to state.[151]

Prognostications

Decisions to withdraw care are profoundly influenced by physicians' prognosis of a patient's potentials for improvement of consciousness. Identifying medical futility in a patient with markedly impaired consciousness allows the surrogate and physician to withdraw life-supporting therapy. It is important for physicians to reiterate to the family that coma progression into vegetative state is not considered an improvement. Sleep-wake cycles, roving eye movements, startle, and other witnessed phenomena are merely reflexive and do not indicate consciousness or awareness. Greater prognostic uncertainties exist for patients in an MCS as they have consistent evidence of consciousness, awareness, and, in some, the ability to communicate.

Physicians have long considered the prediction of disease and injury outcome as one of their most important duties. But just as they rightfully regard prognostication as a professional responsibility, physicians should be aware of their limited ability to accurately predict the probability of recovery from impaired consciousness and of the limited persuasiveness of their prognostication on some patients and families. Furthermore, recovery is a dynamic and fluctuating process with individual differences. Therefore patient and family values are as important as physician prognostication in decision making.

Underrepresented Patients

Underrepresented patients lack the capacity to make medical decisions for themselves and have no legal or surrogate decision maker to do so. Current laws, institutional policies, and organizational recommendations regarding limitation or continuation of life-sustaining therapy vary among states and depend on the patient's background, if known. Regardless of the statutory requirements, in most cases there exists a presumption that physicians should pursue urgent or emergent life-sustaining treatment or life-saving interventions.[152] Institutional protocols on limitation of life-sustaining treatment typically entail constructing an overview of the patient's life, thus providing a framework to guide how the patient might weigh the various risks and benefits of treatment.

Physicians have fiduciary obligations toward the underrepresented that cannot be deferred to or discharged by third parties. However, physicians should also not act without input from third parties such as ethics committees.[153] It is crucial that all efforts are exhausted to track down individuals who may actually be reasonable surrogates and to ensure due diligence in learning about the patient as a person. Third-party involvement can help ensure that decision making is transparent and that appropriate efforts have been made to define the underrepresented patient's best interests, personal values, and preferences. Physicians should be the default decision makers regarding limitation or continuation of life-sustaining treatment, with organizations such as ethics committees playing an advisory role for the underrepresented.

Key Points

- Coma is a state of pathologic unresponsiveness from which the patient cannot be aroused. The eyes are closed, and only reflex responses or no responses at all can be elicited from the patient when applying vigorous stimulation.
- The cause of coma is diverse and follows neuronal injury, reversible or irreversible, to both cerebral hemispheres or to the reticular activating system in the diencephalon and brainstem.
- A supratentorial mass legion located within one hemisphere can induce a lateral herniation syndrome with lateral torsion of the midbrain plus uncal herniation. In contrast, a mass lesion located within the brain midline (i.e., acute hydrocephalus) primarily leads to downward herniation with rostrocaudal compression of the brainstem.
- An acute mass lesion below the tentorium (i.e., a cerebellar hemorrhage) compresses the brainstem early on, leading to cranial nerve deficits, obstructed CSF outflow resulting in hydrocephalus, and, if large enough, herniation of brain tissue upward through the tentorium and downward through the foramen magnum. On examination these patients may present with a complete lack of all cranial nerve and motor function, yet hemispheric function may be preserved.
- Initial attention must focus on the restoration of respiratory, hemodynamic, and metabolic homeostasis in parallel with a search to identify the cause and acuity of the coma state. Generally, a comatose patient's recovery depends on appropriate treatment of the underlying disorder but also very much on monitoring and stabilizing brain function (ICP, perfusion, and so on).
- Status epilepticus is characterized by either clinically detectable (convulsive) or EEG-identified (nonconvulsive) seizure activity. Both require immediate and aggressive treatment to avoid permanent brain damage.

- Alteration in cognitive function (especially attention and concentration deficit) is the earliest manifestation of metabolic encephalopathy. Some disease processes may provide specific diagnostic clues.
- The neurologic examination consists of an assessment of the level of arousal determined by eye opening, verbal responses, and reflex or purposeful movements in response to noxious stimulation of the face, arms, and legs. Neuro-ophthalmologic function is evaluated by spontaneous eye movements, pupillary size and response to light, oculocephalic responses (doll's eyes), and oculovestibular (ice water caloric) responses. Autonomic function is assessed by the respiratory pattern and observing the monitored vital sign changes before and during examination.

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Review Questions

1. A 72-year-old woman is brought to the emergency department (ED) by her daughter because of a change in mental status. The patient was noted to have acute onset of confusion, agitation, and gait disturbance. Her medical history includes hypertension, insomnia, and depression (since the death of her husband 3 months ago). The patient is taking hydrochlorothiazide, amitriptyline, and baby aspirin and has recently started to take fluoxetine. Her vital signs are as follows: temperature 100°F; pulse 120 beats/min; blood pressure (BP) 130/85 mm Hg; respirations 16 breaths/min. Physical examination is positive for confusion, ataxia, dilated pupils, dry mucous membranes, and tachycardia. Laboratory results are pending. Electrocardiogram (ECG) reveals tachycardia with QT-interval prolongation. Urine dipstick results are within normal limits. What is the *most* likely cause of acute mental status change?

a. Salicylate overdose
b. Tricyclic antidepressant (TCA) toxicity
c. Sepsis from urinary tract infection (UTI)
d. Acute intoxication with ethanol

Answer: b. Fluoxetine inhibits cytochrome 2D6, which will cause an increase in the levels of TCAs. The signs and symptoms of TCA overdose include anticholinergic effects, agitation, restlessness, ataxia, tachycardia, prolonged QT interval, hyperthermia, and convulsions. Sepsis from UTI is possible but unlikely with a urine dipstick result within normal limits. An acute cerebellar stroke or acute ethanol intoxication would explain some but not all of the clinical findings.

2. You are consulted to see a 36-year-old patient in the ED with history of epilepsy. She has been stuporous for more than 6 hours and has a right hemiparesis, including the face, arm, and leg. The computed tomography (CT) scan of the brain is normal. The paramedics have already administered glucose, thiamine, and naloxone without any improvement. Which one of the following agents would be contraindicated in this case?

a. Lorazepam
b. Phosphenytoin
c. Flumazenil
d. Valproic acid

Answer: c. A patient with history of epilepsy, focal motor signs, normal CT scan, and stuporous state in the ED is in nonconclusive status epilepticus (NCSE) until proved otherwise. Although stroke is a possibility, a normal CT scan in a patient with focal neurologic signs should exclude intracranial hemorrhage or cerebral infarction. All antiepileptics mentioned could be used in sequential order with the aim to stop NCSE. Flumazenil, on the other hand, a gamma-aminobutyric acid (GABA) receptor antagonist, would be contraindicated in this case, as it would aggravate ongoing ictal activity.

3. A 45-year-old man is brought to the ED after a motor vehicle collision in which he suffered a closed head injury. His initial Glasgow Coma Scale (GCS) score was 6. He was intubated and admitted to the intensive care unit (ICU). Eight hours later the patient remains comatose. Which of the following is considered a reliable predictor of poor outcome at 6 months?

a. Number and location of skull fractures
b. Initially increased intracranial pressure (ICP) requiring a ventriculostomy to normalize ICP
c. Initial poor prognostic electroencephalogram (EEG) pattern with normal somatosensory evoked potential (SEP)
d. Absence of pupil reaction and eye movements at 24 hours

Answer: d. The most reliable predictors of outcome at 6 months after head injury include age, GCS score, pupil reaction, motor response at 1 week, and uncontrolled increased ICP. Lack of pupil reaction at 24 hours predicts death or vegetative state in 90% of patients. The mechanism of head injury, presence or absence of skull fractures, and the extent of other extracranial injuries have little impact on outcome. Initial poor-prognosis EEG findings with normal SEPs still allow the chance of neurologic recovery and the patient should be aggressively supported. When compared the using initial degree of neurologic deficit, patients with traumatic causes for coma have more complete recoveries than do patients with medical coma. Although uncontrolled increased ICP is a reliable indicator of poor neurologic outcome, an initially increased ICP (promptly controlled with a ventriculostomy procedure) is not.

4. A 58-year-old woman is admitted for altered mental status. On examination her GCS score is 8, she has a dense flaccid left hemiparesis, and her eyes show a conjugated gaze deviated to the right with right blown pupil 6-mm fixed and nonreactive. What pathophysiologic mechanism is most likely associated with this clinical picture?

a. Subfalcine herniation left to right
b. Right downward transtentorial herniation
c. Intraventricular hemorrhage with hydrocephalus
d. Unruptured right posterior communicating artery aneurysm

Answer: b. This patient is eliciting classic signs of a massive right cerebral infarct with cerebral edema and downward transtentorial herniation. The comatose state is explained by the stretching of the reticular activating system caused by a right-to-left shift of midline structures (diencephalon). The left hemiparesis is explained by corticospinal tract dysfunction or injury, and the gaze deviation is explained by unopposed activation of the left frontal eye fields displacing the eyes to the right (patient looks to the lesion). The right pupil is dilated because of cranial nerve III stretching and subsequent palsy. The intraventricular hemorrhage alone with hydrocephalus would not explain the focal findings seen in this case. Similarly, an unruptured posterior communicating aneurysm will manifest only with cranial nerve III palsy or injury but not with mental status changes, forced gaze deviation, or hemiparesis. This would be, however, a medical emergency demanding further workup such as CT angiography or magnetic resonance angiography and aneurysm repair.

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Neurologic Criteria for Death in Adults

FRED RINCON

CHAPTER OUTLINE

Historical Perspective and Definitions

Determination of Brain Death
- Clinical Evaluation of Coma and Prerequisites
- Absence of Brainstem Reflexes
- Apnea
- Pitfalls and Mimics

Confirmatory Testing
- Origins of Confirmatory Testing in Brain Death
- Accuracy of Confirmatory Tests
- Recommendations for Confirmatory Testing

Special Circumstances
- Determination of Brain Death After Cardiac Arrest in the Era of Therapeutic Hypothermia
- Extracorporeal Membrane Oxygenation

Conclusions

The clinical examination in brain death is the most unequivocal in neurology. Most of the time, establishing the diagnosis of brain death on clinical grounds is not a difficult task, as long as providers follow established protocols and guidelines for the interpretation of findings during clinical examination.[1,2] However, there may be confusion based on the variability of the interpretation of current guidelines,[3–5] hurdles to clinical examination in specific patient populations such as trauma victims, laws from specific jurisdictions, and the changing face of outcomes after severe brain injury in an era of advancements in critical care and resuscitative medicine. In this chapter we review current procedures and recommendations for the evaluation of comatose patients presumed to be brain dead, the concept of brain death substantiated by anatomic and physiologic bases, important concepts for the determination of brain death in the setting of novel interventions such as hypothermia and extracorporeal circulation, and how to avoid pitfalls during the evaluation of patients presumed to be brain dead.

Historical Perspective and Definitions

The concept of brain death is modern to medicine, but the definition of death has historically been associated with physiologic cessation of cardiopulmonary function. With advancements in mechanical ventilation, life support, and resuscitation medicine, a new state in which a patient's cardiopulmonary functions could be sustained in the absence of neurologic function emerged. In 1959, Mollaret and Goulon described 23 patients with irreversible coma, whose clinical syndrome was characterized by the absence of brainstem function, spontaneous respiratory function, and cardiovascular collapse that ensued without the use of vasopressors, in what became the birth of the concept of brain death.[6] In 1963, Harvard neurologists proposed that a patient be certified as dead in the setting of coma, absence of brainstem reflexes, apnea for 30 minutes, and an isoelectric electroencephalogram (EEG) tracing in all leads for more than 30 minutes,[7] despite the presence of cardiac function. The first guideline (the Harvard criteria) for deciding brain death was established in 1968.[8] This concept has been accepted worldwide, although its fundamental meaning is not exactly globally uniform yet. Some countries, such as the United States, accept the concept of brain death as "whole brain death," which is defined as irreversible loss of all cortical and brainstem function. The Medical Royal Colleges of the United Kingdom established the definition of brain death on a "lower brain" concept of brainstem death.[9] In the opinion of the Royal Medical College, permanent unconsciousness secondary to neuronal death of brainstem structures such as the reticular-activating system (RAS) is irreversible.[9]

In 1981, a Presidential Commission in the United States was formed to address the issue of death by neurologic criteria.[10] The President's Commission established the foundations of the criteria currently used in the United States for the diagnosis of brain death: the cause of brain death should be known and irreversible and no improvement in neurologic condition should occur during a period of observation; the period of observation was left at the discretion of the physician, but periods of 6 to 12 hours were recommended depending on the availability of confirmatory testing such as EEG or cerebral perfusion scans.[10] Although the President's Commission suggested periods of observation of 24 hours for cases of ischemia-anoxia,[10] more recent clinical experience in the era of therapeutic hypothermia and published guidelines suggest a period of observation of up to 72 hours in patients with hypoxic-ischemic coma.[11] The President's Commission guidelines for the determination of brain death culminated in a proposal for a legal definition that led to the Uniform Determination of Death Act (UDDA) in 1981. Under the law, the determination of death must be made with accepted medical standards and can be established only if an individual "has sustained either: 1) irreversible cessation of circulatory and respiratory functions, or 2) irreversible cessation of all functions of the entire brain, including the brain stem." The UDDA establishes the legal definition of death on the basis of neurologic criteria but does not provide guidelines or recommendations regarding how to arrive to such conclusion. To this end, the medical community is free to formulate acceptable parameters or guidelines

on the basis of clinical examination, and availability of diagnostic tests and biomarkers.

In 1995, the American Academy of Neurology (AAN) published the practice parameter to delineate the medical standards for the determination of brain death.[1] The guideline emphasized the three clinical findings necessary to confirm irreversible cessation of all brain functions, including the brainstem: (1) known cause and presence of coma, (2) absence of brainstem reflexes, and (3) apnea.[1] Despite this publication, there is considerable practice variation in the adherence to the AAN guidelines for the determination of brain death, particularly in areas related to definitions of acceptable core temperature, number of required examinations, ancillary testing to be used, and deficiencies in documentation.[3,5] In response to this phenomenon, the AAN published an evidence-based update of the 1995 Practice Parameter[2] to answer the main questions related to practice variability in the determination of brain death.[3,12]

Recovery of neurologic function has not been reported since the clinical diagnosis of brain death was established with the criteria set forth by the 1995 AAN guideline. This guideline and the further revision highlight the prerequisites for brain death determination to avoid potential misdiagnosis and pitfalls.[2]

The brain death concept is universally accepted worldwide and there are no concerns about the validity within physicians. However, diagnostic brain death criteria vary throughout the world. In Europe, for example, there is considerable variation in the use of ancillary testing such as EEG or cerebral blood flow studies. Most countries of the European Union do not require ancillary testing in support of brain death diagnosis.[13] In other countries, different practices reflect the interest of local committees and groups of experts to introduce safeguards. Major differences in these countries are related to the time of observation, the need for apnea and ancillary testing, and the number of health care providers authorized to diagnose brain death.[14]

In the United States, most state laws have adopted the UDDA, and some have added their own amendments. All states and the District of Columbia have statutes for determining brain death based on the UDDA, but certain statutes differ in minor points such as the requirement that determination of brain death should be done by two different physicians, the use of confirmatory testing, and the notification of next of kin before the declaration of brain death. To this end, it is important for the practitioner to understand local hospital policies for the declaration of brain death that should abide by the laws of their respective jurisdictions.

Determination of Brain Death

The most common causes of brain death in the adult population are traumatic brain injury, aneurysmal subarachnoid hemorrhage, hypoxic-ischemic injury, and fulminant hepatic failure.[15] It is estimated that the diagnosis of brain death is made at least 25 to 30 times a year in large referral centers, but this number may be lower in nonacademic centers.[15] The determination of brain death is based on the UDDA and supported by the AAN Practice Parameter.[1,2] The diagnosis is based on the establishment of three main criteria: (1) known cause and presence of coma, (2) absence of brainstem reflexes, and (3) apnea. Therefore the clinical diagnosis, when considering accepted guidelines, is the most unequivocal in neurology.

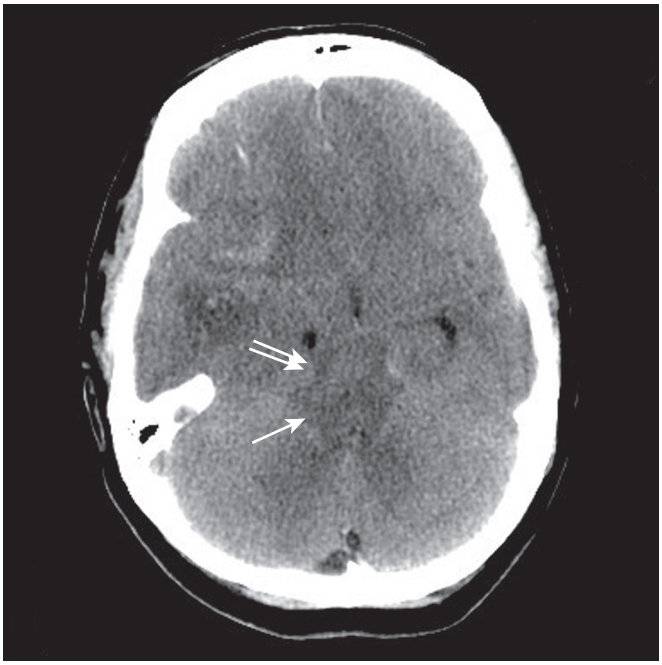
In general, most jurisdictions require that the determination of brain death be made by a licensed physician, which in most of the cases should be an attending physician who has experience in the assessment of comatose patients and the legal requirements applicable to the jurisdiction of practice. Some centers require the testing to be performed by two different physicians, and some centers require one of these physicians to be a neurologist, neurosurgeon, or critical care specialist. In the United States, 42% of top neuroscience centers required the brain death examination to be documented by a neurologist or neurosurgeon, and only 35% required that an attending neurologist or neurosurgeon be involved; of the 42% of centers, residents could document the examination in up to 65% of the centers.[3] In those circumstances in which the patient is a potential organ donor, the clinical team may not be directly involved with the discussions of organ procurement, as a conflict of interest may be apparent.

To provide standardization in the process of diagnosing brain death, the Neurocritical Care Society in the United States has developed a toolkit to educate anyone who may be involved in the determination of brain death. The toolkit includes access to multiple instructional videos, webinars and web-based courses, and sample brain death policy and checklists (https://www.pathlms.com/ncs-ondemand/courses/1223).

Clinical Evaluation of Coma and Prerequisites

Practitioners should first determine the cause of coma by history, physical examination, neuroimaging, and laboratory testing. Exclusion of central nervous system depressants should be attempted by careful history taking, drug screen testing, and calculation of drug clearance using the rule of five times the drug's half-life (assuming a normal hepatic and renal function) or drug plasma levels below therapeutic ranges.[2] In the setting of abnormal hepatic or renal function, or after use of therapeutic hypothermia, caution should be taken before entertaining the diagnosis of brain death based on changes in drug metabolism inherent to these clinical settings to avoid catastrophic and embarrassing misdiagnoses.[16] In these circumstances, more than recommended times for observation are suggested or the use of confirmatory testing may be sought. The legal limit for ethanol is a blood alcohol content of 0.08%, which is a practical threshold below which an examination to determine brain death could reasonably proceed.[2] In patients exposed to pentobarbital for the management of intracranial hypertension, an accepted level in which a clinical examination can proceed without chance of confounding is 10 μg/mL.[2] There should be no temporal administration of neuromuscular blockers, and this can be assessed definitely by the presence of train-of-four twitches with maximal ulnar stimulation. Acid-base status and electrolyte levels must not be severely deviated from the norm, but the presence of signs and symptoms of *diabetes insipidus* does not preclude the diagnosis of brain death; however, treatment with fluids and vasopressors such as vasopressin will target both sodium and blood pressure requirements to allow for adequate neurologic assessment. With more cardiac arrest survivors being exposed to therapeutic hypothermia, practitioners should now achieve a normal core temperature, defined as near-normal temperature or core temperature higher than 36°C, before attempting to determine brain death. Patients should have normal blood pressure, defined as systolic blood pressure equal to or higher than 100 mm Hg, as the neurologic examination is usually reliable at this level of blood pressure.

A temporal cause of severe brain injury must be established. Irreversibility from neurologic injury is recognized by the extent of the injury, the devastation in neurologic findings, and the lack of improvement. Neuroimaging is useful in establishing an acute neurologic catastrophe that is compatible with the clinical diagnosis.



• **Fig. 59.1** Computed tomography scan of a young patient with traumatic brain injury showing right frontal contusion, mild subarachnoid hemorrhage, and severe cerebral edema. The patient had a bilateral transtentorial uncal herniation (*double arrow*, for right-sided uncus); note that the horn of the right lateral ventricle has been pushed toward the midline. The perimesencephalic cisterns are effaced *(single arrow)*. There is slight hypodensity in the midbrain suggesting edema or ischemia.

In most cases, a computed tomography (CT) scan reveals specific findings such as diffuse cerebral edema, mass lesions with severe shift of midline structures, and herniation (Fig. 59.1; also see Fig. 59.4).

Coma is established by the lack of all evidence of responsiveness. That is, eye opening or eye movement to noxious stimuli must be absent. The motor responses to noxious stimuli should not be flexor or extensor but spinally mediated. The clinical differentiation of motor responses may require experience and specific training in neurology or neurosurgery. When flexor posturing of the upper extremities and extension of the lower extremities (decorticate) or extensor posturing of both the upper and lower extremities (decerebrate) are observed, the diagnosis of brain death cannot be entertained and an additional period of observation is recommended. (For an interactive brain death assessment, visit Brain Death Examination at https://www.pathlms.com/ncs-ondemand/courses/1223/video_presentations/11133 or Brain Death Testing Demo at https://www.youtube.com/watch?v=OEuP2C5UEp8.)

The basis of these responses is related to the patency of the rubrospinal and vestibulospinal tracts and lower segments of the medulla that connect with the spinal cord.[17] Brain dead patients typically exhibit spinal cord–mediated motor responses characterized by "en bloc" flexor responses of the lower extremities with flexion of the hip, flexion of the knee, and dorsiflexion of the ankle and toes (the so-called triple flexion response or Babinski en bloc spinal cord sign). More complex movements that have been referred to as brain death–associated reflexes (Lazarus sign, spinal man, spinal reflexes, or spinal automatisms) have been described in patients who otherwise meet all other brain death criteria.[18] The key point to differentiate spinal versus centrally mediated responses is to determine if the responses are also elicited from stimulation above the foramen magnum. This is easily achieved by introducing noxious stimulation through pathways mediated by cranial nerves. When in doubt, the neurologic examination of a comatose patient becomes equivocal, and in these circumstances, additional observation or a confirmatory test may be warranted.

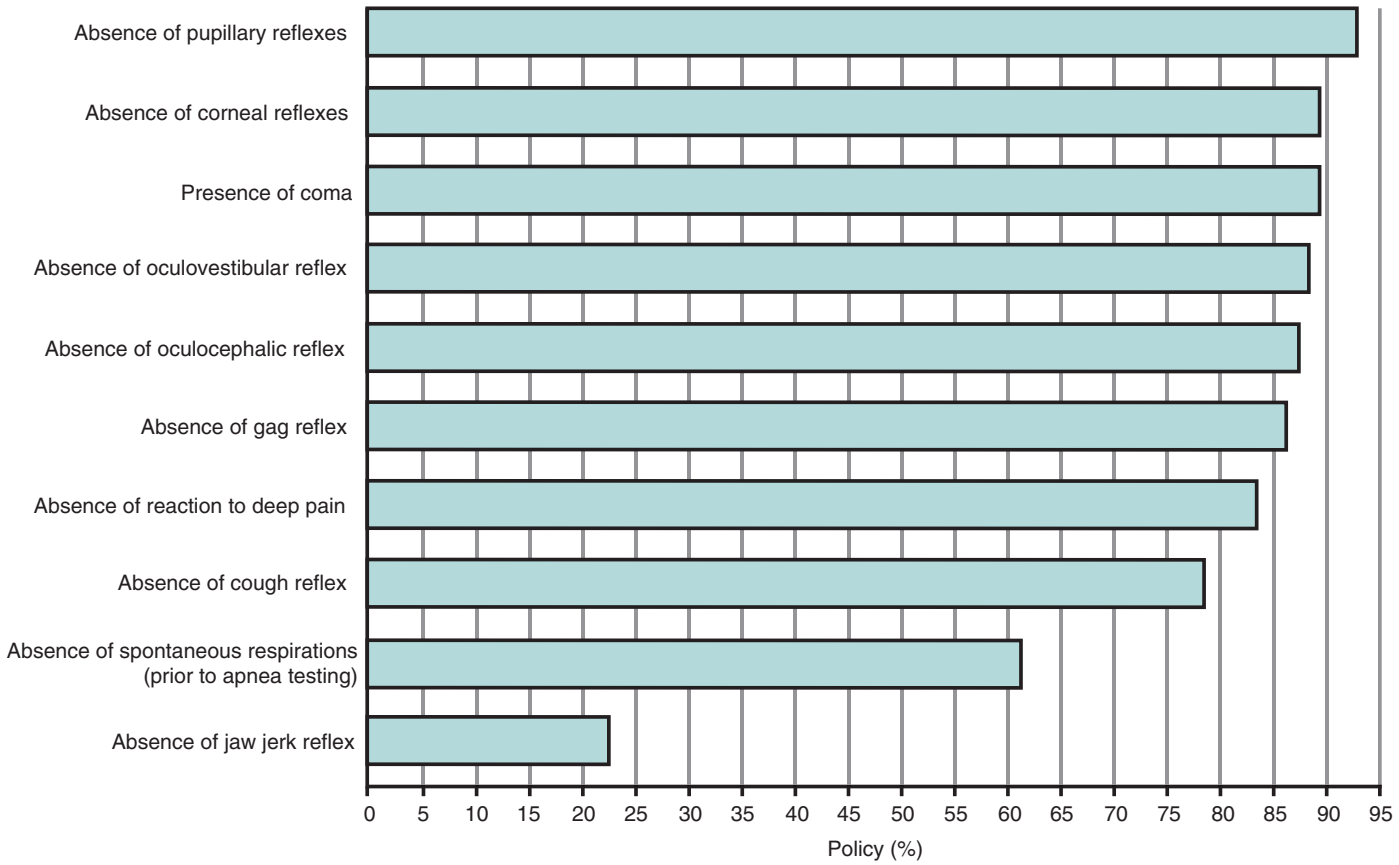
Absence of Brainstem Reflexes

All segments of the brainstem should be tested in the clinical examination. The highest segments are examined by documentation of the pupillary response to bright light in both eyes (cranial nerves II and III). The usual presentation is dilated fixed pupils, which may be asymmetrical. Constricted pupils may mean drug intoxication or lesions at the level of the pons causing de-efferentation from sympathetic fibers and unopposed activation of parasympathetic centers located in the rostral area of the midbrain (Edinger-Westphal nucleus). Absence of ocular movements using oculocephalic and oculovestibular reflex testing can be achieved after ensuring integrity of the cervical spine (cranial nerves III, IV, VI, and VIII [vestibular part]). The oculocephalic reflex is tested by briskly rotating the head side to side and vertically. Vertical oculocephalic movements are important for the determination of brain death as injuries in the lateral portions of the pons may manifest with bilateral palsies of horizontal eye movements but would spare the vertical eye movements. The oculovestibular or cold-caloric reflex is tested by irrigating each ear with 50 mL of iced water and observing the response for up to 1 minute. The absence of corneal reflexes (cranial nerves VII, V, and others) is demonstrated by touching the cornea with a cotton swab or gauze. Painful noxious stimulation in the cranium, trunk, or limbs should not produce any facial movement or grimacing (cranial nerve VII). Absence of pharyngeal (cranial nerve IX) or gag reflex (cranial nerve IX) is demonstrated by stimulating the back of the mouth or oropharynx with a suction device or tongue blade. The tracheal reflex (cranial nerve X) is tested by examining the cough response to tracheal stimulation provided by suctioning. Additional cranial nerve reflexes such as the "jaw jerk" (cranial nerve V) may be assessed for completeness and to follow established guidelines.[1] Any unanticipated movement of any segment of the face, trunk, or limbs during brainstem examination implies intact brainstem efferent connections and precludes the diagnosis of brain death. In trauma victims with facial trauma in whom adequate examination of brainstem patency cannot be substantiated, the use of confirmatory testing may be warranted.

Deviations from accepted guidelines during clinical examination of comatose patients presumed to be brain dead may be associated with false-positive results, so a thorough examination of all segments of the brainstem is required. Areas of particular deviation from the AAN Practice Parameter for the determination of brain death include failure of testing for pain above the foramen magnum, the oculocephalic reflex, the jaw-jerk reflex, and establishing the absence of spontaneous respirations[3] (Fig. 59.2).

Apnea

Complete absence of breathing drive must exist to confirm the diagnosis of brain death. The absence of respiratory drive is tested with a carbon dioxide (CO_2) challenge, which requires all of the following: (1) normotension, (2) normothermia, (3) euvolemia, (4) eucapnia (partial pressure of carbon dioxide in arterial blood [$PaCO_2$] 35–45 mm Hg), (5) absence of hypoxia, and (6) no prior evidence of CO_2 retention (chronic obstructive pulmonary disease,



• **Fig. 59.2** Variability during clinical examination of brain dead patients in top neuroscience centers of the United States. Poor compliance occurred mainly during testing of pain above the foramen magnum and the jaw jerk, as well as documenting absence of spontaneous respirations in brain death examination. *OCR,* Oculocephalic reflex; *OVR,* oculovestibular reflex. (From Greer DM, Wang HH, Robinson JD, et al. Variability of brain death policies in the United States. *JAMA Neurol.* 2016;73:213–218.)

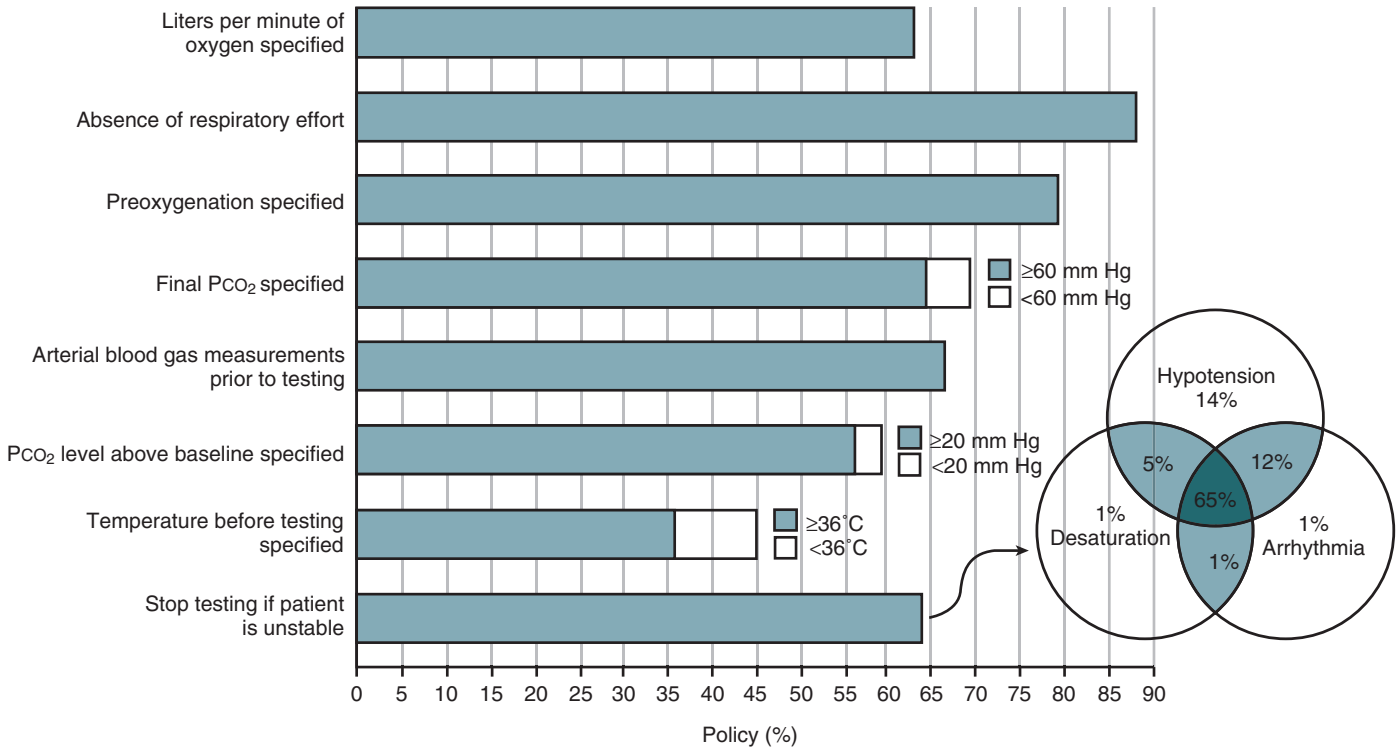
severe obesity, or sleep apnea syndrome).[2] The test is started by preoxygenating the patient with a fraction of inspired oxygen (FIO_2) of 1.0 for 10 minutes to achieve an alveolar oxygen partial pressure (PaO_2) of more than 200 mm Hg using a respiratory rate of 10 per minute to achieve eucapnia. If the patient remains hemodynamically stable and with oxygen saturation more than 95%, the patient is disconnected from the ventilator and oxygenation is preserved by placing a catheter through the endotracheal tube and close to the level of the carina delivering O_2 at 1.0 FIO_2 with a flow of 6 L/min. During the following 8 to 10 minutes, the practitioner should look carefully for respiratory movements (abdominal or chest excursions and may include a brief gasp).[2] The test should be aborted if oxygen saturation drifts lower than 85% for more than 30 seconds. If this is the case, the test can be repeated later using a T-piece, continuous positive airway pressure with 10 cm H_2O, and O_2 with 1.0 FIO_2 with a flow of 12 L/min.[2,19] The test result is considered positive if respiratory movements are absent and the $PaCO_2$ is higher than 60 mm Hg or 20 mm Hg change from baseline supporting the diagnosis of brain death.[2] (See Apnea Testing in Brain Death at https://www.pathlms.com/ncs-ondemand/courses/1223/video_presentations/11134.)

Although the apnea test is not a new procedure, it still lacks consensus standardization regarding the actual test, consent processes, monitored parameters, and evidence-based safety measures that may be used to prevent complications. Practitioners should keep in mind that the apnea test is not without complications. Potential complications during apnea test include hemodynamic decompensation, hypoxia and hypercarbia, and tension pneumothorax.[20]

Pitfalls and Mimics

In clinical practice, certain circumstances can mimic brain injury; these include high cervical spinal cord injury, fulminant acute inflammatory demyelinating neuropathy, organophosphate intoxication, baclofen intoxication, lidocaine toxicity, and delayed muscular blocker clearance (i.e., vecuronium). Pitfalls in the diagnosis of brain death may be related to circumstances involving interference with the appropriate clinical diagnosis of brain death such as patients with (1) facial trauma (inability to appropriately examine cranial nerve responses or to elicit sensory/motor responses from stimulation above the level of the foramen magnum), (2) preexisting pupillary abnormalities, (3) toxic levels of anesthetics, sedatives, tricyclic antidepressants, anticholinergics, antiepileptics, or neuromuscular blocking agents, and (4) severe chronic respiratory acidosis (chronic obstructive pulmonary disease, severe obesity, or sleep apnea syndrome). In these circumstances, a confirmatory test may be warranted.

There is still significant variability in brain death policy application the United States, particularly in definition of appropriate targets for temperature, blood pressure, and $PACO_2$ level at the time of the assessment (Fig. 59.3). This variability highlights the



• **Fig. 59.3** Variability of prerequisites for apnea test procedure for the determination of brain death in the United States. Poor compliance occurred mainly in goal core temperature and baseline and goal end partial pressure of carbon dioxide ($Paco_2$). (From Greer DM, Wang HH, Robinson JD, et al. Variability of brain death policies in the United States. *JAMA Neurol.* 2016;73:213–218.)

need to further standardize the brain death assessment as one of most crucial bedside clinical assessments in critical care.

Confirmatory Testing

The role of confirmatory testing in brain death differs among jurisdictions.[14] In the United States and the United Kingdom, they are discretionary.[1,2,21] According to the AAN guidelines, confirmatory tests are required only when specific components of the clinical examination cannot be reliably assessed.[1,2] In some European countries such as Italy, France, and the Netherlands, among others, these tests are mandatory[14,20]; however, there is still significant variability in the approach to determining brain death in the world.[14]

A specialist in the neurosciences and any other skilled physician should be able to determine brain death using clinical criteria alone, so the main purpose of confirmatory testing besides being a diagnostic safeguard is to support the diagnosis of brain death in the setting of failure to complete a thorough neurologic examination or an apnea test. The important point about confirmatory testing is that these tests should never replace the clinical examination and should never be ordered before attempts to complete a thorough neurologic examination.[22]

Origins of Confirmatory Testing in Brain Death

In the earlier years of refining the clinical picture of brain death, there was a desire to demonstrate absence of brain function with information different from clinical data. In the 1950s Michel Jouvet[23] in France and Charles Miller Fisher[24] in the United States began to use electrocerebral science to study a group of patients who would have poor neurologic outcomes. Although these studies provided the basis for defining brain death by the Ad Hoc Committee of the Harvard Medical School[8] a year later, Beecher, who served as the chairman of the committee, mentioned in an editorial that EEG was "not essential to a diagnosis of reversible coma, but provides valuable supporting data,"[25] and this statement was later endorsed by the American Neurological Association.[26] Additional confirmatory tests, which can be divided into those that test for electrical function and those that test for blood flow, have been introduced and are aimed at confirming cerebral death (Table 59.1). Electrophysiologic tests include EEG, brainstem auditory evoked potentials, and somatosensory evoked potentials (SSEPs); blood flow tests include four-vessel cerebral angiography, transcranial Doppler, CT angiogram, magnetic resonance angiogram, and nuclear brain scan (Fig. 59.4). SSEPs and brainstem auditory evoked potentials are currently not recommended to be used in aiding or confirming the diagnosis of brain death.[1,2] More recent ancillary tests used for the determination of brain death include the bispectral index scale monitor[27] (BIS, mathematical algorithm of EEG), jugular bulb venous oxygen saturation ($Sjvo_2$),[28] and brain tissue oxygenation ($Pbto_2$)[29] but are not yet standardized in aiding in the diagnosis of brain death.

Accuracy of Confirmatory Tests

Practitioners must be careful at the time of interpreting the results of confirmatory tests and be knowledgeable of the technology being used, as there are disparities in the accuracy of confirmatory tests that could lead to potential pitfalls in the determination of

TABLE 59.1 Historical Time Frame for Confirmatory Tests Used in Determination of Brain Death

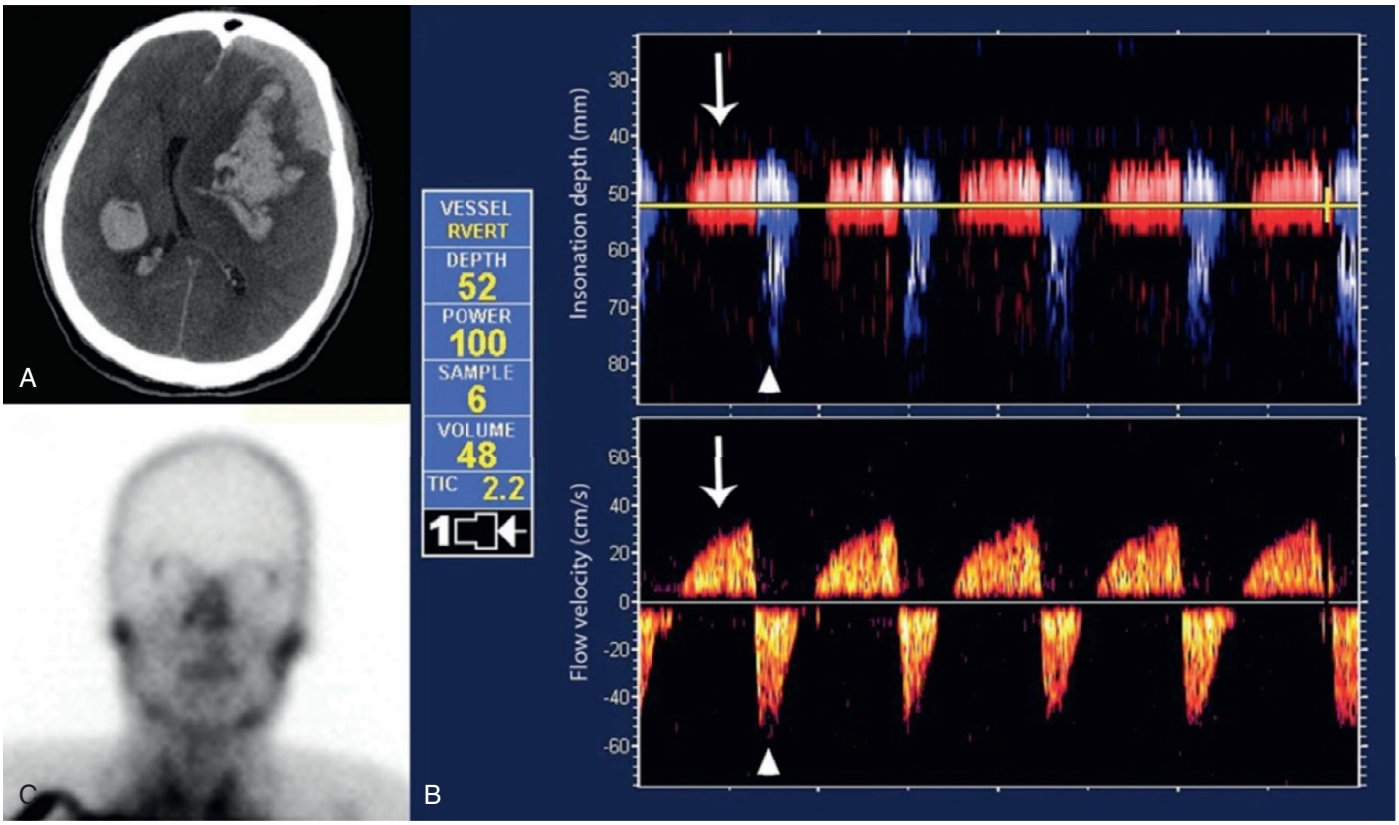
Year	Reported Study[a]	Test
1959	Löfstedt and von Reis[44]	Cerebral angiogram
1959	Fischgold and Mathis[45]	EEG
1969	Goodman et al.[46]	Nuclear brain scan
1974	Yoneda et al.[47]	TCD
1976	Starr[48]	BAEP
1978	Rappaport et al.[50]	CT angiogram
1978	Rangel[51]	CT angiogram
1981	Goldie et al.[49]	SSEP
1992	Jones and Barnes[52]	MRI

[a]Studies cited in complete list of references for this chapter provided online.
BAEP, Brainstem auditory evoked potential; *CT,* computed tomography; *EEG,* electroencephalography; *MRI,* magnetic resonance imaging; *SSEP,* somatosensory evoked potential; *TCD,* transcranial Doppler.
Adapted from Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology.* 2010;75:77–83.

brain death (Box 59.1). Based on the absence of gold standards from a physiologic and pathologic perspective,[30] the results of confirmatory testing may confound the practitioner in two ways: tests results can be labeled as false positives or false negatives when they are compared against each other. False-positive results occur when the test suggests brain death and the patient does not meet clinical criteria. False-negative results are more common (Table 59.2); they occur when the patient is clinically brain dead but the test shows otherwise,[22] which may be more common with EEG.[31]

Recommendations for Confirmatory Testing

Current evidence-based guidelines from the AAN recommend the use of only one confirmatory test for the determination of brain death in those cases in which an additional period of observation, an apnea test, or clinical examination is not feasible to fully establish the clinical criteria of brain death.[2] In a large study of brain death determination at the Mayo Clinic, the apnea test was aborted in 3% of patients and in 7% of patients the apnea test was not performed as it was not deemed to be safe, a situation that occurred more frequently in patients with polytrauma or with chest trauma.[32] In practice, practitioners should anticipate that 1 in 10 patients with devastating neurologic injury will be unable to have an apnea test, and declaration of brain death may not be possible on clinical grounds. Families should be informed about the unlikely event of meaningful recovery and in these circumstances, if the patient is a candidate for organ donation, donation after circulatory



• **Fig. 59.4** Transcranial Doppler (TCD) in brain death: TCD and single-photon emission computed tomography (CT) findings. A, Noncontrast head CT. B, Multidepth TCD power-motion mode *(upper panel)* and single-depth spectral analysis *(lower panel)* show reverberating flow in the right vertebral artery characterized by brief forward flow. C, Brain scintigraphy reveals absent intracranial flow. (From Eder KE, Haussen DC, Searls DE, et al. Reverberating TCD flow pattern in brain death. *Neurology.* 2012;79:e79.)

determination of death may be considered; most hospitals have protocols for donation under donation after circulatory determination of death,[22] and this approach could potentially increase the supply of deceased donor organs.[33]

Special Circumstances

Determination of Brain Death After Cardiac Arrest in the Era of Therapeutic Hypothermia

About 450,000 Americans have cardiac arrest annually.[34] The face of prognostication after cardiac arrest has changed in recent years based on clinical trials suggesting a robust effect of therapeutic hypothermia on clinical outcomes.[35] In 2006, the AAN published an algorithm to facilitate prognostic determination in patients who are resuscitated within 24 hours after cardiac arrest.[11] The AAN algorithm requires modification as more information accrues on the effects of hypothermia and with validation of other tests for poor and favorable outcomes.[36] Several studies have challenged the validity of single-endpoint assessments proposed by the 2006 AAN guideline, and most experts suggest a "multimodal" prognostication algorithm that would include several variables including the physical examination.[37,38] In this model, the patient enters the evaluation after 72 hours of observation after cardiac arrest. At this stage, the presence of coma, absence of pupillary or corneal reflexes, and the absence of bilateral N20 responses on SSEP indicate high likelihood of poor outcome. If neither of these features is present, the provider should wait at least another 24 hours before a second reassessment. In this second stage, two or more of the following indicate high likelihood of poor prognosis: myoclonic status epilepticus on EEG for less than 48 hours, a high neuron-specific enolase level, an EEG with burst-suppression pattern and lack of reactivity, nonconvulsive status epilepticus on EEG, and/or diffuse anoxic injury either on brain CT scan or magnetic resonance imaging. If none of the above criteria are met, then consider further time for observation[37] (Fig. 59.5). A recent study showed that prognostication after cardiac arrest occurs on the basis of insufficient clinical data, which may lead to early withdrawals on the basis of self-fulfilling prophecies of doom.[39]

•BOX 59.1 Potential Pitfalls With Confirmatory Tests Used in Determination of Brain Death

Cerebral angiogram
- Image variability with injection of arch or selective arteries
- Image variability with injection and/or push technique
- No guideline for interpretation, operator-dependent

TCD
- Technically difficult and skill-dependent
- Normal findings in anoxic-ischemic injury

EEG
- Artifacts in intensive care settings
- Information from mostly cortex

SSEP
- Absent in comatose patients without brain death

CT angiogram
- Interpretation difficulties
- Retained blood flow reported in 205 cases
- Possibility to miss flow states because of rapid acquisition of images
- Delayed flow in low-flow states (e.g., shock, heart failure)

Nuclear brain scan
- Areas of perfusion in thalamus in patients with anoxic injury or skull defect

CT, *Computed tomography;* EEG, *electroencephalogram;* SSEP, *somatosensory evoked potential;* TCD, *transcranial Doppler.*
Adapted from Wijdicks EF. The case against confirmatory tests for determining brain death in adults. Neurology. *2010;75:77–83.*

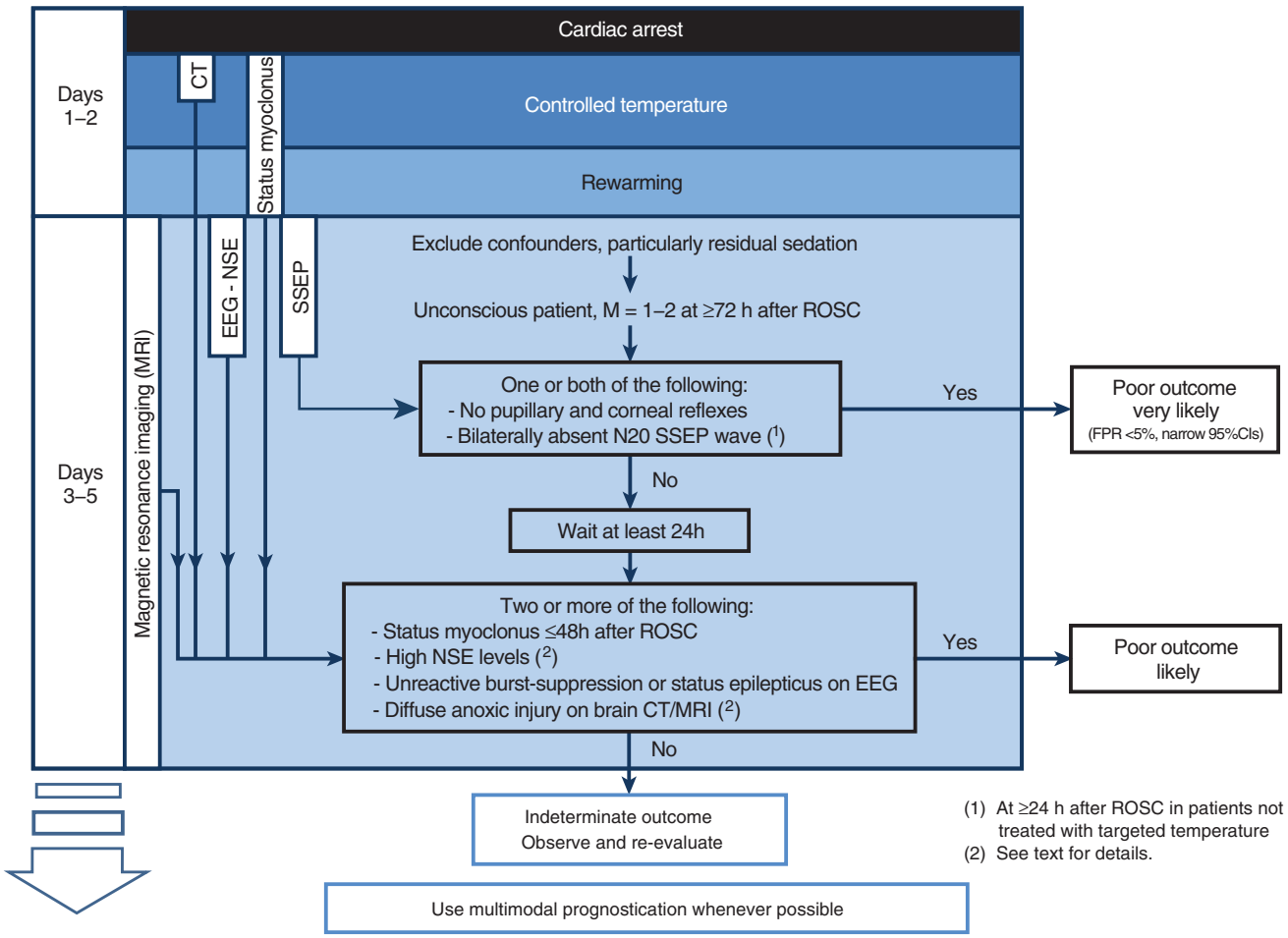
Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is increasingly used as a means of extracirculatory support to patients in severe, reversible cardiac or respiratory failure. Patients presumed to have brain death may have earlier withdrawal of ECMO support,[40] which would limit the possibility of organ donation in patients who would otherwise be declared brain dead. In these circumstances, confirmatory testing may be warranted. A protocol of apnea testing involving the addition of CO_2 to the oxygenator to a target of 60 mm Hg or more than 20 mm Hg from the baseline normal

TABLE 59.2 False-Negative Rates With Confirmatory Tests Used in Determination of Brain Death

Reported Study[a]	No. of Patients	Test[b]	False-Negative Rate
Petty et al.[53]	23	TCD	10% (2 patients)
Flowers and Patel[54]	219	Nuclear brain scan	3% (6 patients)
Munari et al.[55]	20	Nuclear brain scan	5% (1 patient)
De Freitas and Andre[56]	270	TCD	17% (47 patients)
Quesnel et al.[57]	21	CTA	50% (10 patients)
Combes et al.[58]	30	CTA	23% (13 patients)
Escudero et al.[59]	27	CTA	7% (2 patients)

[a]Studies cited in complete list of references for this chapter provided online.
[b]All tests evaluated by comparison with clinical confirmation of brain death.
CTA, Computed tomographic angiogram*; TCD,* transcranial Doppler.
Adapted from Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology.* 2010;75:77–83.



• **Fig. 59.5** Updated decision algorithm for use in outcome prediction for comatose survivors of cardiac arrest. The guideline emphasizes on "multimodal" prognostication. *CT,* Computed tomography; *EEG,* electroencephalogram; *M,* GCS-M; *MRI,* magnetic resonance imaging; *NSE,* neuron-specific enolase; *ROSC,* return of spontaneous circulation; *SSEP,* somatosensory evoked potential. (From Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation.* 2014;85:1779–1789.

CO_2 value may be used in lieu of the conventional protocol for apnea testing, but this protocol requires future validation.[41] Recent case reports have indicated that to assess brain death in patients supported by ECMO, apnea testing can be performed without compromising oxygenation by decreasing without stopping the sweep gas flow and increasing oxygen delivery through the membrane.[42,43]

Conclusions

In the United States, current legislation allows physicians to determine death on the basis of neurologic criteria. The diagnosis of brain death on clinical grounds is not a difficult task, provided providers follow established protocols and guidelines for the interpretation of findings during the clinical examination. The establishment of a known cause and presence of coma, the absence of brainstem reflexes, and apnea support the diagnosis of brain death. Most jurisdictions require that the determination of brain death be made by a licensed physician, which in most cases should be an attending physician who has experience in the assessment of comatose patients and the legal requirements applicable to the jurisdiction of practice. When in doubt, an additional period of observation or a confirmatory test should be done to support the determination of brain death.

Key Points

- The clinical examination of brain dead patients is the most unequivocal in neurology.
- The determination of brain death in a comatose patient with catastrophic neurologic injury requires several consecutive steps supported by well-established guidelines.
- When the clinical diagnosis is in doubt or interferences to obtain a thorough clinical examination are present, a confirmatory test may be used to determine brain death in adults.

- Confirmatory testing should not be used in lieu of clinical examination, and when indicated, only one confirmatory test should be performed.
- A period of observation of up to 24 hours after cardiac arrest in patients exposed to therapeutic hypothermia may be required before fully entertaining the determination of brain death.

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Review Questions

1. A 67-year-old man has a respiratory arrest in the hospital. He was found unresponsive by the nursing staff, without a pulse or blood pressure, with an unknown down time. The patient was intubated and Advanced Cardiac Life Support (ACLS) resuscitation measures were initiated by the code team. In the intensive care unit (ICU), the patient develops tonic jerking motions of the upper extremities with any stimulation. These movements do not stop with benzodiazepine or propofol infusion. On examination, cranial nerves are intact but he does not respond to visual or auditory stimuli. Sleep/wake cycles are preserved. Examination findings and his condition persist for 1 month during which the patient is chronically ventilated but hemodynamically stable. Which one of the following *best* describes this patient's condition?

a. The patient is brain dead.
b. This patient is in a persistent vegetative state (PVS).
c. The diagnosis of this condition can be made 1 week after initial insult.
d. These patients commonly have no evidence of bladder or bowel incontinence.

Answer: b. The patient in this question is in a PVS. He is comatose but retains brainstem function; therefore he cannot be brain dead. PVS commonly occurs after anoxic or traumatic brain injury. It differs from brain death in many ways. First, brainstem function remains intact in PVS. These patients are also not considered medically or legally dead. A multidisciplinary task force defines PVS as "a condition of complete unawareness of self and environment." As stated, brainstem or autonomic function remains intact. These patients show no voluntary, reproducible, or purposeful responses to stimuli. They have no language comprehension or expression. They also are incontinent. Spinal reflexes are variably preserved.

2. Apnea represents one of the diagnostic criteria for brain death. Which one of the following is *most* correct regarding the apnea test and brain death?

a. The arterial partial pressure of carbon dioxide ($PaCO_2$) goal is above 60 mm Hg.
b. In patients with chronic obstructive pulmonary disease (COPD) with presumed hypoxic respiratory stimulation, PaO_2 levels should be allowed to decrease to less than 50 mm Hg before testing.
c. One should always begin the test with a normal pH and alveolar oxygen partial pressure ($PaCO_2$).
d. Testing should last for 10 minutes and continue with mild desaturation (80%–90%) or mild hypotension (80–90 mm Hg systolic).

Answer: c. All published criteria for brain death include irreversibility of brain damage, absence of neurologic function, the use of additional confirmatory testing, and the presence of apnea. Because most patients are ventilated, the failure of normal respiratory stimulation by a predetermined level of $PaCO_2$ must exist in the presence of apnea. This may be difficult, or in some patients, impossible (i.e., COPD, lung disease). Therefore, although a $PaCO_2$ level above 60 mm Hg is acceptable in patients with normal lungs, this level may not be adequate in all situations. Although some patients may require a level of hypoxemia to stimulate breathing (e.g., PaO_2 level <50 mm Hg), this should not be allowed during testing. Furthermore, no instances of hypotension should be allowed during testing. Should this occur, testing should be halted and the hypotension corrected. Should patients not be candidates for apnea testing, other confirmatory tests should be used.

3. A 27-year-old Hispanic woman arrives at a county hospital with multiple closed head injuries after a car collision. In addition, the patient has multiple internal abdominal injuries that caused frank hemorrhage and prolonged hypotension before resuscitation at the crash scene. Initial computed tomography (CT) of the head shows multiple small contusions. The patient was diagnosed as having moderate to severe anoxic brain injury. She remained in the ICU supported by mechanical ventilation and vasopressor support after initial resuscitation and surgery to stop internal bleeding. On neurologic examination, brainstem reflexes were absent. Which one of the following pertains to further confirmation testing for brain death?

a. The most sensitive test remains cerebral angiography documenting absence of intracerebral filling at the carotid bifurcation or the circle of Willis.
b. The finding of an isoelectric electroencephalogram (EEG) on one test is a highly specific and sensitive test for the diagnosis of brain death.
c. Transcranial Doppler (TCD) findings in brain death include absent or reversal of flow in systole and a sharp diastolic upstroke.
d. Somatosensory evoked potentials (SEPs), which test the integrity of sensory pathways, are highly sensitive and specific tests for brain death.
e. Technetium 99m hexamethylpropylene amine oxime (^{99m}TC HM-PAO) brain scan shows rapid uptake of isotope in nonfunctioning areas of brain consistent with brain death.

Answer: a. Although not necessarily required for diagnosis, additional confirmatory tests may be useful to diagnose brain death. The most sensitive test is cerebral angiography. Findings consistent with brain death include a lack of intracerebral filling at the level of the carotid bifurcation or the circle of Willis. The presence of electrocerebral silence on EEG during a 30-minute study remains the EEG diagnostic criteria for brain death. However, diagnosis should not be based on a single EEG test result. SEPs are controversial. Patients in a PVS may have findings similar to those with brain death. TCDs are noninvasive and can be done at the bedside. The test requires an experienced ultrasonographer and can be affected by changes in $PaCO_2$, hematocrit, and cardiac output. Findings on TCD consistent with brain death include absent or reversal of flow in diastole (not systole) and a sharp systolic (not diastolic) upstroke, or small spike waveforms above or both above and below the baseline at the beginning of systole. ^{99m}Tc HM-PAO scanning shows no uptake of isotope in brain parenchyma after brain death. The reported good sensitivity (94%) and specificity (100%) of this test and good correlation with angiography make this test a possible standard in the future.

4. Which one of the following conditions would not preclude a conclusive brain death diagnosis?
a. Serum sodium level of 120 mg/dL.
b. Temperature of 35°C.
c. A blood pressure of 180/90 mm Hg.
d. Use of cisatracurium for neuromuscular blockade.
e. Serum alcohol level of 209 mg/dL.
Answer: c. To diagnose brain death, certain factors must be absent so that the results of brain death testing are not jeopardized. These factors include the *absence* of (1) hypothermia, (2) intoxication, (3) sedative medications, (4) neuromuscular blockade, (5) electrolyte abnormalities, (6) acid-base abnormalities, and (7) endocrine crises.

5. A 28-year-old man with multisystem trauma involving his head was admitted to the ICU. He has remained comatose for 3 days, developed severe hypoxia and acute respiratory distress syndrome (ARDS), required continued levophed infusion to maintain a cerebral perfusion pressure of greater than 60 mm Hg, and developed intracranial hypertension with intracranial pressures (ICPs) in the mid-30s, sustained despite appropriate advanced thermoregulation (hypothermia to 33°C), pentobarbital infusion, and pharmacologic interventions with hyperosmolar and hypertonic solutions. He has extensive facial trauma, and a tracheostomy was inserted emergently as part of the initial management. Currently he has no response to deep pain, has no brainstem reflexes but pupils could not be examined because of palpebral edema, and has no motor responses as evidenced by the primary neurosurgeon and a consultant neurologist. Which of the following is the best course of action at this time?
a. Continue current management and perform gastrostomy for long-term care.
b. Perform an apnea test.
c. Rewarm to normothermia and request an EEG.
d. He is brain dead, and therefore the team can "pronounce" him and send him for organ donation.
e. Rewarm to normothermia and request a cerebral angiography or cerebral perfusion scan.
Answer: e. This patient has sustained catastrophic brain injury. His examination suggests that he may well be brain dead. Continuing medical care may be ineffective and physicians seem to have exhausted all therapies available. However, we cannot entertain this diagnosis as he is currently under therapeutic hypothermia and received pentobarbital. An apnea test, once he is rewarmed and not receiving pentobarbital, may be ideal, but he likely will not tolerate it (hypoxia and hypotension). A confirmatory test such as a cerebral angiography or perfusion scan could be performed in this case on the basis of extended facial trauma and inability to examine components of the brainstem reflexes (pupils) and other confounders such as pentobarbital exposure. An EEG in the setting may produce a false-positive test result.

60 Stroke

THOMAS R. MIRSEN AND HAYAN DAYOUB

CHAPTER OUTLINE

Historical Background
Overview
Advances in Radiology
Thrombolysis in Stroke
Endovascular Mechanical Thrombectomy
Symptomatic Carotid Disease/Stenting
Anticoagulation in Stroke
Antiplatelet Agents in Stroke
Patent Foramen Ovale
Prolonged Cardiac Monitoring
Massive Hemispheric Cerebral Infarct
Critical Care Consultation
Summary

Historical Background

Stroke has a major impact in the United States, with a current yearly incidence of 795,000 new and recurrent strokes.[1] Stroke constitutes the fifth leading cause of death and is a major cause of disability.[2] Historically, stroke was not emphasized in the critical care setting because of the limited scope of interventions in the past. In the early 1990s, neurologic diseases, including but not limited to stroke, accounted for a mere 6% to 7% of admissions to critical care units.[3] Now there is acute treatment for stroke—namely, the use of tissue plasminogen activator (tPA) for ischemic stroke within 3 hours[4] or even 4.5 hours[5] of symptom onset, as well as intraarterial thrombolysis[6] and endovascular clot extraction[7] during the 6 hours after stroke onset. Frequent monitoring in a critical care unit is required after these interventions.

Overview

This chapter reviews the general diagnosis and treatment of ischemic stroke. Stroke includes ischemic infarction as the result of vessel thrombosis (87% of cases), intracerebral hemorrhage (ICH; 10% of cases), and subarachnoid hemorrhage (3% of cases).[2]

Stroke is defined as a focal neurologic deficit of presumed vascular onset, lasting 24 hours or longer, as opposed to a transient ischemic attack (TIA), which is an episode shorter than 24 hours in duration.[8] Many TIAs actually last for less than 60 minutes.[9]

Stroke symptoms, including retinal TIA *(amaurosis fugax),* arise either from the territory fed by the internal carotid artery or from the vertebrobasilar system. The carotid, through its major branches, the anterior cerebral arteries and middle cerebral arteries (MCAs), provides blood to the major portion of the cerebral hemispheres. The vertebrobasilar system, in contrast, perfuses the brainstem and cerebellum, as well as the inferior and medial aspects of the occipital and temporal lobes, and the thalamus.

Carotid symptoms, as listed in Box 60.1, primarily consist of hemisensory loss, hemiparesis, and retinal ischemia (monocular blindness). Left hemispheric ischemia, generally in the perisylvian area, may result in varying degrees of aphasia.[10] Involvement of the sensory association areas within the right parietal lobe can produce the phenomenon of neglect.[11] In neglect, a stimulus is felt when it is alone but not in the presence of a competing stimulus. For example, a touch on the left hand or an object in the left visual field may be perceived when alone, but not when another stimulus is simultaneously presented, generally on the right side (double simultaneous stimulation). In that instance the right-sided stimulus alone is perceived.

Box 60.1 lists symptoms resulting from ischemia in the vertebrobasilar territory, which includes the cerebellum, brainstem, and the medial aspect of the occipital lobe, as well as the thalamus and the inferomedial portions of the temporal lobe. As a result, vertebrobasilar ischemia can produce cranial nerve dysfunction, nystagmus, cerebellar dysmetria, ataxia, and long tract signs such as sensory loss or motor impairment. These may involve one or both sides of the body. Memory disorders and visual field deficits also occur. In extreme circumstances, when the basilar artery becomes occluded, coma or quadriparesis may develop, although the presentation may vary, as described by Kubik and Adams[12] in 1946. As a result of coma or quadriparesis, mechanical ventilation may be required, and the prognosis in such patients is grim. In one study,[13] 22 of 25 patients died, and the other 3 lingered in the "locked-in syndrome" owing to pontine infarction.[14] Such patients can communicate only through eye blinking. Diifferentiating between carotid and vertebrobasilar symptoms is important to avoid unwarranted intervention on stenotic vessels.

Box 60.2 lists those entities that most frequently mimic stroke. Hypoglycemia may produce focal neurologic deficits. Occasionally a mass lesion such as tumor or subdural hematoma may present with fluctuating deficits or be revealed by seizure activity that may be confused with stroke. Mass lesions and hemorrhage are frequently marked by confusion, decreased level of consciousness, or headache, but if the lesion is small, these symptoms may not appear. Consequently, blood sugar measurements and computed

• BOX 60.1 Stroke Symptoms

Carotid Distribution

1. Hemiparesis
2. Hemisensory loss
3. Aphasia
4. Retinal ischemia
5. Neglect
6. Homonymous hemianopia

Vertebrobasilar Distribution

1. Motor dysfunction—crossed or bilateral
2. Sensory loss—crossed or bilateral
3. Gait ataxia
4. Homonymous hemianopia
5. Diplopia, dysphagia, dysarthria, vertigo, hiccups—none of these alone qualify as stroke/transient ischemia attack symptoms
6. Combinations of the above

• BOX 60.2 Stroke Mimics

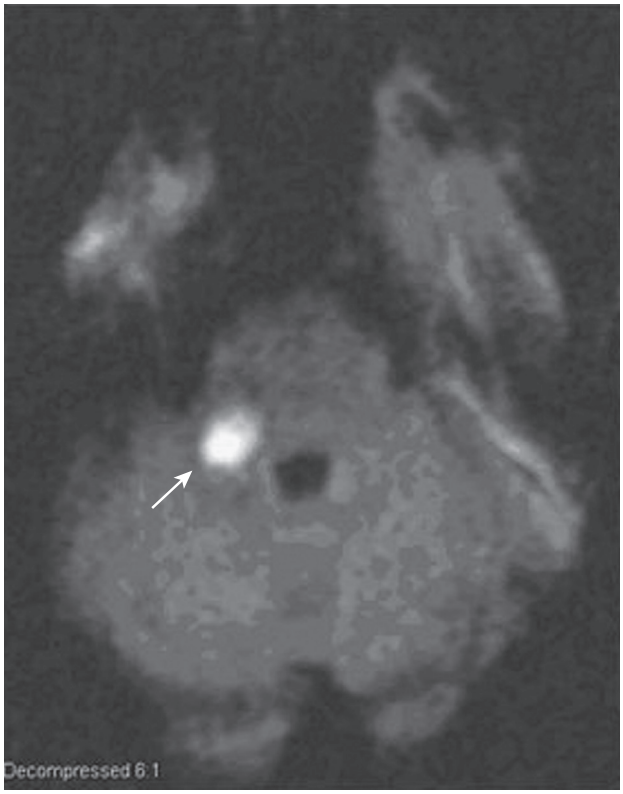
Intracerebral hemorrhage
Seizure
Migraine
Hypoglycemia
Tumor

tomography (CT) scans (without contrast) are obligatory in suspected stroke. Within the first 6 hours of the event, CT results may well be negative. Its main role is excluding the presence of small hemorrhages.

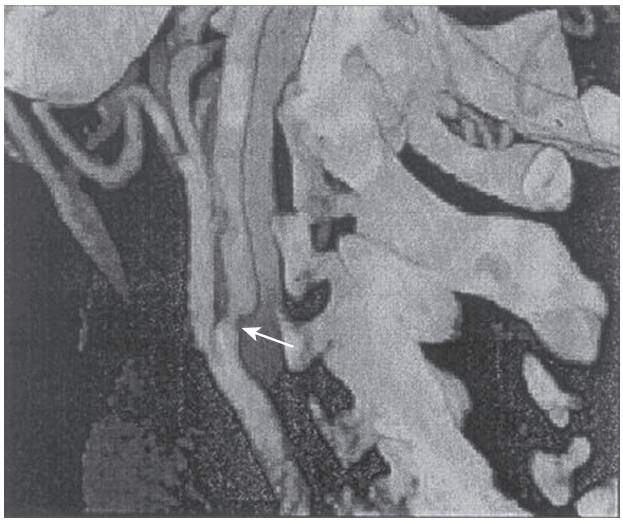
Advances in Radiology

With the advent of diffusion-weighted imaging (DWI), magnetic resonance imaging (MRI) scans (Fig. 60.1) can now be used to detect acute cerebral ischemia within the initial 6-hour period after symptom onset.[15] This allows determination of the presence of stroke in doubtful cases. In the instance of a seizure in a patient with prior stroke, DWI discriminates between seizure alone and new stroke. If an old neurologic deficit worsens, DWI clarifies whether there is new stroke or just intercurrent illness. DWI can also reveal silent areas of cerebral ischemia. The coincident development of ischemia in different vascular territories may point to vasculitis, hypercoagulable state, or cardiac emboli. MRI has been proved to be just as effective as CT in detecting ICH.[16] Unfortunately, MRI is less immediately available, requires more time and cooperation from the patient, and may not be feasible if the patient has claustrophobia or retained ferromagnetic particles. Also, in about 8% of cases, especially milder strokes as the result of small vessel disease or in the posterior circulation, DWI results may prove negative initially.[17]

MR and CT can delineate the cerebral vasculature in detail, starting from the aortic arch and extending to the circle of Willis. Computed tomographic angiography (CTA) is accurate for both the intracranial vasculature[18] and the extracranial segment of the carotid artery[19] (Fig. 60.2). Magnetic resonance angiography is notably less sensitive than CTA in studying intracranial vessels[20] (Figs. 60.3 and 60.4). Consequently, CTA is increasingly the test



• Fig. 60.1 Cerebral infarction as shown by diffusion-weighted imaging *(arrow)* on magnetic resonance imaging. Hyperdensity in the right middle cerebellar peduncle is demonstrated.

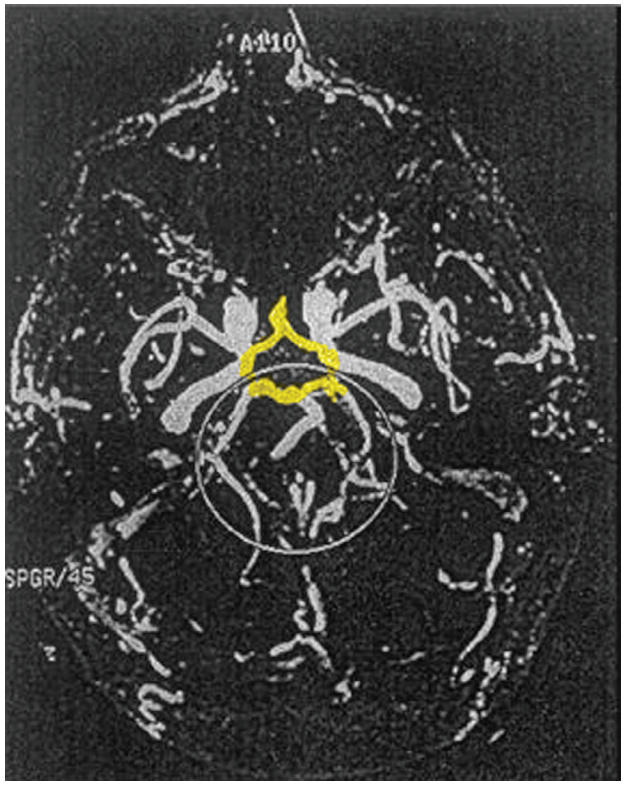


• Fig. 60.2 Computed tomography angiogram of the extracranial carotid artery. An area of stenosis *(arrow)* is shown in the internal carotid artery.

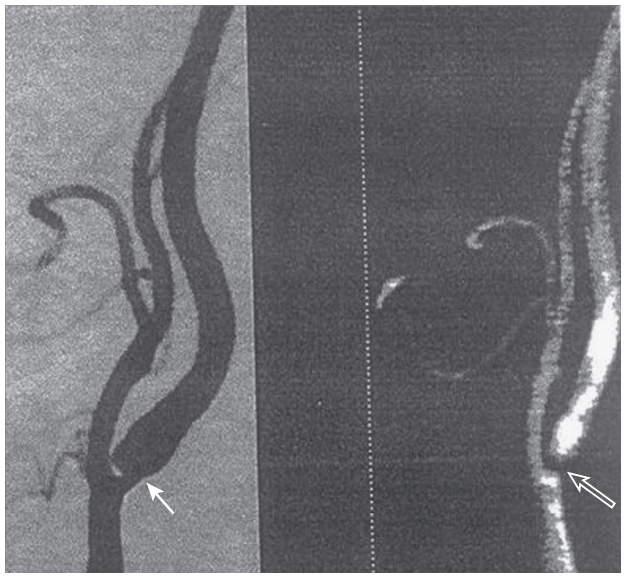
of choice and conventional cerebral angiography is limited to specific indications, as outlined in Box 60.3.

Thrombolysis in Stroke

The era of thrombolysis in acute stroke began with the publication of the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial in 1995,[4] which demonstrated the benefit of



• **Fig. 60.3** Magnetic resonance angiogram demonstrating circle of Willis *(highlighted)* and its vertebrobasilar component *(circle)*.



• **Fig. 60.4** Shown are magnetic resonance angiography *(left)* and computed tomographic angiography *(right)* of the extracranial carotid artery in a patient with internal carotid artery stenosis *(arrows)* located above the common carotid bifurcation.

tPA when given to patients presenting within 3 hours of event onset. Using the National Institutes of Health Stroke Scale (NIHSS) (Table 60.1) score, a reliable measure[21] to measure disability, the improvement was from 20% with minimal or no disability with placebo to 31% with tPA. This was counterbalanced by an increase in the rate of ICH, from 0.6% in the placebo group to 6.4% in the tPA cohort. Half the subjects in the placebo group who sustained ICH died, whereas the mortality rate from ICH in the tPA cohort was 2.9% (less than half). Hemorrhage after tPA use occupies the same area of the brain affected by the initial thrombosis in most, but not all, cases.[22]

• BOX 60.3 Indications for Conventional Cerebral Angiography

- To ascertain the precise degree of arterial stenosis, most often of the extracranial carotid artery, in doubtful cases
- To detect and map intracranial aneurysms and arteriovenous malformations
- To determine patterns of collateral flow in the brain
- To diagnose vasculitis
- To detect intraluminal thrombus
- To enable intraarterial thrombolysis or mechanical clot extraction
- To perform carotid angiography and stenting

Inclusion (Box 60.4) and exclusion (Box 60.5) criteria are applied to attempt to minimize the risk of ICH. Some exclusion criteria are absolute and some are relative (Box 60.6).[23] The time of onset of symptoms is the last time that the patient was seen to be normal. The blood glucose and head CT scan must be checked before initiating tPA. The CT scan must be scrutinized for mass/hemorrhage, and also for early ischemic changes (sulcal effacement, hypolucency, or loss of definition of structures within the brain) and for a hyperdense MCA, suggestive of thrombosis.[24] Whether ischemic changes on CT predict a heightened risk of hemorrhagic transformation is controversial.[22,25] However, CT findings appear more commonly among subjects with scans performed relatively late in the course of their stroke.[25] Their appearance should prompt reevaluation of the time of onset of the stroke. A systematic assessment of hypolucency in the MCA territory, the Alberta Stroke Program Early CT Score (ASPECTS)[26] has been devised, and extensive hypolucencies do correlate with poor outcome. However, it is not clear that thrombolysis should be withheld on that basis alone.[27] Prior ICH, recent stroke, and hypertension at presentation are believed to increase the risk of sustaining ICH. Systemic bleeding may cause hypotension and worsening of the neurologic deficit and must be avoided. Extremes of blood glucose values or the presence of a coincident seizure may make the neurologic deficit seem worse than it is.

A sample for a platelet count must also be drawn before starting thrombolysis, but treatment need not await results unless there is reason to suspect a low platelet count. If the platelet count is less than 100,000 μL, the tPA infusion must be stopped. For a patient receiving anticoagulant therapy, the appropriate clotting parameter must be available before proceeding with treatment. If a patient starts thrombolysis and the coagulation profile proves abnormal, the infusion must be stopped. If a patient is receiving full-intensity low-molecular-weight heparin, tPA must be withheld. Testing for the activity of factor Xa antagonists is not yet standardized, although a normal thrombin time, among other tests, may suggest that thrombolysis is safe.[28]

If the blood pressure is elevated (>180 mm Hg systolic or 110 mm Hg diastolic), labetalol, 5 to 10 mg IV (intravenous), may be given and repeated to a maximum dosage of 40 mg. A nicardipine drip may be used as well. If the blood pressure rebounds, tPA should not be given. If the pressure should rise above 180 mm

TABLE 60.1 National Institutes of Health Stroke Scale

Component	Description	No. of Points
1a. Level of consciousness (LOC)	Alert	0
	Drowsy	1
	Stuporous	2
	Coma	3
1b. LOC questions	Answers both correctly	0
	Answers one correctly	1
	Incorrect	2
1c. LOC commands	Obeys both correctly	0
	Obeys one correctly	1
	Incorrect	2
2. Best gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
3. Visual field	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
4. Facial palsy	Normal	0
	Minor	1
	Partial	2
	Complete	3
5. Motor arm	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	Plegia	4
6. Motor leg	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	Plegia	4
7. Limb ataxia	Absent	0
	Present in upper or lower	1
	Present in both	2
8. Sensory	Normal	0
	Partial loss	1
	Dense loss	2
9. Best language	No aphasia	0
	Mild to moderate aphasia	1
	Severe aphasia	2
	Mute	3
10. Dysarthria	Normal articulation	0
	Mild to moderate dysarthria	1
	Near unintelligible or worse	2
11. Extinction and inattention	No neglect	0
	Partial neglect	1
	Complete neglect	2

Hg systolic or 105 mm Hg diastolic after starting the tPA infusion, IV agents must be given to reduce it (Table 60.2).[29] It is worth emphasizing that blood pressure should be treated acutely only when there exists a specific indication for doing so, as defined in the table.

• BOX 60.4 Thrombolysis Inclusion Criteria at 0–3 h

Acute ischemic stroke with clearly defined time of onset
Neurologic deficit measurable using the NIH Stroke Scale
CT scan of the brain without evidence of intracerebral hemorrhage
Age 18 years or older

CT, *Computed tomography;* NIH, *National Institutes of Health.*

• BOX 60.5 Absolute Thrombolysis Exclusion Criteria

Major head or spine injury within the past 3 months
Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg
Symptoms suggestive of subarachnoid hemorrhage
Gastrointestinal or genitourinary hemorrhage within the previous 21 days
Evidence of significant bleeding or significant fracture on examination
Heparin use within 48 h before treatment and elevated PTT
Therapeutic dosing of low-molecular-weight heparin
Prothrombin time >15 s or INR >1.7
Platelet count <100,000/μL
Current use of direct thrombin or factor Xa inhibitors (within the past 48 hours), with elevated laboratory tests (PTT, INR, platelet count, ecarin clotting time, thrombin time, or factor Xa activity assay)
Presence of intraparenchymal brain tumor
CT scan of the brain with hypodensity involving more than one-third of the cerebral hemisphere
Arterial puncture at a noncompressible site within the previous 7 days

CT, *Computed tomography;* INR, *international normalized ratio;* PTT, *partial thromboplastin time.*

• BOX 60.6 Relative Thrombolysis Exclusion Criteria

Minor deficit or rapid neurologic improvement leaving a minor deficit
Major surgery within the previous 14 days
Prior history of intracerebral hemorrhage
Presence of meningioma
Seizure with postictal residual neurologic deficits
Blood glucose <50 mg/dL or >400 mg/dL
Large myocardial infarction in the past 3 months
Stroke in the last 3 months
Hemorrhagic diabetic retinopathy
Lumbar puncture in the last week

tPA is often not given for a deficit mild enough that reasonable recovery may be expected within 3 months. However, there is not a clear cutoff based on the NIHSS. A partial hemisensory loss, facial palsy, or mild dysarthria would not normally warrant treatment with tPA, but isolated motor or speech deficits would. Difficult choices exist in the setting of mild deficits. Patients with such deficits may recover well, but 30% of patients presenting with mild stroke are left with significant impairment in one series, even after tPA treatment.[30] Moreover, a percentage of subjects will experience worsening of their condition while in the hospital and then no longer be candidates for rescue using thrombolysis. This is particularly likely in the setting of rapid recovery of the initial deficit and if there is an underlying large vessel stenosis.[31] The benefit of tPA in these circumstances has not been studied.

TABLE 60.2 Approach to Elevated Blood Pressure in Acute Ischemic Stroke

Blood Pressure Level (mm Hg)	Treatment
A. Not Eligible for Thrombolytic Therapy	
Systolic <220 mm Hg OR diastolic <120 mm Hg	Observe unless other end-organ involvement (e.g., aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy) Treat other symptoms of stroke (e.g., headache, pain, agitation, nausea, vomiting) Treat other acute complications of stroke including hypoxia, increased intracranial pressure, seizures, and hypoglycemia
Systolic >220 mm Hg OR diastolic 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 min May repeat or double every 10 min (maximum dose 300 mg) OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h Aim for a 10%–15% reduction in blood pressure
Diastolic >140 mm Hg	Nitroprusside 0.5 μg/kg per minute IV infusion as initial dose with continuous blood pressure monitoring Aim for a 10%–15% reduction in blood pressure
B. Eligible for Thrombolytic Therapy	
Pretreatment	
Systolic >185 mm Hg OR diastolic >110 mm Hg	Labetalol 10–20 mg IV over 1 to 2 min, may repeat ×1 OR Nitropaste 1–2 inches OR Nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5- to 15-min intervals, maximum dose 15 mg/h; when desired blood pressure attained, reduce to 3 mg/h If blood pressure does not decline and remains >185/110 mm Hg, do not administer rtPA
During/After Treatment	
1. Monitor blood pressure	Check blood pressure every 15 min for 2 hr, then every 30 min for 6 hr, and finally every hour for 16 hr
2. Diastolic >140 mm Hg	Sodium nitroprusside 0.5 mg/kg per minute IV infusion as initial dose and titrate to desired blood pressure
3. Systolic >230 mm Hg OR diastolic 121–140 mm Hg	Labetalol 10 μg IV over 1–2 min May repeat or double labetalol every 10 min to maximum dose of 300 mg; or give initial labetalol dose, then start labetalol drip at 2–8 mg/min OR Nicardipine 5 mg/h IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h; if blood pressure is not controlled by labetalol, consider sodium nitroprusside
4. Systolic 180–230 mm Hg OR diastolic 105–120 mm Hg	Labetalol 10 mg IV over 1–2 min May repeat or double labetalol every 10–20 min to maximum dose of 300 mg; or give initial labetalol dose, then start labetalol drip at 2–8 mg/min

IV, Intravenous; *rtPA,* recombinant tissue plasminogen activator.

From Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* 2007;38:1655–1711.

Subjects who have been taking antiplatelet agents such as aspirin before their event may receive tPA, but no anticoagulants or antiplatelet agents should be given for the 24 hours after the start of tPA therapy. Arterial punctures, nasogastric tubes, and catheterization should be avoided unless they are essential to care to minimize the risk of bleeding.

Hypotension may develop, raising the concern of systemic hemorrhage. The most feared event after tPA use is the development of ICH. The presenting signs and symptoms appear in Box 60.7. Hypertension is a compensatory response to increased intracranial pressure (ICP), to maintain cerebral perfusion, and bradycardia occurs secondary to it.

Box 60.8 shows the steps to be taken with suspected ICH.[32] It is relatively uncommon for neurosurgeons to intervene on hemorrhages in the setting of tPA because of the risk of further bleeding into the surgical bed. Systemic hemorrhage is handled in a similar fashion, and red blood cell transfusion may be necessary.

• BOX 60.7 Signs and Symptoms of Intracerebral Hemorrhage

New neurologic deficits
Worsening of existing neurologic deficits
Headache
Nausea, vomiting
Decreased level of consciousness, coma
Marked hypertension
Bradycardia

The benefit of tPA is greatest in small vascular occlusions[33] and least in carotid[34] occlusions. Older subjects with particularly severe strokes are most likely to have a poor outcome, but even in this group tPA remains beneficial overall.[35] The sooner tPA is administered, the higher the likelihood of successful recovery.[36] A residual

• BOX 60.8 Management of Suspected Intracerebral Hemorrhage After Use of Tissue Plasminogen Activator

Discontinue the tPA infusion if it remains in progress.
Obtain CT scan of the head (noncontrast) stat
Order PT, PTT, platelet count, fibrinogen level, type and cross-match stat.
In event of hemorrhage, consult hematology and neurosurgery
Give 6–8 units of cryoprecipitate, then 6–8 units of platelets
Administer aminocaproic acid 4–5 gm IV over 1 hour, followed by 1 gm PO or IV per hour
Check fibrinogen every 4 hours and give cryoprecipitate to keep fibrinogen >150 mg/dL
Monitor blood pressure every 15 min
Periodically repeat CBC, PT, PTT
Consider repeat head CT

CBC, *Complete blood cell count;* CT, *computed tomography;* IV, *intravenous;* PO, *oral;* PT, *prothrombin time;* PTT, *partial thromboplastin time;* stat, *immediately;* tPA, *tissue plasminogen activator.*

• BOX 60.9 Additional Thrombolysis Exclusion Criteria at 3.0–4.5 h

These are all relative criteria:
Age over 80
NIHSS of 25 or greater
Combination of prior stroke and diabetes
Oral anticoagulant therapy

CT, *Computed tomography;* NIHSS, *National Institutes of Health Stroke Scale.*

benefit of tPA exists as far out as 6 hours from the ictus. Two studies[37,38] that specifically examined treatment beyond 3 hours failed to show a benefit of administration of tPA within a 5- or 6-hour time frame. More recently, however, the ECASS-III (European Cooperative Acute Stroke Study III) trial[5] established the utility of tPA administration in the 3.0- to 4.5-hour period after stroke onset. The inclusion and exclusion criteria are more restrictive than those for treatment within 3.0 hours (Box 60.9). Initially, there was some concern about the administration of tPA within the 3.0- to 4.5-hour window to subjects with a history of both prior stroke and diabetes. A statistical analysis[39] based on datasets from large registries suggests that neither factor predisposes to poor outcome in reality. No doubt there exists a subgroup of subjects who present after 4.5 hours who remain amenable to treatment, but this group cannot yet be identified.

Various authors have identified different predictors of ICH after treatment with tPA. Levy and colleagues[40] identified the dosage of tPA given, the age of the subjects, and diastolic hypertension as pertinent factors. Larrue and colleagues[22] also found age to heighten the risk of development of ICH, but not the degree of hypertension or the time to treatment. It has become clear that tPA can be given safely in the community[41] and that complication rates of tPA use can be lowered to a satisfactory level by careful adherence to the exclusion criteria.[42]

Radiologic imaging has been proposed as a tool to determine when individual subjects may be suitable for intraarterial intervention, regardless of time from stroke onset. Specific patients may, by virtue of good collateral flow, possess a significant area of ischemic but viable brain that may be salvaged by endovascular treatment, even if intervention begins beyond standard time windows. This algorithm may apply particularly to "wake-up" strokes. Computed perfusion tomography (CT perfusion) can be used to estimate the size of the ischemic area but not infarcted area at presentation,[43] and diffusion-weighted/perfusion-weighted MRI may identify those patients who will benefit from intervention.[44] However, these tools need validation and standardization in large studies to attain clinical efficacy.

• BOX 60.10 Thrombolysis in Cerebral Infarction Scale

Grade 0: no perfusion
Grade 1: penetration with minimal perfusion
Grade 2: partial perfusion
  Grade 2A: only partial filling (less than two-thirds) of the entire vascular territory is visualized
  Grade 2B: complete filling of all of the expected vascular territory is visualized but the filling is slower than normal
Grade 3: complete perfusion

Endovascular Mechanical Thrombectomy

As mentioned earlier, IV thrombolysis with tPA changed the landscape for acute stroke management and improved patients' outcomes.[4] However, this effect was less pronounced in patients with large vessel occlusion, defined as terminal ICA (intracranial segment of the internal carotid artery before its bifurcation), proximal MCA (M1 segment of the MCA), and basilar artery.[34]

Endovascular mechanical thrombectomy is a procedure in which a series of telescoping catheters are introduced through the femoral artery and guided by fluoroscopy into the anterior cerebral circulation via the internal carotid artery, or into the posterior circulation via the vertebral and basilar arteries. Contrast dye is injected and the site of occlusion appears as a sharp interruption of flow.

The techniques used to reestablish flow through an occluded segment have evolved from simple injection of intraarterial recombinant tPA to dissolve an occlusive thrombus locally, to the introduction of suction catheters where negative pressure is applied proximally to the thrombus to aspirate it. Other novel techniques include the introduction of a simple ball tip wire to macerate the thrombus, or complex tipped wires deployed distal to the thrombus and pulled back to "uncork" the blocked artery. Although some of these techniques are still in use sporadically, the current standard intervention for thrombectomy is "stent retrieval"[45] in which a wire with a soft expandable stent at its tip is deployed past and through the occluded segment. As the stent expands, it macerates the thrombus and traps it within its mesh; the stent is then carefully pulled back under negative suction. The procedure may be repeated s few times until successful. A semiquantitative scoring system, the Thrombolysis In Cerebral Infarction (TICI) score,[46,47] is used to assess the efficacy of revascularization. A grade of 2B or 3 (Box 60.10) is considered adequate revascularization.

Mechanical thrombectomy is used following IV tPA if a vessel occlusion persists, or alone in patients who cannot receive tPA.

Although the results of earlier studies[48–50] were equivocal, several recent multicenter randomized prospective trials[51–55] showed efficacy of mechanical thrombectomy (sometimes after IV tPA) compared to standard medical treatment. A meta-analysis of all 8 studies[7] showed that patients who underwent endovascular treatment had significant benefit across the spectrum of disability (odds ratio [OR] 1.56; 95% confidence interval [CI] 1.14–2.13; $P = 0.005$). Functional independence at 90 days occurred among 557 of 1293 patients (44.6%; 95% CI 36.6%–52.8%) in the endovascular therapy group versus 351 of 1094 patients (31.8%; 95% CI 24.6%–40.0%) in the standard medical care group (risk difference, 12%; 95% CI 3.8%–20.3%; OR 1.71; 95% CI 1.18–2.49; $P = 0.005$). Compared with standard medical care, endovascular thrombectomy was associated with significantly higher rates of angiographic revascularization at 24 hours (75.8% vs. 34.1%; OR 6.49; 95% CI 4.79–8.79; $P < 0.001$) but no significant difference in rates of symptomatic intracranial hemorrhage within 90 days (70 events [5.7%] vs. 53 events [5.1%]; OR 1.12; 95% CI 0.77–1.63; $P = 0.56$) or all-cause mortality at 90 days (218 deaths [15.8%] vs. 201 deaths [17.8%]; OR 0.87; 95% CI 0.68–1.12; $P = .27$).

The striking benefit of endovascular therapy in addition to access to specialized neurocritical and neurosurgical care has prompted a structural change in regional care delivery. Patients with acute stroke who are candidates for neurointervention or at risk of hemorrhagic complications should be transferred to comprehensive stroke centers for optimal management.

Symptomatic Carotid Disease/Stenting

Carotid endarterectomy (CEA) dramatically reduces stroke risk in patients with cerebral or retinal ischemia with significant carotid stenosis ipsilateral to the affected hemisphere.[56,57] In the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[57] the risk of stroke fell from 26% over 2 years in the nonsurgical group to 9% over 2 years in the surgical group, with a surgical morbidity and mortality rate of 5.6%. The patients had stenosis of 70% or greater. A more modest benefit was seen in men with stenoses between 50% and 69%—namely, a reduction in stroke risk from 22.2% over 5 years without surgery to 14.9% over 5 years with surgery. This is an absolute reduction of the stroke rate of 7.3% over 5 years, as opposed to an absolute reduction of 17% over 2 years in the group with stenosis greater than 70%. Superior surgical skill is necessary to ensure that the procedure remains beneficial in this cohort.

There must also be a reasonable expectation of survival without major disability over a 5-year period. Thus subjects with moderately advanced dementia, hepatic failure, or renal failure are generally not considered suitable candidates for CEA.

Other considerations indicate which patients carry an increased risk of poor outcome acutely from endarterectomy. Such factors include[58] poor or unstable neurologic status, cerebral ischemia within 24 hours of surgery, congestive heart failure, recent cardiac ischemia, marked hypertension, emphysema, age older than 70 years, and severe obesity. The presence of a contralateral carotid occlusion places subjects at extremely high risk of stroke if left untreated but also carries a high morbidity and mortality risk acutely.[59]

The likelihood of stroke in patients with carotid stenosis rises steadily with increasing severity of stenosis greater than 70%[57] and then decreases again as the stenosis reaches 94% to 99%. However, surgery remains beneficial in this range.[60] In addition, hemispheric symptoms predict roughly twice the danger of stroke as do isolated retinal symptoms.[61] Men benefit more from carotid surgery than women. In contrast to prior findings,[58] there is greater benefit of the procedure in persons older than 75 years. Most importantly, the benefit of endarterectomy is maximal within 2 weeks of the sentinel event and diminishes rapidly if surgery is delayed.[62] When severe disability exists, endarterectomy may be reasonably delayed to await recovery.

• BOX 60.11 High-Risk Criteria for Entry Into the SAPPHIRE Trial

Clinically significant heart disease: congestive heart failure, abnormal stress test, or need for open heart surgery
Severe pulmonary disease
Contralateral carotid artery occlusion
Contralateral laryngeal nerve palsy
Previous radical neck surgery
Previous radiation therapy to the neck
Carotid restenosis after endarterectomy
Age older than 80 years

SAPPHIRE, *Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.*

Protected carotid angioplasty and stenting (CAS) has been compared with CEA in a controlled, randomized trial.[63] Study participants were 18 years of age or older and had either a greater than 50% symptomatic stenosis or a greater than 80% asymptomatic stenosis. They were at high risk, as defined by at least one of the factors listed in Box 60.11.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial showed a trend favoring CAS for the incidence of death and major ipsilateral stroke, both in the year following intervention. These gains fell short of statistical significance, perhaps because the study was terminated prematurely. There was a significant decline in the rate of myocardial infarction (MI) at 1 month after intervention in the CAS group when compared with endarterectomy, caused primarily by a fall in the incidence of non–Q-wave MI. Some of this benefit may reflect the added use of clopidogrel in addition to aspirin for 2 to 4 weeks after treatment in the CAS group. CREST The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[64] was a randomized comparison of CAS and CEA, including both symptomatic and asymptomatic subjects. It revealed increased risk of stroke acutely with stenting, whereas endarterectomy acutely was associated with an increased risk of heart attack, without, however, increased mortality. Over 2.5 years of follow-up, there was no significant difference in outcome. Endarterectomy appears to be superior, again, in patients older than 70 years. Recovery from nonfatal MI is less problematic than recovery from stroke, and the increased stroke risk in the CAS group occurs early. These results do not support adoption of CAS as an alternative to CEA.

Symptomatic intracranial stenosis appears not to benefit from warfarin when compared[65] to high-dose aspirin, in part because of increased risk of gastrointestinal bleeding. Subsequently,[66] intracranial angioplasty and stenting was compared to intensive medical therapy, including the use of aspirin in conjunction with clopidogrel for 90 days. The study was stopped prematurely because of a high risk of periprocedural stroke and a low risk of stroke in the medically treated arm. One cannot support the routine performance of intracranial angioplasty and stenting on symptomatic vessels.

• BOX 60.12 Components of the CHA2DS2-VASc Score

Congestive heart failure or left ventricular systolic dysfunction	1 point
Hypertension (consistently >140/90 mm Hg or on therapy)	1 point
Age of 75 years or above	2 points
Diabetes mellitus	1 point
Prior **s**troke, TIA, or thomboembolism	2 points
Vascular disease (peripheral arterial disease, myocardial infarction, aortic plaque)	1 point
Age 65–74 years	1 point
Sex category (female sex)	1 point

CHADS2, *Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack;* TIA, *transient ischemic attack.*

• BOX 60.13 Indications for Anticoagulation in Stroke

Atrial fibrillation, with or without rheumatic heart disease
Prosthetic heart valve
Deep venous thrombosis, with or without the potential for paradoxical embolus
Hypercoagulable state
Venous sinus thrombosis
Arterial dissection (less definite)

Anticoagulation in Stroke

Anticoagulants occupy an important but limited place in stroke therapy. The acute use of heparin in unselected stroke patients was studied some years ago but not justified.[67] When warfarin is given to unselected stroke patients in a population including a slight majority of subjects with lacunar stroke, it confers no advantage relative to aspirin.[68] Warfarin does not reduce the incidence of stroke among subjects with a decreased ejection fraction (<35%) when compared to aspirin.[69]

Warfarin clearly prevents stroke among subjects with nonrheumatic atrial fibrillation, even if they have never had a stroke or TIA.[70] The risk of stroke falls by 64%. The CHADS2[71] score and now its successor, the CHA2DS2-VASc score[72] (Box 60.12) are used commonly to assess the risk of stroke. A score of 0 on the latter indicates low risk, 1 intermediate risk, and 2 and above high risk.

Individuals with atrial fibrillation who sustain a minor stroke or TIA have a high stroke risk (12% per year), which falls to 4% per year upon treatment with warfarin. A 2.8% yearly risk of all bleeding complications with warfarin exists, as opposed to 0.7% with placebo.[73] It remains uncertain when in the course of stroke to initiate anticoagulant therapy. However, it is clear from a meta-analysis[74] that treatment within 48 hours with heparin or low-molecular-weight heparin does not improve outcome but increases the risk of ICH. Beyond that, acute anticoagulation with oral agents following a stroke should be delayed if there is a sizable infarct as measured by the NIHSS (perhaps a score of ≥12) or on CT (>⅓ of MCA territory), which could progress to herniation and death as a result of ICH. The 185/110 mm Hg cutoff measurement used in the NINDS tPA trial may indicate the blood pressure range of hypertension that would cause one to delay anticoagulation. In contrast, one should move quickly to anticoagulation following TIA or minor stroke occurring in conjunction with atrial fibrillation or any other indication for such therapy.

Other indications for anticoagulation appear in Box 60.13. Some, such as the presence of rheumatic heart disease with atrial fibrillation, prosthetic heart valve, or deep venous thrombosis (DVT), are long established. Anticoagulation carries more urgency when a DVT coexists with a communication across the atrial septum, such as patent foramen ovale (PFO), because there is risk of both recurrent stroke and pulmonary embolism.

The utility of warfarin is limited by the need for regular blood work and difficulty in regulating its dosage. Factor II and factor Xa inhibitors have recently been studied for stroke prevention in the setting of atrial fibrillation. Dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) are marketed in the United States. Apixaban reduces the risk of stroke[75]—when compared with aspirin—in patients deemed unsuitable for warfarin use, without an increase in major or intracranial hemorrhage. When compared to warfarin, apixaban reduces the risk not only of stroke but also of both intracranial hemorrhage and serious hemorrhage.[76] Rivaroxaban[77] appears equivalent to warfarin in stroke prevention and is less likely to produce intracranial hemorrhage but carries a higher risk of major gastrointestinal hemorrhage. Dabigatran, at the dosage of 150 mg twice daily[78] is associated with a smaller stroke risk and, like rivaroxaban, a lesser risk of intracranial hemorrhage but a higher risk of major gastrointestinal hemorrhage exists compared with warfarin.

The main concern with these agents is the lack of means to reverse their effect in the setting of hemorrhage. One patient taking dabigatran has died[79] from relatively minor head trauma leading to progressive intracranial hemorrhage. It may be possible to reverse the effects of rivaroxaban, but not dabigatran, through the use of prothrombin complex concentrate,[80] although dabigatran may be cleared through dialysis.[81] Fortunately, these agents have short half-lives and are cleared rapidly.[82] Nevertheless, care is enjoined in their use, both in the setting of renal insufficiency and in conjunction with aspirin.[83] Idarucizumab fully reverses the anticoagulant effects of dabigatran[84] and is now marketed as Praxbind. However, hemorrhage in patients using factor II and factor Xa antagonists will remain troublesome until means to reverse the anticoagulation produced by all these agents are developed, together with the capability to monitor the process in real time.

Venous sinus thrombosis is an uncommon condition that manifests with headache and papilledema, as well as focal symptoms, and often leads to ICH.[85] Diagnosis is by T2-weighted MRI and magnetic resonance venography, or by head CT and CT venography.[86] Treatment is with heparin acutely, even in the presence of ICH.[87] More recent reports have established the safety of low-molecular-weight heparin followed by 3 months of warfarin therapy for this condition, although only a trend toward favorable outcome emerged.[88] Retrograde thrombolysis through the venous system with tPA in conjunction with IV heparin is effective in more serious cases.[89]

Spontaneous dissection of the carotid and vertebral arteries is the subject of a review by Schievink.[90] This is a significant cause of stroke in younger individuals. Carotid dissection often presents with neck pain, radiating to the head, and with components of Horner syndrome (ptosis, miosis, and anhidrosis). Vertebral dissection

• BOX 60.14 Causes of Hypercoagulable States

Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden
Prothrombin gene mutation
Antiphosphilipid antibodies
Lupus anticoagulant

• BOX 60.15 Indications for the Use of Clopidogrel After Cerebral Ischemia

Recent acute coronary syndromes
Recent stent placement
Absolute aspirin intolerance including aspirin allergy
Coexistent symptomatic peripheral arterial disease

presents with pain in the neck or back of the head initially. Either may proceed to cerebral infarction or to retinal infarction in the case of carotid dissection. Magnetic resonance angiography diagnoses carotid dissection quite accurately and vertebral dissection less so.[91] Anticoagulation is commonly used but has not been subjected to a rigorous trial. The presence of dissection does not appear to contraindicate the performance of thrombolysis by whatever route.[92]

Box 60.14 lists the hypercoagulable states.[93] Most of these lead mainly to the development of venous thrombosis, although antiphospholipid antibodies and the lupus anticoagulant may produce both venous and arterial thrombosis. The duration of anticoagulation rests on the judgment of the treating physician. Three to 6 months of therapy is commonly undertaken if the episode of thrombosis is isolated.

Antiplatelet Agents in Stroke

Secondary stroke prevention continues to depend on aspirin, as it has for many years. A meta-analysis conducted in 1994[94] showed that antiplatelet therapy, primarily with aspirin, reduces the risk of stroke, MI, and vascular death by 25%. A similar analysis[95] focusing on stroke found a lesser benefit of aspirin, on the order of 13%. The optimal dosage of aspirin remains unknown, but low dosages such as 81 mg are commonly used to reduce the risk of systemic bleeding, which is dose-related.[96,97]

The limited effect of aspirin on stroke recurrence led to a search for other antiplatelet agents. Clopidogrel, a thienopyridine, has exhibited minimal benefit compared with aspirin in preventing stroke.[98] It has subsequently proved useful together with aspirin in the treatment of unstable angina[99] and acute MI[100,101] and after stent placement in the coronary vessels.[102]

However, two separate studies[103,104] have not only failed to show improved outcomes in stroke with such combination therapy when compared with either agent alone, but have also shown increased risk of systemic bleeding. Combination therapy may be useful in the setting of acute cerebral ischemia. Aspirin alone is beneficial in acute stroke when instituted within 48 hours of onset,[105] and one study conducted in China has shown benefit of clopidogrel when given in addition to aspirin within 24 hours of stroke onset.[106] A study is ongoing[107] to confirm these findings in an American population. Comparison of a newer thienopyridine, ticagrelor, against aspirin in the treatment of minor stroke and TIA has shown no difference in outcome.[108] Clopidogrel remains the drug of choice under certain restricted circumstances (Box 60.15). Clinicians often change therapy from one antiplatelet agent to another following the development of a cerebral ischemic event, but there is a significant failure rate with any of them. Aspirin will remain the agent of choice for most patients, in part because of its low price.

Patent Foramen Ovale

PFO is a recently recognized cause of cardiac embolization to the brain. PFO is detected by two-dimensional echocardiography with injection of agitated saline solution or by transesophageal study. In one report it appeared in 18% of young control subjects and in 40% of subjects with cryptogenic stroke. PFO was more common as well in younger as opposed to older patients with cryptogenic stroke (stroke of unknown origin following standard evaluation).[109] The combination of PFO with atrial septal aneurysm in stroke patients younger than the age of 55 years has been associated with a high (15.2% over 4 years) risk of recurrent stroke.[110] Others[111] have found a large diameter (>4 mm) of the PFO to predict increased risk of stroke recurrence. PFO can be treated with warfarin, aspirin, surgical closure, and now endovascular closure. No data suggest conclusively that one treatment surpasses the others.[112] Although there may be a modest benefit of closure, the procedure carries a potential risk of atrial fibrillation, and there is clear risk of procedural complication. At this time, closure of a PFO may be indicated in the absence of another explanation for multifocal infarction or after failure of medical therapy to prevent recurrent stroke.

Prolonged Cardiac Monitoring

Recent investigations have shown that prolonged cardiac monitoring reveals a significant incidence of atrial fibrillation lasting at least 30 seconds in subjects with stroke of unknown etiology (cryptogenic stroke). Thirty-day monitoring has shown a 16% incidence,[113] whereas implantable loop recorders have shown a 12% incidence at 1 year, rising to 30% after 3 years of monitoring.[114] In both studies, patients often began anticoagulation when atrial fibrillation was found, especially if it lasted for periods of 5 minutes or more. However, there is no consensus as to which type of monitoring is preferable, nor is it proven that the monitoring in fact reduces stroke incidence.[115]

Massive Hemispheric Cerebral Infarct

Infarction of the entire MCA territory leads to the development of the "malignant MCA" syndrome.[116] This major injury leads to death in 78% of cases in the first week after the ictus, as the result of cerebral edema leading to transtentorial herniation, and the survivors are quite disabled. Brain swelling peaks at 3 to 5 days after stroke onset.

The presence of early CT changes—namely, hypodensity of more than 50% of the MCA territory—indicates a poor prognosis.[117] In the absence of appropriate intervention, midline displacement of the pineal gland greater than 4 mm predicts death reliably. Large volume of infarction (Fig. 60.5) and displacement of the

• **Fig. 60.5** Massive middle cerebral artery (MCA) infarct. Hypolucency of the entire right MCA territory *(open arrows)* and compression of the right lateral ventricle *(white arrows)* are demonstrated.

septum pellucidum also indicate a poor outcome.[118] At initial presentation, aphasia or neglect may be present, depending on the hemisphere affected. Characteristically, the patients display hemiplegia and a dense hemisensory loss, although the leg may be relatively spared. Quite often, there is a forced eye deviation and hemianopia may coexist. The mortality rate is higher in older individuals with this syndrome,[119] but transtentorial herniation is a more significant cause of death among younger subjects with ischemic stroke.[120] Presumably younger individuals have less cerebral atrophy and less room within the cranial vault to accommodate brain swelling.

Treatment of this syndrome has so far proved disappointing, as reviewed by different authors.[121–123] The review by Wijdicks[123] is particularly comprehensive. Standard therapies include hyperventilation and the administration of IV mannitol. Mannitol is a dehydrating agent, an osmotic diuretic, that aims at reducing cerebral volume and thus ICP. It is given initially at a dosage of 1 g/kg, followed by recurrent dosing 4 times daily with 0.25 to 0.5 g/kg. The goal of therapy is a serum osmolality of 315 to 320 mOsm/L. Mechanical ventilation with hyperventilation produces hypocarbia, which leads to cerebral vasoconstriction, reduced cerebral blood volume, and decreased ICP. The target range for partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is not well defined. Steiner and colleagues[122] state that lowering the partial pressure of carbon dioxide (PCO_2) from "35 to 29 mm Hg lowers ICP by 25% to 30% in most subjects." The benefit of these interventions in clinical practice appears to be short-lived. Because hyperventilation is associated with decreased blood flow, it should be viewed as a temporizing measure only.

• BOX 60.16 Indications for Critical Care Consultation

Intubation and mechanical ventilation
Administration of continuous infusions of antihypertensive agents
Administration of pressor agents
Monitoring not feasible in other settings
Intraventricular drainage

More promising therapies include hypothermia and decompressive hemicraniectomy. Hypothermia in one pilot trial[124] lowered ICP temporarily when instituted within 14 hours of onset of major MCA stroke. Hypothermia has also been used[125] shortly after thrombolysis. The use of a device placed in the inferior vena cava lowers body temperature much more quickly than surface cooling,[126] although there is a concern regarding the development of DVT. Hypothermia to 33°C for 24 hours, after tPA administration within 6 hours of stroke onset, is safe, apart from an increased risk of pneumonia.[127] A larger randomized trial of hypothermia after thrombolysis was stopped prematurely but showed trends toward increased mortality and increased pneumonia among the hypothermia patients.[128]

Decompressive hemicraniectomy with durotomy in early studies appeared beneficial when compared with medical treatment,[129] particularly when intervention occurred before the appearance of signs of incipient herniation.[130] However, the surgically treated patients in these two reports differed significantly from the control patients. The surgical patients were younger, and subjects with large left hemispheric infarcts producing global aphasia were not considered for surgery. Some, if not all, of the benefit in the surgically treated group may be explained by this imbalance between the control and treated groups. More recently, three randomized trials have been cojducted[131–133] and a preplanned pooled analysis[134] of their results published. Two of these studies were terminated prematurely.[131,132] All the studies revealed reductions in mortality rate, but benefits in functional outcome were lesser and not consistently significant. The pooled analysis, looking at the benefit of hemicraniectomy in patients younger than 60 years of age treated within 48 hours, showed significant benefits both in mortality rate and in functional outcome, such that hemicraniectomy has been adopted into general practice. A subsequent study, DESTINY II (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY II),[135] has shown benefit of hemicraniectomy in subjects older than 60 years. Mortality fell, but the subjects remained significantly disabled, with Rankin Scale scores of 3 or greater. The decision to proceed must take note of patient and family opinions as to acceptable quality of life.

Surgical intervention also exists for cerebellar infarction, which, when large, may expand and place pressure on the brainstem.[136] Both ventriculostomy to relieve hydrocephalus acutely and decompressive craniotomy are used. The main determinant of survival and recovery is the absence of coma on presentation. Surgery is the accepted treatment, but the exact timing of intervention remains uncertain.[137]

Critical Care Consultation

Critical care consultation for stroke patients is indicated for a number of reasons (Box 60.16).

Summary

In conclusion, stroke therapy is advancing significantly. Thrombolysis and endovascular therapy have developed over the past 20 years. Advances in radiology have improved imaging of strokes and of blood vessels and will facilitate patient selection for acute intervention. Endarterectomy has become established in the treatment of carotid disease and angioplasty and stenting for the treatment of high-risk cases. New anticoagulants have appeared, although they are not free of risk. No longer is aspirin the only antiplatelet agent available. Decompressive surgery can save lives that would otherwise be lost. Much of this activity has taken place in the critical care unit. As our means for intervention increase, so will the role of critical care in reducing death and disability from stroke.

Key Points

- Determine time of onset of all new strokes.
- Consider IV thrombolysis with tPA if within 4.5 hours of onset.
- Consider endovascular intervention for basilar thrombosis or if within 6 hours of stroke onset.
- Consider rescue therapy with mechanical clot extraction if IV tPA is not efficacious and there is an arterial clot.
- Observe published guidelines for blood pressure control.
- Use MRI and magnetic resonance angiography or CT and CTA to visualize the brain and its vasculature.
- Proceed promptly to carotid endarterectomy or carotid angioplasty and stenting.
- Administer anticoagulants when indicated.
- Use antiplatelet agents according to specific indications.
- Treat malignant MCA infarction with craniectomy.
- Consider surgical intervention for large cerebellar infarcts.
- Consider prolonged cardiac monitoring after cryptogenic stroke.

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The complete list of references can be found at www.expertconsult.com.

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Review Questions

1. A 58-year-old patient with history of hypertension and paroxysmal atrial fibrillation (AF) is admitted to the emergency department (ED) for new-onset global aphasia, right face, arm, and leg within 3 hours. The National Institutes of Health Stroke Scale (NIHSS) score is 18. The only treatment option associated with improved functional outcomes at 3 months is which of the following?

a. Intravenous (IV) heparin drip
b. Recombinant tissue plasminogen activator (tPA)
c. Intraarterial tPA
d. Therapeutic induced hypothermia

Answer: b. IV thrombolysis with recombinant tPA is the only intervention associated with improved functional outcome at 3 months. The 1995 National Institutes of Neurological Disorders (NINDS) trial demonstrated an effect on functional outcome but not mortality rate at 3 months. Subsequent studies and reanalysis have demonstrated this robust effect. Heparin may not be indicated in paroxysmal AF–related stroke, at least in the first days, because of the higher risk of hemorrhagic convertion. Intraarterial thrombolysis with tPA has been studied in this setting. There are some modest results indicating that rates of recanalization are better without meaningful translation into outcomes. Hypothermia has not been associated with improved outcomes in ischemic stroke but ongoing trials are testing this hypothesis.

2. Which of the following is *not* a contraindication for IV tPA within the 3- to 4.5-hour window?

a. Prior stroke
d. History of diabetes mellitus
c. Unruptured aneurysm
d. Age older than 80 years

Answer: c. A history of unruptured or treated cerebral aneurysms is not a contraindication for the administration of IV tPA. However, one must be careful to determine if the reason for the admission or neurologic symptoms is related to a ruptured cerebral aneurysm (i.e., worst headache of life, subarachnoid blood in the computed tomography [CT]). Age older than 80 years, history of prior ischemic stroke, diabetes mellitus, and anticoagulation (even if the international normalized ratio [INR] is <1.7) are all contraindications for the administration of IV tPA within the 3- to 4.5-hour window.

3. Which of the following does *not* increase the chance of hemorrhagic conversion after ischemic stoke?

a. Diabetes mellitus
b. Uncontrolled hypertension
c. Lower score in the NIHSS
d. Thrombocytopenia

Answer: c. The score in the NIHSS is inversely related to the risk of hemorrhagic conversion. This means that larger strokes will be associated with a higher risk of hemorrhagic conversion. Hyperglycemia, uncontrolled hypertension, and thrombocytopenia are all independent predictors of hemorrhagic transformation after cerebral infarction. The risk increases with the administration of IV tPA.

4. Which of the following is the best treatment option for cerebral edema associated with lower mortality rate and improved functional outcome in a 48-year-old woman with a large left middle cerebral artery infarction secondary to a left internal carotid artery dissection?

a. Targeted temperature management for induction of hypothermia
b. Decompressive hemicraniectomy (DHC)
c. Hypertonic saline
d. Hyperosmolar therapy

Answer: b. The only intervention, based on three major randomized clinical trials, associated with improved mortality rate and functional outcome for large hemispheric infarction (also known as malignant middle cerebral artery stroke) is DHC. All other interventions are associated with improved measures in cerebral edema, intracranial pressure, and cerebral complications, but not with mortality rate or functional outcome benefit.

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Myasthenia Gravis and Guillain-Barré Syndrome

CHERYLEE W.J. CHANG

CHAPTER OUTLINE

Guillain-Barré Syndrome
- Incidence
- Pathophysiology
- Clinical Presentation
- Differential Diagnosis
- Diagnostic Testing
- Clinical Course
- Treatment
- Prognosis

Myasthenia Gravis
- Clinical Presentation
- Pathophysiology and Prognosis
- Diagnosis
- Treatment
- Medications to Avoid
- Mortality

Complications
- Respiratory Failure
- Pain and Sensory Disturbance
- Other Complications

Historically, the most common neuromuscular condition that required prolonged mechanical ventilation (MV) was poliomyelitis.[1,2] The epidemics of the 1940s and 1950s resulted in large polio wards with negative-pressure ventilators.[2] With the advent of the Salk vaccine, however, this is no longer the case. Currently, Guillain-Barré syndrome (GBS) and myasthenia gravis (MG) account for the majority of patients with neuromuscular illness requiring intensive care.[3]

Guillain-Barré Syndrome

Incidence

GBS is an acute inflammatory polyneuropathy with a reported incidence of 1.1 to 1.7 per 100,000 persons per year in 1980.[4,5] A recent meta-analysis of 13 studies of GBS performed between 1935 and 2002 reported crude incidence in North America and Europe from 0.81 to 1.89 (median, 1.11) cases per 100,000 person-years. The rate of GBS increases exponentially with age, with a regression analysis showing a 20% increase in the average GBS rate for every 10-year increase in age with an incidence of 2.22 per 100,000 after 70 years of age. The risk of GBS is higher for males than females.[6]

Pathophysiology

GBS, also known as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is an immune-mediated injury affecting the motor and sensory peripheral nerves. Although initially described as a demyelinating process with loss and dysfunction of the myelin sheath, an axonal variant with damage or degeneration of the nerve cell axon is also described.[7] With the former, classically, nerve conduction velocity studies confirm a demyelinating process with slowing of the conduction velocity and an increase in the distal latency of the neurons. In the axonal variant, there is a decrease in the amplitude of the compound motor action potential. This axonal variant, also known as an acute motor axonal neuropathy (AMAN), had been considered to have a slower recovery pattern and worsened prognosis; however, more recently it is recognized that these patients can show two patterns of clinical recovery. In contrast to the uniform recovery of patients with AIDP, some patients with AMAN have a rapid recovery, whereas others have a more prolonged course; however, even the most severely disabled patients are usually able to walk independently within a few years.[8,9] Rapid recovery is explained by a subset of patients who have early resolution of physiologic conduction failure at the nodes of Ranvier in the motor fibers or by collateral sprouting of surviving axons.[10]

GBS is an autoimmune disease that is triggered by a preceding bacterial or viral infection. *Campylobacter jejuni,*[11] *Haemophilus influenza,*[12] *Mycoplasma pneumonia*, cytomegalovirus,[13] Epstein-Barr virus, and Lyme virus have been associated with GBS. More recently, mosquito-borne viruses such as the alphavirus, Chikungunya,[14] and the flavivirus Zika have been associated with GBS. It is estimated that GBS develops in 1 in 4000 (0.24/1000) affected with a Zika viral infection. This is lower than the estimate following a *C. jejuni* infection (0.3–1.17/1000).[15,16] The delayed interval between a Zika or Chikungunya viral infection and onset of neurologic symptoms of 3 to 12 days is consistent with a postinfectious autoimmune mechanism as opposed to the direct neurotropic effects of other flaviviruses such as the West Nile Virus and Japanese encephalitis virus.[14]

In the AMAN form of GBS, the infectious organisms share homologous epitopes to a component of the peripheral nerve. The molecular mimics are glycans expressed on lipooligosaccharides from a microbial stimulus such as *C. jejuni* that induces a humoral response with primarily complement-fixing immunoglobulin (Ig) G1 and IgG3 antibodies that cross-react with axonal components mainly against gangliosides G_{M1} and G_{D1a}, but also against GM_2, GD_{1b}, and GT_{1b}.[17–19] Antibodies fix complement, recruit macrophages, and deposit membrane complex in the axolemmal membrane. If the immune injury to the neuronal membrane disrupts the anatomic integrity of the nerve, the patient will exhibit slow recovery. When the immunologic injury is targeted to the membranes in the nerve terminals or nodes of Ranvier causing a nerve conduction blockade, a more rapid recovery is expected.[10,20] In AIDP, the immune reaction is targeted to epitopes of the Schwann cell or myelin. Interestingly, the more common form of GBS in Europe and North America is AIDP, whereas AMAN is more frequently reported in East Asian countries such as China and Japan. This is likely due to geographic genetic variants of the viruses.[21]

Clinical Presentation

GBS often presents as a symmetric ascending flaccid paralysis typically starting in the legs followed by arm weakness. Because GBS is a demyelinating or axonal degenerating process of the lower motor neuron, patients are areflexic, although early in the course, deep tendon reflexes may be present. Symptoms may also include paresthesias if the sensory nerves are involved. The autonomic system can be involved. These patients exhibit cardiac arrhythmias, including severe, life-threatening bradycardia, orthostatic hypotension, sweating abnormalities, urinary retention, and gastrointestinal dysfunction, or unreactive, dilated pupils.[22,23] The degree of weakness is often graded using the British Medical Research Council (MRC) scale for muscle strength. On this scale, 5 indicates normal power; 4 opposes resistance; 3 opposes gravity; 2 moves the joint with active movement with gravity eliminated; 1 is a flicker or trace contraction; and 0 reflects absent contraction. Severe weakness is defined as MRC grade or 2 or lower.[24]

A clinical variant of GCS includes a classic triad of ataxia, areflexia, and ophthalmoplegia causing diplopia. This is known as the Miller Fisher syndrome (MFS). An overlap syndrome of GBS and MFS can result in evolution of further cranial nerve involvement with facial and bulbar weakness and varying degrees of limb weakness and respiratory failure. MFS is often associated with serum antibodies to GQ_{1b}.[25–27] The GQ_{1b} epitope has been found in the lipopolysaccharide of *C. jejuni* isolated from patients with MFS.[26] An anti-GQ_{1b} mouse monoclonal antibody immunostains the paranodal regions of the extramedullary portion of the human oculomotor, trochlear, and abducens nerves and weakly stains the deep cerebellar nuclei.[25] In addition, biochemical analysis shows that the human oculomotor nerve contains more GQ_{1b} than does the ventral and dorsal horn of the spinal cord.[17] Therefore it is thought that the anti-GQ_{1b} antibodies account for the ophthalmoplegia found in MFS. Some have suggested that patients with MFS may be less responsive to immunomodulatory therapy than those with classic GBS.[28]

Other closely related autoimmune entities along the continuum of GBS and MFS include an isolated acute ophthalmoplegia with elevated anti-GQ_{1b} IgG titers[29] and Bickerstaff brainstem encephalitis (BBE) with elevated anti-GQ_{1b} IgG antibody titers in up to 66%.[30] Again, both have an antecedent history of infectious symptoms within 4 weeks of the onset of neurologic symptoms. BBE is characterized by a progressive, relatively symmetric ophthalmoplegia and ataxia with mental status changes including coma or stupor or pyramidal signs such as hyperreflexia or pathologic reflexes. Pupillary abnormality and bulbar palsy are also seen. Like MFS, neither the isolated acute ophthalmoplegia entity nor BBE have significant limb weakness with strength 5 or 4 on the MRC scale unless there is an overlap syndrome with classic symptoms of GBS.

Differential Diagnosis

The clinical history and pattern of rapidly progressive limb weakness can help pinpoint the diagnosis. The differential diagnosis may include botulism, organophosphate poisoning, MG, or a spinal cord lesion (Table 61.1). However, GBS presents with a history

TABLE 61.1 Clinical Patterns of Acute Neuromuscular Weakness

Cause	Cranial Nerve Involvement	Limb Weakness	Reflexes	Sensory	Autonomic Changes
Guillain-Barré syndrome	Common, facial diplegia	Distal (ascending)	Absent	Common	Possible (20%)
Miller Fisher syndrome	Hallmark: ophthalmoplegia	Variable Hallmark: ataxia	Absent	Rare	Rare
Myasthenia gravis	Common, ptosis, facial, oculomotor	Proximal (shoulders and thighs)	Normal	Present	Present
Botulism	Symmetric diplopia, ptosis, dysarthria, dysphagia	Descending	Absent or decreased	No	Yes (e.g., ileus, mydriasis, reduced salivation, urinary retention)
Organophosphate poisoning	Bulbar dysfunction, dysarthia, dysphagia	Diffuse	Decreased	Late	Yes (e.g., bradycardia, sialorrhea, bronchorrhea, lacrimation, diarrhea, miosis causing blurry vision)
Brainstem	Common, ocular movement	Crossed findings (face/limbs)	Increased	Common	Rare
Spinal cord	No	Quadriparesis or paraparesis	Decreased then increased	Loss below level	If above thoracic level

of a viral or diarrheal prodrome followed in 1 to 2 weeks by a rapidly progressive, monophasic disease course typically lasting 1 month. The pattern of weakness typically includes a symmetric ascending paralysis with bilateral facial weakness.

A patient with botulism may also have a symmetric pattern, but initial symptoms are descending with initial facial and bulbar weakness. The symptoms associated with botulism typically include diplopia, ptosis, dysarthria, and difficulty swallowing followed by a descending pattern of appendicular weakness. Arreflexia is seen with both GBS and botulism; however, botulism does not have sensory findings. Autonomic findings can be found in both conditions, but botulism is more likely to include mydriasis and urinary retention.

Patients with organophosphate poisoning should have an exposure history. Because organophosphates are acetylcholinesterase inhibitors, symptoms are those of excessive cholinergic stimulation with fasciculations followed by diffuse weakness, blurry vision, miosis, and bulbar dysfunction, and autonomic dysfunction such as bradycardia, sialorrhea, bronchorrhea, lacrimation, emesis, and diarrhea. Decreased reflexes and late sensory findings can also occur.

Patients with MG, which is detailed later in this chapter, present with proximal weakness of the shoulder and hip girdle with difficulty holding their arms over their head (e.g., to brush their hair) or difficulty climbing stairs. Commonly, MG presents with ocular findings including ptosis, diplopia owing to oculomotor dysfunction, and facial weakness. Reflexes are typically normal. Sensory and autonomic dysfunction have not been well recognized but can be seen with MG.

Other forms of rapidly progressive weakness that arise from the central nervous system include brainstem pathology, such as tumor, hemorrhage, or ischemic stroke; however, motor findings are typically asymmetric and crossed—for example, ipsilateral face with contralateral arm and leg weakness. Deep tendon reflexes are brisk owing to involvement of the upper motor neurons. Depending on the level of injury, eye movement and sensation are also affected. Spinal cord pathology will have typically caused a sensory and motor level that is referable to the level of spinal cord injury. In patients with injury above the thoracic level, autonomic changes, such as bradycardia and hypotension, can be seen owing to dysfunction of the sympathetic system that has thoracic innervation.

Diagnostic Testing

Electrophysiology testing of the nerves demonstrates slowing of the nerve conduction, an increase in latency, or an axonal loss with decreased amplitude of the compound motor action potential. In addition, cerebrospinal fluid (CSF) testing can be helpful. Although a small percentage (<15%) may have a mild pleocytosis (5–50 cells/μL),[31] the hallmark of GBS is an elevated CSF protein level with lack of cells that is known as CSF albuminocytologic dissociation. In one study, nearly 50% of patients had elevated CSF protein concentration in the first few days and 83% had elevated concentration by 8 to 14 days.[31]

The serum level of anti-$G1_b$ IgG antibody may be a more sensitive marker for detecting MFS, because CSF albuminocytologic dissociation was found in 59% of 123 MFS patients during the first 3 weeks of illness, whereas the serum anti-GQ_{1b} IgG antibody result was positive in 85% with the peak within the first week of illness.[32]

Neurodiagnostic imaging studies are not useful in diseases of the peripheral nervous system such as GBS; however, in the spectrum of the autoimmune, BBE has been associated with abnormal high-intensity areas on magnetic resonance imaging (MRI) T2-weighted images in about one-third of patients.[33] Areas involved include the brainstem, thalamus, cerebellum, and cerebrum, and symptoms may wax and wane depending on the clinical course.[34]

Clinical Course

Patients reach their nadir by 4 to 6 weeks. The progressively worsening phase typically lasts less than 1 week in half of patients, less than 2 weeks in 80%, and less than 4 weeks in 97%.[31] Typically there is a plateau of 7 days to several months, although the recovery phase ensues thereafter. Nine percent to 10% of patients exhibit treatment-related fluctuation that by definition occurs within 8 weeks of start of treatment.[31,35] In one cohort, about 5% of patients exhibited a clinical deterioration after 8 weeks of weakness onset. When more than two recurrent deteriorations occur, the clinician should consider the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). The clinical course of CIDP is stepwise and fluctuating. It typically has a less severe course and is less likely to be associated with respiratory failure and cranial nerve dysfunction.[20] CIDP is treated with corticosteroids, whereas AIDP is not.[35]

Treatment

Plasma Exchange

Given the autoimmune etiology of GBS, treatment targets inactivation of complement, removal of idiotypic antibodies, cytokine inhibition, and saturation of Fc receptors on macrophages. To remove the antibodies, plasma exchange (PE) was first introduced as a potential treatment in 1978.[36] Subsequently, multiple trials comparing PE with supportive care alone have shown significant improvement in outcome at 4 weeks.[37–39] Studies typically use disability scales such as the Hughes Functional Grading Scale to grade outcome: grade 0 is a normal functional state; grade 1 is the ability to run with minor signs and symptoms; grade 2 is the ability to walk 5 m independently; grade 3 is the ability to walk 5 m with assistance; grade 4 is bedbound or chairbound status; grade 5 indicates the requirement for assisted ventilation; and grade 6 is death.[40]

The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome trial showed that four courses of PE treatments were better than two courses in bedbound patients who were not ventilated mechanically. Specifically, of 155 patients treated with 4 PE courses, 64% recovered full muscle strength after 1 year compared with 48% of 149 treated with 2 courses.[41] In a parallel trial, 161 ventilator-dependent patients were randomly assigned to receive four or six courses of PE and showed no significant differences in recovery. Overall, PE decreases the likelihood of worsening when treatment is started when the patient is still ambulatory and decreases the time on MV and time to independent ambulation by 50%. For this reason, although the optimal number and volumes exchanged is not yet established,[42] based on previous trials,[45,47] the recommendation is to perform 5 exchanges totaling 200 to 250 mL/kg every other day or over about 10 days. Additional information from the French Cooperative Group showed that fresh frozen plasma was associated with more adverse incidents than albumin when used as a replacement fluid during PE.[43]

Intravenous Immunoglobulin

Intravenous Ig (IVIg) can modulate complement activation products, neutralize idiotypic antibodies, saturate Fc receptors on macrophages to prevent activation, and suppress various inflammatory mediators such as cytokines, chemokines, and matrix metalloproteinases.[44] The

first trial of IVIg was in 1988.[45] Multiple randomized controlled trials of immunotherapy have shown that both PE and intravenous administration of pooled γ-globulin (IVIg) are equally effective for the treatment of GBS.[46–51] The standard dose is 0.4 g/kg daily for 5 days.

The choice of using IVIg over PE may include the availability of the different modalities locally; however, for patients with issues such as severe hemostasis, unstable hemodynamics, or uncontrolled sepsis, IVIg is likely to be better tolerated. In this subset of patients who received IVIg for 6 days compared with 3 days of treatment, a randomized, double-blind, multicenter phase II trial showed that mechanically ventilated patients benefited significantly, with a drop from a mean of 152 days (range 54–332 days) to 86 days (range 13–151 days) when given the 6-day course of treatment.[52]

Current recommendations for nonambulatory or mechanically ventilated patients with GBS includes treatment with PE or IVIg as early as possible and at least within 4 weeks of symptom onset.[42,53] For milder cases of GBS in which ambulation is preserved, recommendations are to consider treatment within 2 weeks of symptom onset.

In severe GBS, combined therapy of PE followed by IVIg in 128 patients compared to PE in 121 patients showed no significant advantage in 4-week disability outcome, time to independent walking, duration of ventilation, or death, or in 12-month outcome of death or disability.[49] In a nonrandomized trial comparing PE followed by IVIg in 24 patients to PE alone in 13 patients also showed no difference in outcome.[54] Therefore combination therapy of PE and IVIg for GBS is not recommended as it increases cost but has not been shown to improve outcome.

Although either plasmapheresis or immunoglobulin therapy has been shown to be equally effective in altering the course of GBS, multiple studies of enteral and parental corticosteroids have not.[46,55] A multicenter randomized trial of prednisolone in patients with BGS showed greater improvement in the control group than the prednisolone group with a higher rate of relapses in those treated with prednisolone.[40] For this reason, corticosteroid treatment is not used for GBS.

Prognosis

The prognosis for the Miller Fisher variant is good; recovery typically begins within 2 to 4 weeks of symptom onset and full recovery occurs within 6 months. BBE, despite altered mental status changes, also has a good outcome; 50% of patients show complete remission with no residual outcomes by 6 months.[30]

Most patients with GBS begin recovery within the first weeks. However, after discharge, 72% may have sensory disturbances and 89% have residual weakness. At 1 year, about one-third of patients feel completely cured,[56] although up to 14% may have persistent disability.[57] Approximately one-third are unable to return to their previous work.[56] Some patients have reported recovery in up to 2.5 to 6.5 years after onset.[58] However, of those who survive, most do well with more than 80% able to walk independently at 6 months.[57] Even 79% of those who require MV eventually regain independent ambulation.[59]

As noted previously, compared with patients with AIDP, those with AMAN typically have either a slow recovery (inability to walk independently at 6 months) or rapid recovery (improvement by 2 Hughes grades or more within the first 4 weeks). Patients with AIDP have a more uniform recovery time for improvement of one grade.[8,9]

GBS has a mortality that varies between 1% and 18%, with the higher rate of 10.4% to 38.3% found in those who require MV.[59–61] The most common causes are pneumonia, sepsis, acute respiratory distress syndrome, pulmonary embolism, or autonomic dysfunction with dysrhythmias.[57] Predictors of mortality include older age, MV, cardiac complications, and sepsis.[5,62]

Myasthenia Gravis

MG affects approximately 15 to 20 per 100,000 people in the United States.[63] A systematic literature review of 31 studies published between 1980 and 2007 estimated a worldwide incidence of 30.0 per 1,000,000/year with a noted increase over time that is attributed to greater awareness and improved methods of diagnosis rather than a true increase in incidence.[64] In a U.S. national inpatient database, MG has a bimodal distribution such that it could be considered a disease of young women and old men. Women have a two to three higher admission rate during the first 5 decades, whereas men have a higher rate of admission during the sixth, seventh, and eight decades. In this database, older age and respiratory failure were the predictors of death.[65]

Clinical Presentation

The clinical characteristics of MG include a fatigable muscle weakness of the limb, ocular, facial, oropharyngeal, and respiratory muscles. In those with limb weakness, the initial presentation often is weakness of the proximal—that is, limb girdle muscles with difficulty climbing stairs or raising arms over one's head in tasks such as brushing one's hair. More than 50% of patients present with diplopia and ptosis; others have difficulty with mastication, whereas bulbar findings such as dysarthria and dysphagia are the presenting symptoms in about 15%.[66–68] If MG is associated with a thymoma, also known as paraneoplastic MG, it often presents with ocular, bulbar, neck, and respiratory symptoms rather than appendicular weakness.[69] Those presenting with ocular and bulbar symptoms may be differentiated from another acute neurologic diagnosis—botulism toxin poisoning—by clinical history as it lacks an exposure event, even though both can present with similar clinical findings. Of those with a primarily ocular presentation, the generalized disease develops in approximately half within 2 years.[66,70] The Osserman classification is utilized by the Myasthenia Gravis Foundation of America and allows the standardization of clinical symptoms (Table 61.2).[71]

Pathophysiology and Prognosis

Although both MS and GBS are autoimmune diseases, unlike GBS, in which antibodies target the peripheral nerve, MG affects the neuromuscular junction (NMJ). Autoantibodies are directed against the muscle acetylcholine receptor (AChR) in approximately 85% of patients[72] or to the muscle-specific tyrosine kinase (MuSK) in approximately 50% to 70% of patients who do not have autoantibodies against the AChR.[73–75] Both sites are on the postsynaptic membrane of the NMJ. Autoantibody binding to proteins at these sites leads to impaired neuromuscular transmission and muscle weakness. MuSK is an enzyme critical for the formation and maintenance of the NMJ by agrin-induced AChR clustering.[73,76] Anti-AChR and anti-MuSK antibodies account for more than 90% of cases of MG.[77]

The anti-AChR antibodies in MG are of the IgG subclass 1 or 3 and affect the NMJ by three mechanisms: (1) causing complement activation with destruction and focal lysis of the postsynaptic folds at the NMJ and the destruction of the AChR and AchR-related

TABLE 61.2 Osserman Classification Used by the Myasthenia Gravis Foundation of American to Standardize Clinical Symptoms[71]

Class I	Any ocular muscle weakness
Class II	Ocular muscle weakness of any severity, MILD limb weakness
Class IIa	Predominantly limb and/or axial muscle weakness
Class IIb	Predominantly bulbar and/or respiratory muscle weakness
Class III	Ocular muscle weakness of any severity, MODERATE weakness of other muscles
Class IIIa	Predominantly limb and/or axial muscle weakness
Class IIIb	Predominantly bulbar and/or respiratory muscle weakness
Class IV	Ocular muscle weakness of any severity, SEVERE weakness of other muscles
Class IVa	Predominantly limb and/or axial muscle weakness
Class IVb	Predominantly bulbar and/or respiratory muscle weakness
Class V	Intubation with or without mechanical ventilation

proteins at the end plate; (2) cross-linking the adjacent AChRs, which causes early internalization and degradation of the receptors; and (3) blocking the acetylcholine-binding site. Anti-AChR antibody levels generally correlate with but do not precisely predict disease severity and response to treatment.[74]

The anti-MuSK antibodies in human MG are predominantly of the IgG 4 subclass and do not activate complement.[78] Their action may be that they bind to the N-terminal portion of the extracellular domain of MuSK, which has been shown in vitro to inhibit agrin-induced AChR clustering, which causes AChR dispersion and end plate disruption.[73,79] Interestingly, it appears that anti-MuSK IgG interferes with the anchoring of MuSK to the collagen tail (ColQ) of the end plate acetylcholinesterase (AChE), which is responsible for the hydrolysis of acetylcholine (ACh). At the NMJ, three tetramers of AChE are linked by ColQ; however, disruption of this complex by anti-MusK antibody makes the AChE complex less effective.[80] Similarly, human congenital defects of ColQ cause an end plate AchE deficiency and result in a myasthenic syndrome.[81,82] This may provide an explanation for the finding that MuSK antibody–positive patients are less responsive to AChE inhibitors.

Antibodies to other muscle antigens are also found in patients with MG. Up to 95% of patients with thymoma and 50% of patients with late-onset MG without thymoma have autoantibodies to striated muscle antigens such as titin and ryanodine receptors (RyR). Titin is a large protein that develops the passive force in stretched sarcomere.[83] Ryanodine is the calcium channel of the sarcoplasmic reticulum that releases calcium into the sarcoplasm and results in muscle contraction. In vitro RyR antibodies can inhibit calcium release. MG patients with RyR antibodies have been described as having a characteristic presentation of bulbar, respiratory, and particularly neck weakness.[84] Also, titin and RyR antibodies also may target cardiac muscle antigens, and myositis and myopathy with atrophy are seen in some thymomatous MG patients.[85] With the high likelihood of finding titin or RyR antibodies in the presence of thymoma, their presence can facilitate the diagnosis of thymomatous MG as they typically indicate a thymic pathology.[86]

More recently, antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) were found to be present in 1% to 3% of all patients with MG[87] and in 9.2% of patients with double-seronegative MG.[88] LRP4 is a newly identified receptor for agrin that increases agrin interaction with MuSK to activate the kinase and initiate downstream signaling cascades for AChR clustering essential for NMJ formation.[89] These antibodies inhibit binding of LRP4 to its ligand and belong to the IgG1 subclass that activates complement. These patients typically have mild to moderate symptoms; however, more information is needed to elucidate differences in their response to therapy. The remaining patients were considered to have idiopathic or "seronegative" MG; however, they too have autoantibodies, and like those with antibodies against AChR and MuSK, will benefit from treatment targeting immunosuppression or immunoabsorption.[90]

The thymus is the site of maturation for T cells. Thymic hyperplasia and thymoma are risk factors for MG with anti-AChR antibodies.[91–93] MG develops in 50% of patients with thymoma,[94,95] whereas 15% of MG patients have thymomas.[96] A thymoma associated with MG is typically a neoplasm derived specifically from thymic cortical epithelial cells. Cortical thymomas have properties that propagate the maturation of immature naïve CD4 T cells and export mature naïve T cells into the periphery and create this paraneoplastic syndrome. In contrast, thymomas histologically similar to medullary thymic tissue lack developing T cells and are not usually associated with MG.[97,98]

Thymomas occur equally in males and females and are uncommon in children and young adults. The incidence rises in middle age and peaks in the seventh decade of life.[99] The overall incidence in the United States is 0.13 per 100,000 person-years.

Thymomatous MG has a pattern similar to late-onset MG. Both are associated with a later age of onset, lower AChR antibody titer, the presence of titin or RyR antibodies, a more severe course, the frequent need for immunosuppressant medications, and a higher mortality rate. In contrast, patients with early-onset nonthymomatous MG typically have an elevated AChR antibody concentration, almost no titin or RyR antibodies, a lower requirement for immunosuppressive medications, a less severe course, low MG-associated mortality rates, and a favorable thymectomy outcome.[100]

Classification of MG into different subtypes such as those found in Table 61.3 may be helpful to identify and predict prognosis and the clinical response to various treatment modalities.[101–103] New work identifying subgroups based on early onset, late onset, thymomatous, MuSK, LRP4, seronegative, and ocular MG is attempting to adapt existing therapy to the characteristics of the individual patient.[104]

Diagnosis

The diagnosis of MG is based in part on the clinical history of fatigable weakness in the patterns discussed earlier. Edrophonium, a short-acting parenteral AChE inhibitor, was previously available to administer at the bedside to determine whether the patient had improved strength compared to a placebo of saline solution.[105] It is no longer widely available. Neostigmine, an AChE inhibitor that is longer-acting and easily available because it is used for reversal of neuromuscular blocking agents in the postoperative arena, can also be used.[106,107] Close care is needed during administration of a parenteral AChE inhibitor, especially the longer-acting neostigmine, to monitor for parasympathetic effects such as bradycardia,

TABLE 61.3 Serologic and Clinical Presentation of Myasthenia Gravis Subgroups[84,100–104,136]

	AChR Antibody	MuSK Antibody	Striated Muscle Antigens Titin Antibody Ryr Antibody	Age at Onset Sex	Clinical Findings	Response to Therapy	Response to Thymectomy	Prognosis
Ocular MG	50%–75%	None	None	Older Males	Ocular	Good	Good	Good (but 50% can develop generalized MG in 2 yr)
Early-onset generalized MG	80%–85% (high titer)	None	None-rare	<50 yr	General	Rarely needs immunosuppression	Good	Less severe Low mortality
Late-onset generalized MG	None–rare	None	50% 54% titin 33% RyR	≥50 yr	General	Often requires immunosuppression	Poor	Severe
Thymomatous-associated MG	Positive, nearly 100% (low titer)	None	95% 50% titin 47% RyR	Ranges: Older but <40 yr if RyR	General If RyR: ocular, bulbar, respiratory weakness	Often requires immunosuppression	Fair	RyR: invasive, malignant thymoma Severe Higher mortality
Generalized MG MuSK positive	None	100%	None	Younger Female	Facial, bulbar, neck, respiratory weakness paraspinal, esophageal muscles	Poor response to AChE inhibitors	Poor (no thymic changes)	Severe, progressive course
MG with thymic hyperplasia	89%	None	None	Younger Female	General	Good	Good	Good
ACh antibody negative	Negative	Negative	Present	Younger Female	General	Poor		Fair

ACh, Acetylcholine; *AChE*, acetylcholinesterase; *MG*, myasthenia gravis; *RyR*, ryanodine receptor.

sialorrhea, and bronchoconstriction. Atropine should be readily available for administration during the testing. An ice-pack test can be used in ocular MG patients who present solely with mild ptosis. An ice pack is placed over lightly closed eyes for 2 minutes with resultant improvement in ptosis.[108]

Confirmation can be made by electrodiagnostic studies with a characteristic decremental response to a 2- to 3-Hz repetitive nerve stimulation on electromyographic examination. This classic finding is seen in two-thirds of MG patients.[109] Single-fiber electromyography is more sensitive but less specific and technically more difficult. Increased jitter, or variability of the time interval between the action potential of two single muscle fibers in the same motor unit with a normal fiber density is suggestive of MG.[110,111]

Serologic examination for autoantibodies against AChR, MuSK, LRP4, and striated muscle (i.e., titin and RyR) should be performed to confirm the diagnosis and help direct therapy. Anti-AChR antibodies are detected in approximately 85% of patients with generalized MG and 50% to 75% of patients with ocular MG. As noted earlier, AChR and MuSK antibodies account for 90% of patients with MG. The detection of antibodies to titin and RyR strongly suggests the presence of a thymoma; however, in any case, if a diagnosis of MG is made, a computed tomography scan of the chest examining the anterior mediastinum for the presence of a thymoma should be performed.

Treatment

Acetylcholinesterase Inhibitors

If a patient with known MG has a worsening weakness, this is a myasthenic crisis and the patient may need close observation in a monitored or intensive care unit (ICU) for impending ventilatory failure. The initial pharmacologic treatment of MG includes AChE inhibitors. AChE terminates the impulse transmission at the cholinergic synapses by rapid hydrolysis of ACh. Inhibition results in a greater concentration of circulating ACh in the synaptic cleft. Long-acting oral AChE inhibitors such as pyridostigmine are used. For the reasons already discussed, patients with MG associated with anti-MuSK antibodies may not always benefit from treatment with cholinesterase inhibitors.[112,113]

When treating MG patients with increasing weakness, the differential diagnosis may include a cholinergic crisis from overtreatment with AChE inhibitors because overstimulation of the NMJ may cause fasciculation, paralysis, or weakness. However, unless other signs of cholinergic stimulation are present (such as bradycardia, sialorrhea, urinary urgency, lacrimation, diarrhea,

bronchorrhea, bronchospasm, or miosis), it is more likely that the patient will benefit from increased doses of AChE inhibitors. If the patient requires MV, once intubation is complete, it often may be beneficial to either stop administration or decrease the AChE inhibitor dosage in an attempt to restore sensitivity to the receptors; or when extubating the patient, to decrease the oral secretions that result from the cholinergic stimulation of the AChE inhibitor.

Immunosuppression

The next choice of treatment in MG includes immunosuppressive medications such as corticosteroids, typically prednisone or methylprednisolone. It is important to recognize that when initiating corticosteroid treatment, clinical symptoms, and specifically bulbar and respiratory weakness, may first worsen. Dysphagia with the inability to handle oral secretions accompanied by a decreased respiratory reserve and cough may result in the need for MV.

In severely weak patients who do not yet have the diagnosis of MG but in whom the diagnosis is suspected, the first-line agent is AChE inhibitors. Again, if corticosteroids are also initiated, the patient should be closely monitored for worsening weakness and respiratory failure. Slow incremental dosing of steroids is safest, especially in the setting where the patient is not in a closely monitored setting. If the patient is in not in the ICU, a ramp-up dosing of prednisone might include alternate-day dosing of oral prednisone starting with 10 mg, increased in 10-mg steps up to 100 mg on alternate days or to 1.5 mg/kg of body weight, whichever is lower. When patients are stable or after surgery, tapering typically is slow—for example, by 10 mg every 2 weeks until 40 mg is reached with further tapering by 5 mg every month until either discontinued or the desired baseline dosage is achieved.

If long-term treatment with steroids is needed, then steroid-sparing immunosuppressants are used. These include cyclosporine, tacrolimus, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, and rituximab.[114] Approximately 80% of patients with MG and 95% of thymoma patients with MG require immunosuppressive treatment for longer than 1 year.[115]

It is interesting to note that the immunosuppressant tacrolimus has been found to enhance RyR-induced sarcoplasmic calcium release, which is blocked by autoantibodies to RyR. Thus tacrolimus may be particularly beneficial in patients with thymoma as they frequently have RyR autoantibodies.[69,116]

Immunoabsorption

IVIg is a well-accepted treatment for moderate to severe MG. Based on one class I study of 24 patients with worsening MG treated with IVIg 2 g/kg compared with 27 patients who received placebo, the outcome was improved with active treatment in patients with moderate or severe MG.[117] Based on this, the American Academy of Neurology (AAN) guidelines notes level B evidence that IVIg is "probably" effective in the treatment of MG.[53] An older study of 173 MG patients with exacerbation of symptoms showed improvement but no superiority of IVIg 1g/kg given on 2 consecutive days compared with a single dose of 1 g/kg.[118] The current recommended dose is a targeted total dose of 1 to 2 g/kg, typically given at doses of 0.5 g/day for 2 days or 0.4 g/day for 5 days. The duration of efficacy lasts approximately 3 to 4 weeks.[119]

Despite the frequent use of PE in patients with MG, the 2011 AAN PE guidelines regarding the efficacy for myasthenic crisis or thymectomy cited the lack of randomized, blinded controlled studies for the inability to support or refute the efficacy of PE in MG.[42,120] Similarly, a Cochrane meta-analysis first published in 2002 and updated in 2011 after a new search for studies and content had no change in its conclusion that PE offered no improvement at 2 or 4 weeks over prednisone or IVIg. They concluded that the existing studies had a high risk for bias and weak statistical power, although case series and one RCT with severe exacerbation did show a difference between PE and IVIg.[121]

Since then, a small randomized trial of 84 patients with moderate to severe MG compared IVIg 1 g/kg per day for 2 consecutive days to PE of 1.0 plasma volume exchange for 5 days in moderate to severe MG. Fourteen days after treatment, the proportion of patients showing an improvement as determined by a quantitative myasthenia score was similar with 69% with IVIg and 65% with PE. Both treatments were well tolerated. The presence of AChR antibodies and greater baseline disease severity predicted a better response to therapy.[122] From this information, one might extrapolate that either treatment could be used as effectively.

The combination therapy of both IVIg with PE was explored in one small retrospective study of 72 patients.[123] Those who received the combination had a statistically improved outcome and shorter length of stay (LOS) of 20.0 days compared with 30.7 days with PE alone. The LOS in those treated with IVIg alone did not differ from those who received the combination. However, these data should be interpreted with caution because side effects such as allergic reactions, hypocoagulability, and bronchorespiratory infections were significantly more frequent in the PE group than in the other two groups (36.9% PE; 4.2% IVIg; 3.6% combination). These complications with PE have not been seen in other trials and would suggest bias among treatment groups.

Given the current limitations in the quality of the evidence, recent meta-analyses and current treatment recommendations support no evidence for superiority in the efficacy or safety of IVIg or PE in the treatment of acute exacerbations of MG.[124] The AAN guidelines acknowledge that despite lack of strong evidence for efficacy of PE in myasthenic crisis and prethymectomy MG, PE is used in many medical centers for these indications.[42] Clinically, the practitioner has the option to use either and the choice is typically made on the availability and access to each treatment. From the cost perspective, patients in MG crisis treated with IVIg in some studies had a shorter ICU LOS by up to 3 days and hospital LOS by 5 to 8 days, with decreased inpatient costs compared to PE.[125,126]

Complications Associated With Immunoabsorption

In a large cohort of 1606 hospitalized patients with MG, those in crisis treated with PE had more complications than those treated with IVIg (30.06% vs. 14.79%, $P < 0.001$).[126] Previously, complications associated with PE included infection[127]; however, currently more common complications include hypotension in as many as 8% of treatments, arrhythmias, anxiety, cold sensation, paresthesias, or transient hyperthermia. Laboratory abnormalities may include anemia, thrombocytopenia, hypokalemia, hyponatremia, and hypocalcemia.[128]

IVIg has been associated with headaches, fever, mild hypertension, chills, nausea, urticaria, and aseptic meningitis. The clinician should be attentive to those with cardiac, coronary, or cerebrovascular disease, as IVIg is hyperviscous and may precipitate deep venous thrombosis, ischemic stroke,[129] myocardial infarction,[130] or renal failure.[131] Rarely, anaphylaxis can develop in patients who are IgA deficient—for example, those with anti-IgA antibodies who are treated with IVIg.[132] Although attributed to IgG or IgE anti-IgA antibodies, the etiology is not fully elucidated.[133]

Thymectomy

If a thymoma is found, the treatment is thymectomy with a consideration for prethymectomy immunoabsorption with PE or

IVIg to minimize the risk for postthymectomy MG exacerbation. However, even when the computed tomography scan shows no thymic abnormality (i.e., nonthymomatous MG), recommendations still include thymectomy. The first case series of 6 patients reported in 1941 showed a 50% response rate.[134] Subsequent retrospective studies showed overall but variable benefit in clinical response and remission rate. However, a more recent trial randomly assigned 126 nonthymomatous MG patients to thymectomy with prednisone or prednisone alone.[135] After thymectomy, MG patients had improved clinical outcomes, required less immunosuppressive therapy (i.e.. prednisone and azathioprine therapy), and had fewer clinical symptoms and need for hospitalization to manage disease exacerbations over a period of 3 years. Recent findings that the presence of anti-AChR antibodies correlates with thymic germinal centers and the degree of thymic follicular hyperplasia explain the benefit of thymectomy even in early-onset nonthymomatous MG patients.[93] For patients with ocular myasthenia, 70% can be cured or have symptom improvement after thymectomy.[136]

Medications to Avoid

Some medications can worsen MG by actions in the presynaptic terminal, including a decrease in ACH release by inhibition of calcium influx into the presynaptic terminal, changes in the postsynaptic ion permeability preventing action potential transmission past the post synaptic terminal, and blockade of the postsynaptic AChR preventing binding of ACH.[137] Medications that should be avoided are found in Table 61.4. Not all are absolutely contraindicated, but the practitioner should weigh the risk and benefits of the administration of such medications and should be knowledgeable about the potential to increase weakness and worsen myasthenic symptoms.

Mortality

Mortality during a myasthenic crisis is highest in those with acute respiratory failure, major cardiac complications such as congestive heart failure, and acute renal failure. As one might expect, age and respiratory failure are associated with a higher complication rate.[126] Previously, the mortality rate was as high as 42% in the 1960s[138]; however, likely owing to advances in MV and critical care, mortality in those requiring MV now varies between 4% and 14.8%.[139,140]

Complications

Respiratory Failure

Depending on the cohort, respiratory failure requiring MV develops in 9% to 30% of patients with GBS.[5,141,142] Approximately 60% to 90% of MG patients in myasthenic crisis admitted to an ICU will require intubation and MV.[139,140] Unlike pulmonary disease, where MV typically is a failure in oxygenation, in neuromuscular disease such as GBS and MG, the major causes for intubation are (1) lack of neuromuscular strength needed for an effective cough, deep breathing, and adequate tidal volume and (2) dysphagia that prevents the ability to protect the airway from aspiration of oral secretions. These patients are at high risk for atelectasis and pneumonia, which prolongs MV, LOS, and as noted earlier, increases mortality.

In both diseases, the vital capacity, residual lung volume, and negative inspiratory force fall owing to respiratory muscle weakness and a reduction in chest wall compliance caused by atelectasis and restriction of chest wall movement. Diaphragmatic weakness alone can reduce vital capacity (VC) by 25% during sitting and lying.[143] Additional respiratory compromise occurs as the result of weakness of the thoracic and abdominal musculature. Passive inspiration requires contraction of the diaphragm. Active inspiration requires the sternocleidomastoid muscle, which elevates the sternum with innervation from the eleventh cranial nerve (spinal accessory nerve); however, when parasternal muscles and external intercostal muscles contract, they raise the ribs to increase thoracic volume laterally. Scalene muscles contract to elevate the ribs in an anteroposterior direction and splints the chest wall. This allows the intercostal muscles to be more effective in expanding the thorax while the diaphragm descends.

Quiet expiration results from passive recoil from the thorax and lungs. Active expiration requires contraction of the internal intercostal muscles, with the exception of the interchondral section, to depress the ribs. Finally, contraction of the abdominal muscles depresses the lower ribs and compresses the abdominal contents against the diaphragm to further decrease the volume of the thorax. This maneuver increases the intrapulmonary pressure above atmospheric pressure to facilitate exhalation. Of note, because the thoracic and abdominal musculature is necessary for active breathing, although diaphragmatic innervation occurs at cervical levels 3 through 5, patients with a cervical cord lesion below this level can exhibit respiratory failure.

Monitoring for impending neuromuscular respiratory failure includes periodic measurements of handheld bedside spirometry for forced vital capacity and negative inspiratory force. A normal vital capacity (VC) is approximately 65 mL/kg. A poor cough occurs at around 30 mL/kg and requires additional chest physiotherapy to clear secretions and minimize atelectasis. Typically a VC of less than 20 mL/kg ideal body weight or a rapidly declining VC on serial measures are indications for elective endotracheal intubation.[144–146]

In GBS, the best clinical predictors of MV have been identified as a rapid onset of symptoms to hospital admission of fewer than 7 days, facial or bulbar weakness, an inability to cough, and the MRC motor score with specifically the inability to stand, inability to lift the elbows, and inability to lift the head.[57,146,147]

Predictors of successful extubation have shown that a higher vital capacity of at least 20 mL/kg correlates best. A lower negative inspiratory force of −50 cm H_2O compared with −28 cm H_2O can also be predictive.[148] Also, pulmonary comorbidities and autonomic dysfunction may be predictors of extubation failure.

Prolonged MV, defined as 14 days or longer, is helpful to determine patients who will benefit from tracheostomy. One prospective study of 552 patients with GBS showed that 27% of patients required MV, and of these, 71% required prolonged MV. The strongest predictors were muscle weakness, defined as those who were unable to lift their arms from the bed at 1 week after intubation, and electrophysiology studies showing axonal degeneration or unexcitable nerves at 1 week.[142]

The use of noninvasive ventilation has been reported in a few patients with GBS.[149,150] However, because these patients often have a progressive course of worsening and may have bulbar dysfunction, noninvasive ventilation is thus unlikely to be successful. Patients with GBS are best treated with endotracheal intubation.[151]

Noninvasive ventilation has been used more successfully in MG patients with a myasthenic crisis.[152,153] Subsequent failure requiring eventual endotracheal intubation was best predicted by the initial

TABLE 61.4 Medications to Avoid in Myasthenia Gravis[137]

Medications to Avoid	Examples	Recommendation for Avoidance	Mechanism of Weakness
Antibiotics			
Aminoglycosides	Gentamycin Streptomycin	Contraindicated	Blocks ACh receptor, prevents release of ACh
	Tobramycin Amikacin	Less likely problematic	
Antimalarials	Quinine Chloroquine	Contraindicated	Presynaptic blockage of voltage-dependent sodium channels and postsynaptic potentiation of depolarization
Macrolides	Erythromycin, Tetracycline Azithromycin	Relative	Affects presynaptic transmission
Fluoroquinolones	Moxifloxacin Ciprofloxacin Levofloxacin Ofloxacin	FDA black box warning	Unknown
Ketolide	Telithromycin	FDA black box warning	Unknown
	Polymyxins	Contraindicated	Presynaptic and postsynaptic effects
Cardiovascular			
Antiarrhythmics	Procainamide Propafenone	Contraindicated	Decreases the release of ACh Sodium influx blocker
β-Blockers	Propranolol Atenolol Ophthalmic timolol	Relative	Unclear—may be at the neuromuscular junction or muscle membrane
Calcium channel blocker	Verapamil Amlodipine	Relative	Presynaptic and postsynaptic blockade of L-type calcium channels
Anticonvulsants			
	Phenytoin	Relative	Depressed postsynaptic response to ACh; inhibition of calcium channel; increase in muscle membrane threshold
	Carbamazepine	Relative	Triggers immune response
	Gabapentin	Relative	Binds voltage-gated calcium channel
Chemotherapeutic Agents			
	Doxorubicin Etoposide Cisplatin	Relative	Unknown
Others			
	Interferon	Relative	Autoantibody production
Neuromuscular blocking agents	Atracurium Cisatracurium Vecuronium	Relative	Blocks ACh receptors
Statins		Relative	Unknown
Corticosteroids		Relative	Direct blocking of ACh receptor through ionic channels
Botulinum toxin		Contraindicated	Impairs synaptic transmission
Magnesium		Relative	Impairs synaptic transmission
Penicillamine		Contraindicated	Binds the ACh receptor; induces antibodies to receptor

ACh, Acetylcholine; *FDA*, U.S. Food and Drug Administration.

presence of hypercapnia, defined as a partial pressure of carbon dioxide greater than or equal to 45 mm Hg[154] or 50 mm Hg.[155]

Pain and Sensory Disturbance

Neuropathic pain can be as high as 89% in patients with GBS.[156] In one study, 36% of patients reported pain that preceded weakness, whereas 66% reported pain in the acute phase of the first 3 weeks of their illness. Up to 38% still had pain at 1 year.[157] Treatment can include opioids and anticonvulsants such as carbamazepine, gabapentin, and pregabalin.

Although MG is typically considered a muscle disorder characterized by fatigue and muscle weakness, the altered cholinergic neural transmission also affects the sensory system.[158] Abnormal sensory input can cause restlessness in lower limbs in up to 43.8% of patients with MG.[159] Pain scores of moderate or high severity are as high as 50%.[160] Numbness and paresthesias are found in at least 10%. Approximately 67% of patients with MG have higher tactile

perceptual thresholds compared with healthy controls.[161,162] They also have visual complaints that are not explained by oculomotor disturbance but from optic nerve abnormalities because visual evoked responses are impaired.[163] Autonomic disturbances can also be seen in MG that may vary from decrease to hyperactivity in sympathetic and parasympathetic tone.[164] It may be difficult to differentiate these symptoms as causative from the primary disease rather than from the medication effects of AChE inhibition, but orthostatic dizziness, abnormal thermoregulation, impaired gastrointestinal motility, and pupillary changes have been reported.[165,166] The incidence of sensory dysfunction with MG is not well known as previous large studies have focused on motor findings alone.[167] Others are working to establish a sensory rating scale in MG that includes changes in tactile perception and olfactory, vision, taste, audition, corneal, autonomic, and sleep function.[158]

Other Complications

As expected in any patient who is nonambulatory or bedbound, patients with GBS and MG are at risk for pneumonia, thromboembolic disease, and decubiti. More than half of patients who were mechanically ventilated had a LOS longer than 3 weeks.[168] Critical care should be focused on appropriate chemoprophylactic therapy and the classic elements of the ABCDEF care bundle that focus on: 1) assessing, preventing, and managing pain; 2) both spontaneous awakening trials and spontaneous breathing trials to facilitate liberation from the ventilator; 3) choosing appropriate analgesic and sedative medications and doses; 4) assessing, preventing and managing delirium; 5) providing early mobility and exercise; with 6) Family and patient engagement to empower them and facilitate recovery for the best outcome.[169]

Key Points

- GBS is typically a demyelinating disease of the peripheral nervous system, although axonal variants occur.
- The pattern of weakness with GBS is an ascending areflexic paralysis, but it can also manifest with a Miller Fisher syndrome of ophthalmoplegia, ataxia, and areflexia.
- MG may be divided into subgroups depending on the clinical presentation and the autoantibody type found in a myasthenic patient. Most patients have antibodies to AChR or MuSK. These subtypes may assist in determining the therapeutic response to prognosis.
- Increasing or initiating steroids in a myasthenic patient may worsen symptoms and precipitate ventilator failure requiring intubation. The clinician should also be aware of other medications that may precipitate weakness in a patient with MG.
- Respiratory failure in patients with neuromuscular weakness typically occurs because of dysphagia and the inability to protect the airway as well as the ability to take deep breaths and maintain an adequate tidal volume. Ventilatory reserve in these patients and impending respiratory failure can be monitored by bedside spirometry with vital capacity above 20 mL/kg.

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Review Questions

1. A 45-year-old man had a diarrheal illness with a low-grade fever that lasted for 4 days. One week later, he noted tingling and numbness in his feet followed by leg weakness. The following day he was unable to walk and went to the emergency department. He is admitted to the intensive care unit (ICU) for impending respiratory failure. His examination shows flaccidity of his arms and legs. A lumbar puncture shows a white blood cell count of 3 cells/mL, protein of 95 mg/dL, glucose level of 80 mg/dL and is culture negative. The nerve conduction study shows slowing with increased latency. The electromyogram is normal. The treatment of choice includes which of the following?

a. Azathioprine
b. Intravenous immunoglobulin (IVIg) followed by plasmapheresis.
c. Plasmapheresis.
d. Prednisone
e. Pyridostigmine

Answer: c. This is a case of Guillain-Barré syndrome (GBS), an autoimmune disease that induces homologous epitopes to the peripheral nerve. It is characterized by a demyelinating process that results in slowing of the nerve conduction velocity and is associated with an albuminocytologic dissociation with elevation of cerebrospinal fluid protein without pleocytosis. GBS follows an antecedent upper respiratory tract infection in about 38% of patients, although it can be diarrheal in about 24% of cases. GBS is not responsive to corticosteroids and long-term immunosuppression with medications such as azathioprine. It is responsive to both IVIg or plasmapheresis, although the combination has not been shown to improve outcome but will increase the cost of care. Pyridostigmine, an acetylcholinesterase inhibitor, is indicated in myasthenia gravis but has no role in the treatment of GBS.

2. Which of the following is least likely to precipitate ventilatory failure in a patient with myasthenia gravis?

a. Azithromycin
b. Cefepime
c. Gentamicin
d. Prednisone
e. Verapamil

Answer: b. There is a long list of medications that can exacerbate weakness in patients with myasthenia gravis. Chief among these calcium channel blockers, β-blockers, antiarrhythmic agents, and antibiotics such as aminoglycosides, macrolides, and fluoroquinolones. Others include antimalarials, corticosteroids, and anticonvulsants such as carbamazepine, gabapentin, and phenytoin. Cephalosporins, however, are well tolerated.

3. A 70-kg 65-year-old man who is 5 foot 9 inches tall is diagnosed with myasthenia gravis and has been receiving increasing doses of pyridostigmine. He is admitted to the ICU with ptosis, difficulty swallowing, and is mildly short of breath. Vital signs include a temperature of 38.5°C, heart rate of 85 beats/min, blood pressure of 150/80 mm Hg, respiratory rate of 16 breaths/min, and oxygen saturation of 96%. His breath sounds are clear and the chest radiograph shows no infiltrates. He is able to move all extremities but has mild fatigability to repetitive testing of his deltoids. Handheld spirometry shows a negative inspiratory force of −50 cm H_2O and vital capacity of 1.8 L. Which of the following is the best immediate therapy?

a. Corticosteroids
b. Endotracheal intubation
c. IVIg
d. Plasmapheresis
e. Pyridostigmine

Answer: e. This patient is exhibiting signs of a myasthenic crisis and the most immediate treatment for improvement would be to administer an acetylcholinesterase inhibitor. He does not have signs of overtreatment with a cholinergic crisis, which would include bradycardia, diarrhea, and bronchorrhea, and there are few risks to administering more pyridostigmine. With a myasthenic crisis, steroids may be indicated but can worsen symptoms. Plasmapheresis or IVIg may be indicated but will not have an immediate effect to improve his symptoms. Endotracheal intubation should always be considered in a patient in myasthenic crisis; however, if the patient is not in respiratory distress, handheld spirometry can help determine the need for intubation. A negative inspiratory force of less than 20 cm/H_2O or vital capacity of less than 20 mL/kg would be indicators for immediate intubation. This is not the case with this patient. Therapy with pyridostigmine may help avert the need for intubation; however, the patient will need to be continuously monitored for signs of worsening.

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Seizures in the Critically Ill

MELISSA MERCADO AND THOMAS P. BLECK

CHAPTER OUTLINE

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Prognosis

Seizures complicate the course of up to 10% of adult patients admitted to intensive care units (ICUs) for nonneurologic conditions[1,2] and occur more frequently in specialized neuroscience ICUs.[3] There are several reasons for which intensivists of all fields should be comfortable with the recognition and management of seizures. First, seizures are often the first indication of a central nervous system (CNS) complication in their patients, and a rapid etiologic diagnosis is likely to improve their outcomes. Furthermore, because epilepsy is a common disorder (affecting about 2% of the general population), patients with preexisting seizure disorders occasionally require ICU admission for intercurrent conditions, during which time their risk of breakthrough seizures will invariably be heightened. And most importantly, several interventions required for treatment of refractory seizures, such as mechanical ventilation and vasopressor usage, require the expertise of an intensivist in addition to a neurologist.

History

Although seizures have been recognized at least since Hippocratic times, their relatively high rate of occurrence in critically ill patients has only recently been recognized. Seizures as a side effect of critical care treatments (e.g., as a complication of lidocaine infusion for ventricular arrhythmias) are also a recent phenomenon.

The first recorded description of status epilepticus (SE) is by Gavasetti in 1586.[4,5] Sir Thomas Willis described the complications of untreated SE in 1667:

> *…as to what further belongs to the prognostication of the Disease, if it end not about the time of ripe age, neither can be driven away by the use of medicines, there happens yet a diverse event in several sick Patients, for it either ends immediately in Death, or is changed into some other Disease, to wit, the Palsie, stupidite, or melancholly, for the most part incurable. As to the former, whenas the fits are often repeated, and every time grow more cruell, the animal functions are quickly debilitated; and from thence, by the taint, by degrees brought on by the Spirits, and the Nerves serving the Praecordia, the vital function is by little and little enervated, till at length, the whole body languishing, and the pulse is loosned, and at length ceasing, at last the vital flame is extinguished.*[6]

Attempts at treating SE in the nineteenth century included bromide,[7] morphine,[8] and ice applications. Barbiturates were introduced in 1912, followed by the identification and use of phenytoin (PHT) in 1937; these were the first rational treatments for SE.[9] Paraldehyde gained brief prominence in the next decades.[10] The most recent major improvement is the use of benzodiazepines, pioneered by the French in the 1960s.[11]

Epidemiology

More data are becoming available concerning the epidemiology of seizures in ICU patients. In a 2-year prospective study of a medical ICU, we found an incidence of approximately 35 patients with seizures per 1000 admissions.[1] Most recently, retrospective studies including patients with primary nonneurologic diagnoses found an incidence of electrographic seizures of up to 22% of medical ICU patients[12] and 16% in surgical ICU patients.[13] The incidence of seizures is probably higher in pediatric ICUs than in medical ICUs.[14–16]

The epidemiology of SE is somewhat better understood. Estimates of the incidence of generalized convulsive SE in the United States range from 50,000 cases/year[17] to 250,000 cases/year.[18] Between 6% and 12% of epilepsy patients present with SE,[19] and about 20% of seizure patients will experience an episode of SE within 5 years of their first seizure.[20] Towne and colleagues demonstrated that 8% of an unselected series of comatose medical ICU patients had unsuspected nonconvulsive status epilepticus (NCSE).[21]

TABLE 62.1 Etiology of Status Epilepticus in Adults in the Richmond, Virginia, Study

Etiologic Factor/Disorder[a]	Distribution (%)
Low antiseizure drug levels	34
Remote (prior history of CNS insults)	
Chronic cerebral infarction	19
Chronic intracerebral hemorrhage	3
Previously diagnosed CNS tumor	2
Acute cerebrovascular disease (vascular occlusion, embolism, or hemorrhagic infarction)	22
Hypoxia/anoxia	18
Metabolic disturbance	15
Alcohol related (withdrawal or intoxication)	13
Primary or metastatic CNS tumor	7
Drug overdose	3
CNS infection	3
Head trauma	3
Idiopathic/cryptogenic	3
Acute primary intracerebral hemorrhage or subarachnoid hemorrhage	1

[a]Some patients had more than one etiology.
CNS, Central nervous system.

Certain ICU patients appear to be at increased risk for seizures, but the degree of that increased risk has not been quantified. An independent predictor in medical ICU patients is the presence of sepsis. Oddo and colleagues showed that about 30% of patients with sepsis have periodic epileptiform activity or NCSE when recorded for 24 hours or longer on an electroencephalogram (EEG).[12] Thus intensivists should have a low threshold for EEG monitoring when septic encephalopathy is not improving with antimicrobial treatment or is out of proportion to illness severity. Other risk factors include chronic or acute renal failure, administration of medications that may lower seizure threshold (such as penicillins, carbapenems, cefepime,[22] meperidine, cyclosporine, and neuroleptics) and any rapid osmolar shifts such as those induced during treatment of sodium abnormalities or hemodialysis. Hyperglycemic crises, either nonketotic or ketotic, have a high likelihood of focal seizures,[23,24] and treatment of these should focus on correcting the electrolyte abnormality.

In the Richmond, Virginia, SE study, the most common cause of SE in adults was stroke (acute or remote, ischemic or hemorrhagic), followed by withdrawal from antiseizure drugs, and SE related to ethanol withdrawal, anoxia/hypoxia, and metabolic disorders (Table 62.1).[25] Systemic infection was the most commonly diagnosed cause of SE in children; this was followed by congenital abnormalities, anoxia, metabolic disorders, antiseizure drug withdrawal, CNS infections, and trauma.

Nosology and Semiology

Numerous systems have evolved for the classification of seizures; the most frequently used today is that of the International League Against Epilepsy[26] (Box 62.1). This schema allows classification based primarily on clinical criteria, without inferences about cause.

• BOX 62.1 International Classification of Epileptic Seizures

I. Focal (aware, impaired awareness, or unknown awareness; ± to bilateral tonic-clonic)
  A. Motor
    1. Tonic
    2. Atonic
    3. Myoclonic
    4. Clonic
    5. Epileptic spasms
    6. Hypermotor
  B. Nonmotor
    1. Sensory
    2. Cognitive
    3. Emotional
    4. Autonomic
II. Generalized
  A. Motor
    1. Tonic-clonic
    2. Tonic
    3. Atonic
    4. Myoclonic
    5. Myoclonic-atonic
    6. Clonic
    7. Clonic-tonic-clonic
    8. Epileptic spasms
  B. Absence
    1. Typical
    2. Atypical
    3. Myoclonic
    4. Eyelid myoclonia
III. Unknown onset (aware, impaired awareness, or unknown awareness)
  A. Motor
    1. Tonic-clonic
    2. Tonic
    3. Atonic
    4. Epileptic spasms
  B. Nonmotor
IV. Unclassified

From Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. *2017;58:522–530.*

Focal aware (previously "simple partial") seizures arise focally in the cerebral cortex, without taking over either the limbic system or subcortical nuclei. The patient remains aware of the environment during the ictus, and except for the seizure itself appears unchanged. Bilateral limbic system dysfunction results in a *focal seizure with impaired awareness* (previously "complex partial seizure"); the patient's awareness and ability to interact with the environment are diminished (but not always completely abolished). *Automatisms* are movements that the patient seems to make without being aware of them; typical automatisms include swallowing, masticatory movements, and fumbling with nearby items. *Focal to bilateral tonic-clonic* seizures (previously "secondary generalized") imply invasion of either the other hemisphere (with loss of consciousness) or, more commonly, subcortical structures, with the development of a generalized convulsion.

Generalized seizures seem to arise from the entire cerebral cortex and the diencephalon at the same time. Consciousness is lost from

the start of the seizure. True *absence* seizures are usually confined to childhood; they consist of the abrupt onset of a blank stare usually lasting 5 to 15 seconds, without lateralizing phenomena, from which the patient abruptly returns to normal. *Generalized myoclonic* seizures begin with brief, bilaterally synchronous jerks without an initial change in consciousness, followed by a generalized convulsion. They occur in several of the genetic epilepsies, but in the ICU are more commonly the consequences of anoxia or metabolic disturbances such as renal failure.[27] *Clonic* seizures involve repetitive movements; they may be generalized (synchronous movements of all extremities and both sides of the face) or focal (e.g., one side of the face and the arm of the same side). *Tonic* seizures are episodes of tonic extension of the arms, legs, and trunk; they must be distinguished from extensor posturing and from tetanic spasms.[28] *Tonic-clonic* seizures begin with tonic extension, followed by a brief phase of rapid vibration of the extremities, evolving into bilaterally synchronous clonus, and concluding with a postictal phase in which incontinence is common and brief apnea is occasionally noted. They may start as generalized or, more commonly, occur as the manifestation of spread of a focal seizure (*focal to bilateral tonic-clonic*).

SE is defined by the Neurocritical Care Society as "five or more minutes of continuous seizure activity or seizure activity without return to baseline."[29] SE is classified by a somewhat similar system as seizures, with alterations to match the observable clinical phenomena (Box 62.2).[30,31] SE has most recently been divided based on whether there are prominent motor symptoms present or not. *Generalized convulsive SE* (GCSE) is the type most commonly encountered in ICUs and poses the greatest risk to the patient. As with generalized convulsive seizures, GCSE may be either primarily generalized or may start as *focal SE evolving into bilateral generalized convulsions*. *Epilepsia partialis continua* is a special form of *focal motor SE* in which a small area of the body makes repetitive movements, sometimes for months or years after a CNS insult. This type of SE is most commonly associated with nonketotic hyperosmolar hyperglycemia and does not tend to respond to conventional antiseizure drug treatment.[32] *Focal nonmotor SE with impaired awareness* (previously "*complex partial SE*") presents with a state of diminished awareness, although frank loss of consciousness is rarely noted. The patient may exhibit automatisms, but commonly the diagnosis comes as a surprise when an EEG is obtained.

Nonconvulsive SE (NCSE) in the ICU is most commonly the consequence of partially treated GCSE and is defined by the International League Against Epilepsy as SE "without prominent motor symptoms."[31] As a means of simplifying the categorization of convulsive SE and NCSE, terms such as *complex partial SE* have been removed from the classifications. Most notably, NCSE can exist with or without coma, an example of which is *focal aphasic NCSE*, during which patients lack language abilities yet remain aware of their surroundings.

Up to 40% of SE patients may continue to have seizures, meeting criteria for *refractory SE* (RSE), which has been defined as ongoing seizure activity for more than 60 minutes despite administration of both a first-line benzodiazepine and a second-line antiseizure drug.[29,33] *Superrefractory SE* (SRSE) occurs once seizures continue in patients for more than 24 hours despite third-line anesthetic agent administration.

Pathogenesis

The reported "causes" of SE can be separated, if imperfectly, into predispositions and precipitants. *Predispositions* are relatively fixed conditions that increase the likelihood of SE, such as a brain tumor, in the presence of a precipitant. *Precipitants*, in contrast, are transient conditions that can produce SE in most, if not all, people but tend to affect those with predispositions at lesser degrees of severity (e.g., barbiturate withdrawal).

• BOX 62.2 Clinical Classification of Status Epilepticus

I. With prominent motor symptoms
  A. Convulsive SE (CSE, synonym: tonic-clonic SE)
    1. Generalized convulsive
    2. Focal onset evolving into bilateral convulsive SE
    3. Unknown whether focal or generalized
  B. Myoclonic SE (prominent epileptic myoclonic jerks)
    1. With coma
    2. Without coma
  C. Focal motor
    1. Repeated focal motor seizures (Jacksonian)
    2. Epilepsia partialis continua
    3. Adversive status
    4. Oculoclonic status
    5. Ictal paresis (i.e., focal inhibitory SE)
  D. Tonic status
  E. Hyperkinetic SE

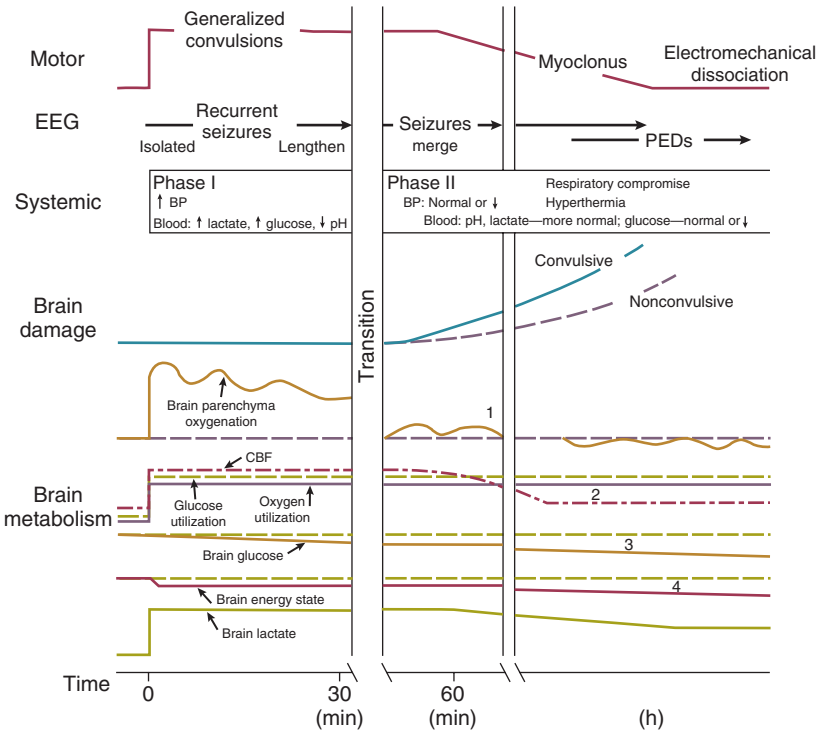
II. Without prominent motor symptoms (i.e., nonconvulsive SE)
  A. NCSE with coma (including so-called "subtle" SE)
  B. NCSE without coma
    1. Generalized
      a. Typical absence status
      b. Atypical absence status
      c. Myoclonic absence status
    2. Focal
      a. Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
      b. Aphasic status
      c. With impaired consciousness
    3. Unknown whether focal or generalized
      a. Autonomic SE

CSE, *Convulsive status epilepticus;* NCSE, *nonconvulsive status epilepticus;* SE, *status epilepticus. From Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus.* Epilepsia. *2015;56: 1515–1523.*

Pathophysiology

The causes and effects of SE at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. One must first understand the consequences of a single seizure and then contrast this information with the effects of prolonged or frequent seizures merging into SE. Longer durations of SE produce more profound alterations with an increasing likelihood of permanence and of becoming refractory to treatment. Fig. 62.1 illustrates the variety of processes involved in a single seizure and in the transition to SE.[34]

The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid (EAA) receptors. Although the endogenous ligands of these channels are glutamate and aspartate, the channels are named for synthetic compounds that potently activate them. From the standpoint of the intensivist concerned



• **Fig. 62.1** Pathophysiology of status epilepticus (SE). Summary of pathophysiologic events during experimental SE. Note that the abscissa is discontinuous. Numerals in the figure indicate the following events: *1*, loss of cortical responsiveness to changes in oxygen tension; *2*, a fall in cerebral blood flow *(CBF)*; *3*, depletion of brain glucose; and *4*, a decline in the total brain energy state. *BP,* Blood pressure; *CBF,* cerebral blood flow; *EEG,* electroencephalogram; *PEDs,* periodic epileptiform discharges. (Adapted from Lothman EW, Bertram EH. Epileptogenic effects of status epilepticus. *Epilepsia.* 1993;34[suppl 1]: S59–S70.)

with SE, three channels are particularly important because their activation may raise intracellular free calcium to toxic concentrations. The first channels primarily conduct sodium ions (the AMPA [amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] channels). The second are the N-methyl-D-aspartate (NMDA) channels, which admit sodium and calcium when the cell has been depolarized (which relieves the resting blockade of the ionophore by magnesium). The third channels, the metabotropic or ACPD (aminocyclopentane-trans-1,3-dicarboxylic acid) channels, mobilize calcium from intracellular stores via coupling to G-protein–linked second messengers. These EAA systems are normally crucial for learning and memory.

The cellular consequences of the excessive EAA channel activation include (1) accumulation of toxic concentrations of free intracellular calcium; (2) activation of autolytic enzyme systems; (3) production of oxygen-derived free radicals; (4) generation of nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylation of several enzyme and receptor systems, making seizures likely; and (6) increasing intracellular osmolality, thereby producing neuronal swelling. If adenosine triphosphate production should fail (because the substrate becomes inadequate or is diverted into EAA-related events), membrane ion exchange systems stop functioning, and the neuron swells further. These events are responsible for the neuronal damage associated with SE.

Many other important biophysical and biochemical alterations occur during and after SE. The intense neuronal activity activates immediate-early genes and produces heat shock proteins, providing strong indications of the deleterious effects of SE and insight into the mechanisms by which neurons protect themselves.[35] Wasterlain and colleagues summarized the many mechanisms through which SE damages the nervous system.[36]

Absence SE is an exception among these conditions. It appears to consist of rhythmically increased inhibition and does not produce clinical sequelae or neuropathologic abnormalities.

The mechanisms that terminate seizure activity are uncertain. Counterregulatory ionic events are also triggered by the epileptiform discharge; the most important is activation of inhibitory interneurons, which feed back to the bursting cells via γ-aminobutyric acid (GABA) ionotropic receptor family A ($GABA_A$) synapses. Given the relative rarity of SE in a population in which at least 1 in 50 patients has had a seizure, one must infer that these mechanisms are generally effective. The leading candidates for seizure-terminating systems are inhibitory mechanisms, primarily GABAergic neuronal aggregates. This hypothesis receives strong support from the clinical observation that human SE frequently follows withdrawal from GABA agonists (e.g., benzodiazepines).

Multiple neurobiochemical changes occur that contribute to the refractoriness of seizures. There is evidence of internalization of GABA receptors, lowering the responsiveness of seizure activity to GABAergic drugs such as benzodiazepines, as well as an increase in NMDA receptors at the synaptic membrane, further increasing excitatory glutamatergic activity.[37,38] The repetitive firing that characterizes SE alters the extracellular microenvironment. The most important change is probably the elevation of the extracellular potassium concentration. Although extruding potassium is an effective strategy to maintain normal electronegativity, the excessive amounts of potassium ejected during SE overcome the ability of astrocytes to buffer it. Patients with cerebral edema, glial scarring,

or alien tissue lesions have extracellular space abnormalities that impair the potassium buffering ability of glial cells. Raising extracellular potassium is a potent epileptogenic stimulus.

The tremendously increased cellular activity of SE elevates tissue demand for oxygen and glucose. To meet this demand, cerebral blood flow initially increases threefold or greater. However, after about 20 minutes, energy supplies become exhausted. This accentuates the demand for local catabolism to support ion pumps (in a vain attempt to restore the internal milieu during the flood of sodium and calcium). Many researchers believe that this is the major cause of epileptic brain damage in GCSE. Other forms of SE may not be subject to such severe hypercatabolism but still pose a risk.

When focal seizures generalize, subcortical structures begin to play an active role in the clinical phenomena observed. Spread of the electrical activity into the substantia nigra and other subcortical regions appears to be necessary before a tonic-clonic convulsion occurs.

At the anatomic level, SE can produce cerebral edema, which follows ictal damage to the blood-brain barrier. Prolonged SE produces chronic neuropathologic changes. Before the 1970s, these changes were often attributed to the systemic effects of SE (e.g., hypoxia and hyperthermia). However, SE itself produces these changes even in patients who are paralyzed, supported by mechanical ventilation, and maintained at normal temperature and blood pressure. The hippocampus, which is one of the most important areas for memory function, contains the most susceptible neurons, but the cerebral cortex is also vulnerable. These regions express high densities of EAA receptors and may be relatively deficient in systems for handling unusual elevations of free intracellular calcium. Cells that contain nitric oxide synthase seem relatively protected.

In addition to damaging the CNS, GCSE produces serious, often life-threatening, systemic effects.[39] Pressures in the systemic arterial system (under sympathetic control) and in the pulmonary arterial system (raised via efferents from pontine and medullary centers) are dramatically elevated from the moment of seizure onset. Epinephrine and cortisol release prompts further elevations of systemic arterial pressure and also produces hyperglycemia. Increased muscular work raises the circulating lactate concentration. Respiration becomes ineffective; both airway obstruction and diaphragmatic contraction impede air movement. The consequent hypoxia further elevates lactate levels. Ventilatory failure impairs carbon dioxide excretion while carbon dioxide production increases markedly, adding a respiratory component to the acidosis. In GCSE, the arterial blood pH frequently falls below 7.0. The muscular work accelerates heat production; when coupled with decreased dermal blood flow (produced by sympathetic stimulation), GCSE can quickly raise the core temperature to 40°C or higher.

If GCSE is not completely controlled within the first 20 minutes, motor activity begins to diminish in intensity, and ventilation usually improves. Therefore even without treatment, the metabolic acidosis improves. Core temperature may continue to climb, however, probably reflecting hypothalamic dysfunction. The initial hyperglycemia diminishes; after an hour or more, hepatic gluconeogenesis may fail, and hypoglycemia develops.

Patients with GCSE frequently have secondary complications as well. Aspiration of oral or gastric contents commonly produces chemical pneumonitis, with bacterial pneumonia often following. Rhabdomyolysis is common and is occasionally followed by acute renal failure. Compression fractures, joint dislocations, and tendon avulsions are other common sequelae of GCSE.

Clinical Manifestations

Recognition of Seizures in the ICU

Because of the close observation patients receive in the critical care setting, most seizures are witnessed. Three problems occur in ICU seizure recognition: (1) NCSE in patients with already impaired awareness, (2) seizures in patients receiving neuromuscular junction blockade, and (3) the misinterpretation of movement disorders and psychiatric disturbances as seizures. (In any ICU patient in whom abnormal movements or unexplained changes in awareness develop, thiamine deficiency [Wernicke encephalopathy] should be excluded immediately by giving high-dose thiamine.)

ICU patients often have altered awareness in the absence of seizures, reflecting their underlying condition, complications of those conditions (such as septic encephalopathy[40]), and drugs that depress alertness (intentionally or not). Although clonic motor activity in these patients remains visible, it may be difficult to determine whether a subsequent further decline in alertness reflects a seizure or some other process.

Patients receiving neuromuscular junction blocking agents do not manifest any of the usual signs of seizures. As long as such patients receive concomitant sedation with GABA agonists (e.g., benzodiazepines, propofol), the likelihood of seizures is small. The autonomic signs of seizures (hypertension, tachycardia, pupillary dilation) are not readily distinguished from the effects of pain or the patient's response to inadequate sedation. Thus any patient who manifests these findings and who has a potential reason for seizures (e.g., intracranial disease) should have an EEG to exclude this possibility.

Many sorts of abnormal movements occur in patients with severe metabolic disturbances or anoxic brain damage. Some of them can be distinguished from seizures by observation; such movements are frequently evoked or exacerbated by sensory stimuli and can sometimes be suppressed by changing the patient's posture. However, Hirsch and colleagues have demonstrated that seizures in ICU patients may be induced by external stimuli[41]; if any doubt about the nature of such movements persists, an EEG should be performed.

During therapeutic cooling for patients in a coma after cardiac arrest, seizures may be difficult to detect clinically, especially when neuromuscular junction blockade is used.[42] Because up to 30% of cardiac arrest patients may experience seizures, EEG monitoring should be performed as soon as possible in all cardiac arrest patients who remain comatose.[43]

Manifestations of Status Epilepticus

GCSE usually begins as tonic extension of the trunk and extremities with no preceding focal ictal activity. Consciousness is immediately lost, and after several seconds the tonic phase gives way to clonic (rhythmic) extension of the extremities, with flexion occurring during each brief relaxation. Usually this clonic phase wanes in intensity over 1 to 3 minutes. The patient developing SE may then repeat the cycle of tonic activity followed by clonic movements, or may continue to have intermittent bursts of clonic activity without recovery between. Less commonly encountered forms of GCSE are *myoclonic SE,* in which bursts of brief myoclonic jerks increase in intensity until a convulsion occurs.

Focal evolving to bilateral convulsive SE in the ICU begins with a focal seizure that progresses to a tonic-clonic convulsion. Even under the watchful eye of the ICU staff, the initial focal clinical activity may be overlooked.

Tonic SE is almost always confined to patients (usually children) with serious preexisting cerebral disorders. Its importance in critical care practice follows from the observation that benzodiazepines may *precipitate* tonic SE; paradoxically, these agents are also used to treat it.

There are several forms of *generalized NCSE*. Of greatest importance to intensivists is NCSE as a sequela of inadequately treated GCSE. In this circumstance, a patient with GCSE is treated with one or more antiseizure drugs, often in inadequate doses, after which visible convulsive activity stops. However, the patient does not awaken (or otherwise return to baseline), and SE is actually continuing. As a rule, patients who have not begun to awaken after 20 minutes should be assumed to have entered NCSE. This form of SE is sometimes termed *subtle SE,* and careful observation sometimes reveals low-amplitude clonic activity in some part of the body (most commonly, the face or the hands). Most investigators view NCSE as an extremely dangerous problem, because the neuronally destructive effects of SE continue unabated, often for several hours. This condition requires emergent treatment under EEG monitoring to prevent further cortical damage.

The usual form of *focal SE* in the ICU follows a stroke or is seen in patients with rapidly expanding cerebral masses (e.g., abscesses). Although clonic motor activity is the most easily recognized form, the seizure will take on the functional characteristics of the adjacent functional tissue. Thus somatosensory or special sensory manifestations may occur; the ICU patient who is already neurologically impaired may not be able to report these symptoms. *Aphasic SE* may occur if the seizure begins in a language area; this must be distinguished from a stroke. Physical examination usually reveals at least some mild lateralizing findings.

Diagnostic Approach

The Intensive Care Unit Patient With New-Onset Seizures

When a patient already in an ICU has a seizure, the staff has a natural tendency to somehow stop the ictus. This may, unfortunately, lead to both diagnostic obscuration and iatrogenic complications. Beyond trying to protect the patient from harm, very little can be done with sufficient rapidity to influence the course of the seizure. In particular, padded tongue blades (or similar items) should not be placed in the mouth, because they are more likely to obstruct the airway than to preserve it. Similarly, seizures in most patients have stopped before any medication, even administered into a preexisting intravenous (IV) line, can reach the brain in an effective concentration. A common scenario is the administration of IV diazepam, which begins to take effect after the seizure is over; the patient is now both postictal and pharmacologically sedated and becomes apneic.

The most important "intervention" during a single seizure is careful observation. This is the best time to collect evidence of a focal onset, which implies structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized convulsion should also be viewed as evidence of focal disease.

In addition to the standard historical information to be requested from patients and family members after a seizure, the ICU patient has several special predispositions that must be investigated. As previously noted, certain medications are an important cause of ICU seizures, especially in patients with diminished renal or hepatic function, or in those with damage to the blood-brain barrier. A complete list of potentially epileptogenic drugs is beyond the scope of this chapter; the medications of any patient who has a seizures should be reviewed with this possibility in mind.

Drug withdrawal is another common problem. Although ethanol withdrawal is the most common offender, discontinuing any hypnosedative agent (e.g., barbiturates, benzodiazepines, baclofen, gabapentin) may prompt convulsions 24 to 96 hours later. This may be a particular problem in the ICU, where such agents may be withheld from patients because the staff is afraid that the drug's effects will obscure the neurologic examination.

The physical examination should be conducted with special emphasis on the points mentioned earlier for the postictal examination. In addition, evidence of cardiovascular disease (as a source for cerebral emboli) and systemic infection should be sought. Careful examination of the skin and fundi are sometimes revealing. The presence of papilledema is obviously important, but its absence does not exclude increased intracranial pressure.

In addition to routine biochemical studies, screening for drugs of abuse should be performed on patients with unexplained seizures. Cocaine has emerged as a prominent cause of seizures in many urban hospitals[44] and newer proconvulsant synthetic substances should still be suspected in the presence of negative results of a toxicology screen. Hypocalcemia is rarely a cause of seizures beyond the neonatal period, and its discovery should not be the end of the diagnostic workup. Hyperparathyroidism has been linked anecdotally to seizures, with the inference that parathormone is neurotoxic. Similarly, hypomagnesemia has an unwarranted reputation as a cause of seizures, especially in the malnourished alcoholic patient.

In our prospective study of neurologic complications in medical ICU patients, 38 of 61 patients (62%) with seizures had a vascular, infectious, or neoplastic explanation for their fits.[1] Computed tomography (CT) scanning should be performed on all ICU patients with new seizures once their condition is stable enough for transport. The decision whether to administer contrast agent for a CT or perform magnetic resonance imaging scan depends on the clinical setting and on the appearance of the plain scan. In patients at risk for cerebrovascular events who present with "seizure activity" more suggestive of extensor posturing, it is imperative to obtain intracranial vessel imaging without delay to rule out a basilar artery thrombosis.

The EEG is the most vital diagnostic tool for the seizure patient. Continuous EEG monitoring is recommended in any ICU patient with the following conditions: persistent encephalopathy after seizures; patients with fluctuating mental status of unknown etiology; periodic epileptiform discharges on routine EEG; requirement for pharmacologic paralysis and risk for seizures; and clinical paroxysmal events suspected to be seizures.[45] Although the detailed interpretation of EEGs is beyond the scope of this chapter, the intensivist can easily learn to recognize basic seizure types and other important EEG abnormalities in critically ill patients.[46]

The need for a lumbar puncture depends on the clinical situation. In view of the common causes of seizures in the critical care setting, those who need cerebrospinal fluid (CSF) analysis will usually require a CT scan before the lumbar puncture. If a CNS infection is suspected in such patients, empiric antibiotic treatment should be strongly considered while these studies are being performed, rather than waiting for the scan to be performed and cerebrospinal fluid results to be obtained.

The Patient Presenting With or Developing Status Epilepticus

In contrast to the ICU patient with a single seizure, the patient with SE requires concomitant diagnostic and therapeutic efforts.

TABLE 62.2 Electrographic-Clinical Correlations in Generalized Convulsive Status Epilepticus

Stage	Typical Clinical Manifestations[a]	Electroencephalographic Features
1	Tonic-clonic convulsions; hypertension and hyperglycemia common	Discrete seizures with interictal slowing
2	Low- or medium-amplitude clonic activity, with rare convulsions	Waxing and waning of ictal discharges
3	Slight, but frequent, clonic activity, often confined to the eyes, face, or hands	Continuous ictal discharges
4	Rare episodes of slight clonic activity; hypotension and hypoglycemia become manifest	Continuous ictal discharges punctuated by flat periods
5	Coma without other manifestations of seizure activity	Periodic epileptiform discharges on a flat background

[a]The clinical manifestations may vary considerably, depending on the underlying neuropathophysiologic process (and its anatomy), systemic diseases, and medications. In particular, stages of the electrographic progression may be sufficiently brief to be overlooked. Partially treating status epilepticus may dissociate the clinical and electrographic features.

The first issue is to make a diagnosis of SE. Because most seizures stop within 5 to 7 minutes,[47] it is reasonable to begin treatment after 5 minutes of continuous seizure activity or after the second or third seizure occurs without recovery between the spells.

Continuous EEG monitoring is frequently useful in SE,[48] but treatment should not be delayed to obtain it when the diagnosis is apparent. A variety of EEG findings may be present, depending on the type of SE and its duration (Table 62.2). The electrical phenomena of SE at the whole brain level, as seen in the scalp EEG, reflect the seizure type that initiates SE (Fig. 62.2). Thus, absence SE begins with a generalized 3-Hz wave-and-spike EEG pattern. During the course of SE, there is usually some slowing of this rhythm, but the wave-and-spike characteristic persists. In contrast, GCSE goes through the sequence of EEG changes outlined in Table 62.2. The initial high-frequency discharge becomes progressively less well formed over minutes; this pattern implies that neuronal activity is less synchronous. Whether this indicates that inhibitory systems are attempting to terminate SE, a progressive decay in the ability of synaptic mechanisms to maintain synchrony, or global deterioration in neuronal function remains to be determined. The most typical pattern early in SE is that of rhythmic, high-frequency (>12 Hz) activity that increases in amplitude and decreases in frequency, finally terminating abruptly and leaving postictal low-amplitude slowing in its wake.

Management Approach

The Intensive Care Unit Patient With New-Onset Seizures

Deciding whether to administer antiseizure drugs to an ICU patient who experiences a single seizure or a few seizures requires a provisional etiologic diagnosis, an estimate of the likelihood of seizure recurrence, and an understanding of the utility and limitations of available antiseizure drugs. For example, the patient who has seizures during ethanol withdrawal will probably not benefit from chronic antiseizure drug treatment, and the administration of phenytoin (PHT) will not prevent more withdrawal convulsions during the same episode. Such a patient may need prophylaxis against delirium tremens with benzodiazepines, but the seizures themselves seldom require treatment. The patient who has seizures during barbiturate or benzodiazepine withdrawal, in contrast, should usually receive short-term treatment (usually with lorazepam [LRZ]) to prevent the development of SE. Seizures caused by drug intoxications or metabolic disturbances should similarly be treated for a brief period but do not indicate chronic antiseizure drug therapy.

The ICU patient with CNS disease who has even a single seizure should usually start a chronic antiseizure drug regimen, with the decision to continue medication reviewed before hospital discharge. It is now apparent that initiating antiseizure drug therapy after the first *unprovoked* (e.g., not drug-related or withdrawal-related) seizure helps delay the onset of subsequent seizures, but it does not change their eventual incidence.[49] Starting treatment after the first seizure in a critically ill patient who has a condition predictive of seizure recurrence may be even more important if the patient's problems include coagulopathies, myocardial ischemia, or other conditions that would be seriously complicated by a convulsion.

The Neurocritical Care Society recently published extensive guidelines for the treatment of SE,[29] which should be consulted for detailed information about the drugs discussed briefly here.

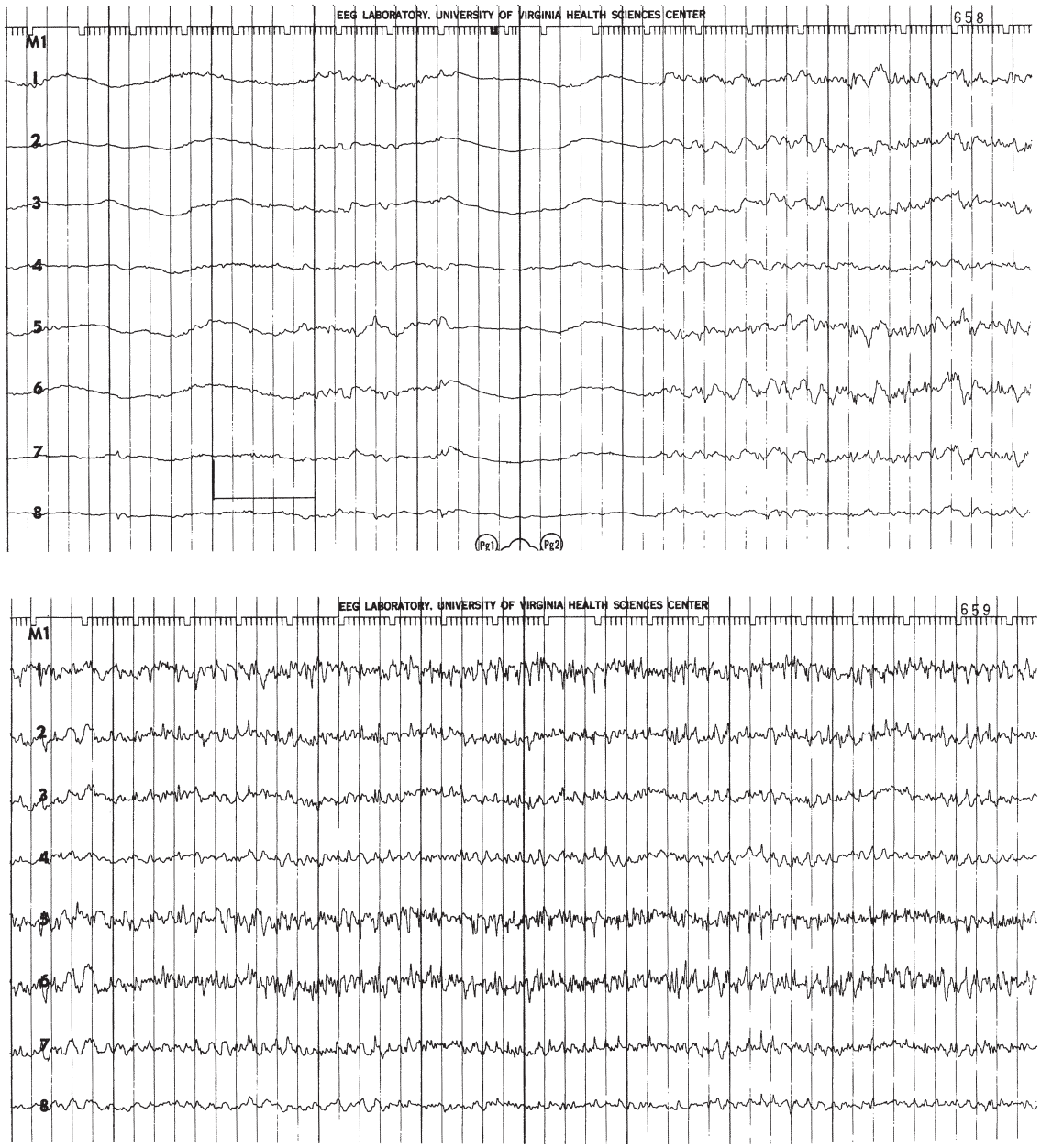
In the ICU setting, PHT (20-mg/kg loading dose, no faster than 50 mg/min, followed by an initial maintenance dose of 5 mg/kg per day) is often chosen to prevent subsequent seizures because of its relative ease of administration. Slowing the infusion rate to less than 25 mg/min can usually prevent hypotension and cardiac arrhythmias that may complicate its rapid IV administration. Because of the possible precipitation of third-degree atrioventricular block, an external cardiac pacemaker should be available when patients with conduction abnormalities receive IV PHT. Although fosphenytoin is safer than PHT if it extravasates, this agent does not have less cardiovascular toxicity. Fosphenytoin can also be used for intramuscular loading; PHT (pH 12) should not be administered intramuscularly because it produces myonecrosis.

The total PHT serum concentration should be kept in the "therapeutic" range of 10 to 20 μg/mL while the patient is in the ICU unless further seizures occur; the level may then be increased until signs of toxicity occur. If the patient is unable to express these signs (e.g., ataxia) because of his or her underlying condition or its treatment, failure to prevent seizures at a concentration of 25 μg/mL is usually an indication to add a second antiseizure drug (see later text). Although the usual goal of chronic antiseizure drug treatment is to administer the smallest dose of a tolerated single agent that completely controls seizures, such an approach is often impossible in the critical care environment. When the patient's condition is more stable, an attempt to decrease minor side effects or to convert to monotherapy may then be made.

PHT is normally about 90% protein-bound. Patients with renal dysfunction will have lower total PHT levels for a given dose

because the drug is displaced from its binding sites, but the "free" (unbound) level is not affected. Thus in patients with renal failure, and perhaps in others who are receiving highly protein-bound drugs (which will compete for PHT binding sites), it may be advantageous to measure free PHT levels. Because only the free fraction is significantly metabolized, the dose need not be altered with changing renal function. Calculations of the unbound concentration based on the serum albumin concentration are unreliable. The half-life for PHT clearance in patients with normal liver function varies from about 20 hours for the IV form and the oral solution to more than 24 hours for the extended-release oral capsules. Hence, a new steady-state serum concentration will take 4 to 6 days to establish. The drug need not be given more often than every 12 hours; the dosage interval for the enteral forms depends on the preparation but may be even longer. Hepatic dysfunction will mandate a decrease in the maintenance dose; if the serum albumin is very low, the loading dose can be reduced as well.

Hypersensitivity to PHT is the major adverse effect of concern to the intensivist. This allergy may be manifested solely as fever, but more commonly it includes a rash and eosinophilia. Febrile reactions appear to be more common with IV than with enteral loading. The Stevens-Johnson syndrome occurs rarely. The diagnosis and management of adverse reactions to PHT and other antiseizure drugs have been reviewed.[50] PHT is associated with a number of long-term adverse effects, and prophylactic administration in the



• **Fig. 62.2** Electroencephalographic recording during status epilepticus. The first panel illustrates the onset of the seizure; the subsequent panels show its evolution. Montage: longitudinal bipolar; channels *1* to *4*, left temporal; and channels *5* to *8*, left parasagittal. Calibration: vertical, 50 μV; horizontal, 1 second.

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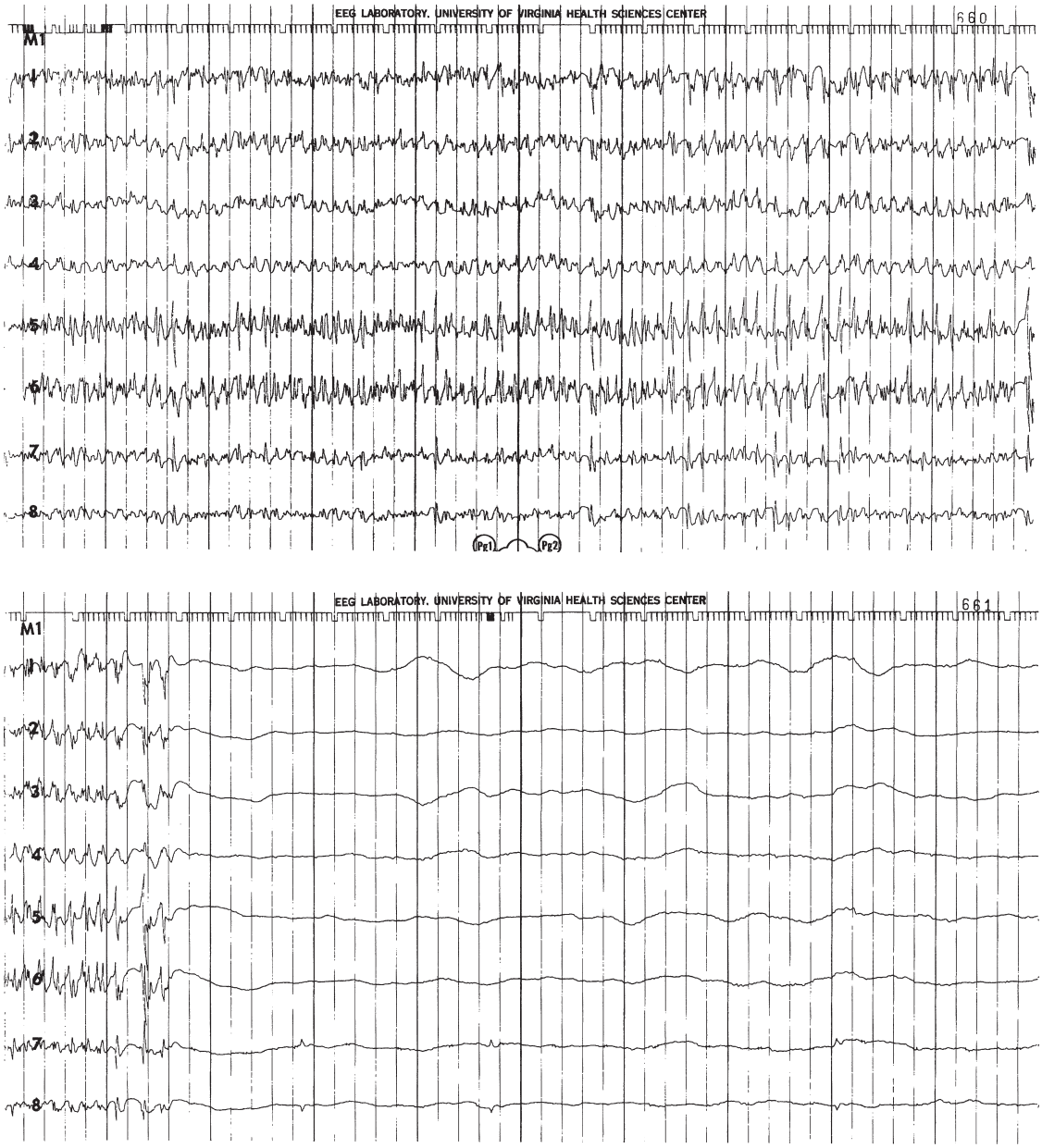


• **Fig. 62.2, cont'd**

setting of intracerebral hemorrhage, subarachnoid hemorrhage, or traumatic brain injury is not advised because of its association with worsening outcomes.[51–53] In these settings, levetiracetam may serve as a better choice. Valproate should be avoided in settings in which liver disease or hyperammonemia may be problematic but is otherwise a useful drug available both orally and intravenously. A loading dose of 30 mg/kg is reasonable, followed by a maintenance dose of 30 to 60 mg/kg per day.

The place of the newer antiseizure drugs in critical care is not well established. Levetiracetam has gained substantial popularity because of its limited drug interactions as well as benign side effect profile; it is predominantly excreted by the kidney, so the dose must be adjusted in renal insufficiency. The usual dose for seizure prevention is between 500 and 1500 mg/day, although doses up to 6 g/day have been used. The role of serum concentrations for assessment of efficacy or toxicity is not yet established. Lacosamide is also available intravenously and is started at a dose of 200 mg twice daily.

Phenobarbital (PB) (10- to 20-mg/kg loading dose, followed by an initial maintenance dose of 1.5 mg/kg per day) remains useful as an antiseizure drug for patients who cannot tolerate other antiseizure drugs, or for those who have breakthrough seizures after *adequate* PHT loading. The target level for PB in ICU patients should be 20 to 40 µg/mL. Either hepatic or renal dysfunction may affect PB metabolism. The half-life for PB clearance is about 96 hours. Thus maintenance doses of this agent need be given only once a day, and a steady-state level will take about 3 weeks to be established. Sedation is the major adverse effect; allergy is rare.

Carbamazepine, one of the most useful chronic antiseizure drugs, is seldom introduced to critically ill patients because its insolubility

has precluded a parenteral formulation. Oral loading with carbamazepine in conscious patients may produce coma lasting several days. It should be recalled as a cause of hyponatremia in patients receiving it chronically.

Status Epilepticus

The patient in GCSE has an obvious medical emergency; unfortunately, the NCSE patient also requires emergent treatment but is less straightforward to recognize. In a patient with any of these conditions, the clinician must move quickly to stop seizures to prevent further brain destruction.[54] A suggested management protocol for these conditions is presented in Box 62.3, and Fig. 62.3 shows a management algorithm for SE. Patients with focal SE without impaired awareness appear to be at substantially less risk of developing widespread cerebral damage and also appear less likely to respond to the aggressive approach outlined in Box 62.3. In this group, correction of underlying metabolic derangements is most important. Of the available antiseizure drugs, PB and benzodiazepines seem most likely to be efficacious.

Some frequent errors in the use of medications to terminate SE include (1) use of inadequate doses of potentially effective agents and, conversely, (2) continued administration of drugs that are ineffective in the patient being treated. The first point most frequently applies to PHT; the proverbial "gram of Dilantin" is not adequate for patients weighing more than 50 kg.

• BOX 62.3 Suggested Therapeutic Sequence for Terminating Status Epilepticus

I. Recognize SE, which is defined as at least 5 min of persistent generalized, convulsive seizure activity or two or more seizures within 15 min, between which there is incomplete recovery of consciousness.

II. Airway, breathing, circulation
Often the most rapid way to ensure airway protection is to rapidly terminate SE. If endotracheal intubation under neuromuscular junction blockade is necessary, use a nondepolarizing agent. If increased intracranial pressure is a concern, premedicate with lidocaine (1 mg/kg). The patient should be considered to still be in SE until neuromuscular transmission is reestablished, or until an EEG demonstrates that SE is no longer present.
If the patient is hypotensive, begin volume replacement and/or vasoactive agents as clinically indicated. Hypertension should not be treated until SE is controlled, because terminating SE will usually substantially correct it, and many of the agents used to terminate SE can produce hypotension.

III. Unless the patient is known to be normoglycemic or hyperglycemic, administer dextrose (1 mg/kg) and thiamine (1 mg/kg).

IV. First-line benzodiazepine
1. Administer LRZ 0.1 mg/kg. Dose may be repeated every 5 minutes if seizures persist. Most adult patients who will respond will have done so by a total dose of 8 mg.
2. If SE persists or if the patient does not have proper intravenous access, administer MDZ 0.2 mg/kg (IV or IM; 10 mg maximum per dose).

NOTE: Be cognizant of the potential of these drugs to eliminate the visible convulsive movements of GCSE while leaving the patient in NCSE. Patients who do not begin to respond to external stimuli 15 minutes after the apparent termination of GCSE should be considered at risk for NCSE and undergo emergency EEG monitoring.

V. Second-line anti-seizure drug
Administration of a second-line agent after the initial benzodiazepine dose is recommended even if the patient's convulsions have ceased. Options include the following:
1. Fosphenytoin 20 mg/kg (150 mg/min maximum rate)
2. Phenytoin 20 mg/kg (50 mg/min maximum rate)
3. Phenobarbital 20 mg/kg
4. Valproic acid 30 mg/kg
5. Levetiracetam 15 mg/kg (add-on agent once previous options are used)
6. Lacosamide 200 mg (add-on agent once previous options used)

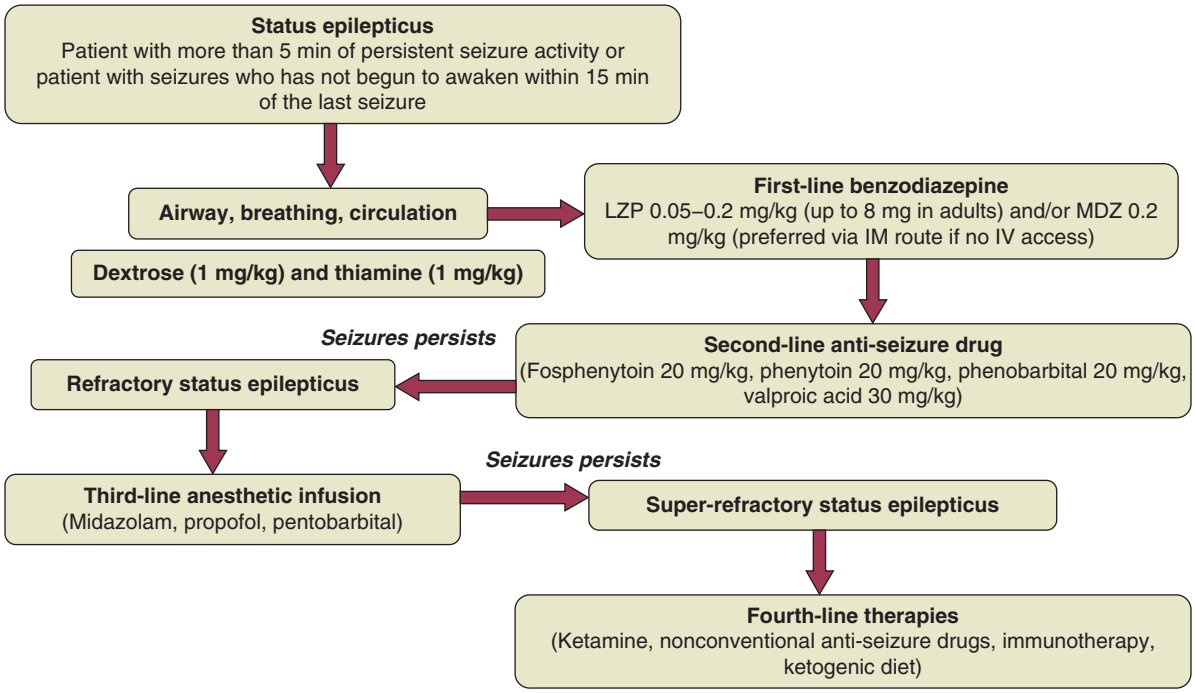
VI. Refractory status epilepticus is defined as ongoing seizure activity that does not terminate with a first-line benzodiazepine and second-line antiseizure agent. In these instances, intubation, ICU transfer, and continuous EEG monitoring are indicated, as well as initiation of a third-line anesthetic agent such as the following:
1. Midazolam 0.2-mg/kg loading dose followed by a maintenance infusion at a rate of 0.05–2 mg/kg per h
2. Propofol 50–250 μg/kg per min loading dose followed by a maintenance infusion at a rate of 5–60 μg/kg per min
3. Pentobarbital 12-mg/kg loading dose followed by a maintenance infusion at a rate of 0.25–2 mg/kg per h

NOTE: Initiation of a sedative drip will require mechanical ventilation if the patient has not yet been intubated. Higher doses of these sedative agents may be needed in certain clinical situations. With any breakthrough seizure requiring uptitration of sedative drips, second-line antiseizure drug therapeutic levels should be maximized or another antiseizure drug should be added. Slow sedative taper should be initiated once the patient is seizure-free for more than 24 h.

VII. Patients with ongoing electrographic seizure activity that is not terminated by a first-line benzodiazepine, a second-line antiseizure drug, and a third-line anesthetic infusion are classified as having superrefractory status epilepticus. In these rare cases, initiation of any of the following fourth line therapies is recommended:
1. Ketamine 1- to 5-mg/kg loading dose (may repeat every 5 min up to 3 times) followed by a maintenance infusion at a rate of 1.5–5.0 mg/kg per h (higher doses may be needed in certain clinical situations)
2. Addition of other nonconventional antiseizure drugs (topiramate, clonazepam, clobazam, vigabatrin)
3. Immunotherapy (methylprednisolone, IV immunoglobulin, plasma exchange)
4. Ketogenic diet (with assistance of nutrition services)

VIII. Treat complications.
1. Rhabdomyolysis should be treated with a vigorous saline solution diuresis to prevent acute renal failure; urinary alkalinization may be a useful adjunct. If definitive treatment of GCSE takes longer than expected because of hypotension or arrhythmias, neuromuscular junction blockade under EEG monitoring might be considered.
2. Hyperthermia usually remits rapidly after termination of SE. External cooling usually suffices if the core temperature remains elevated. In rare instances, cool peritoneal lavage or extracorporeal blood cooling may be required. High-dose pentobarbital generally produces poikilothermia.
3. The treatment of cerebral edema secondary to SE has not been well studied. When substantial edema is present, SE and cerebral edema are likely to be manifestations of the same underlying condition. Hyperosmolar agents may be valuable if edema is life-threatening. Edema owing to SE is vasogenic, so steroids may be useful as well.

EEG, *Electroencephalogram;* GCSE, *generalized convulsive status epilepticus;* IM, *intramuscular;* IV, *intravenous;* LRZ, *lorazepam;* MDZ, *midazolam;* NCSE, *nonconvulsive status epilepticus;* SE, *status epilepticus.*



• **Fig. 62.3** Management algorithm for status epilepticus. *IM,* Intramuscular; *IV,* intravenous; *LZP,* lorazepam.

Specific Agents

Benzodiazepines

A study in the Veterans Affairs medical system compared LRZ, diazepam followed by PHT, PHT alone, and PB as first-line agents and demonstrated that LRZ is the definitive agent of first choice for terminating SE.[55] The advantages of LRZ over PHT include (1) its longer duration of action against SE (4–14 hours as opposed to 20 minutes) and (2) a higher initial response rate.[56] One study concluded that children receiving PHT for SE were far more likely to require intubation for ventilatory failure than comparable children receiving LRZ[57]; the same was true for all ages in the San Francisco Prehospital Status Study.[58]

Recently the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) showed intramuscular midazolam (MDZ; 10 mg) to be as effective as IV lorazepam in the prehospital treatment of seizures, and this agent should be highly considered in patients with seizures who do not have IV access.[59] MDZ is also exceptionally useful for RSE, but it is hampered by tachyphylaxis,[60] which occurs because the $GABA_A$ receptors bearing benzodiazepine-sensitive subunits are removed from the neuronal cell membrane and replaced with receptors bearing benzodiazepine-insensitive ones.[61] Respiratory depression is the major adverse effect of all agents in this class when administered intravenously.

Hydantoins

PHT is an effective anti-SE agent but cannot be delivered rapidly enough to be used as a first-line agent. Its major advantage is a very long duration of action once an adequate dose has been administered (the 20-mg/kg loading dose reliably produces a total serum concentration above 20 µg/mL for 24 hours). Concerns about its IV administration were discussed earlier. If the patient is no longer in SE during PHT administration, a slower rate should be used.

PHT is highly insoluble, and it must be dissolved in sodium hydroxide and propylene glycol at a pH greater than 11 to remain in solution. Therefore extravasation can produce severe necrosis. The drug can also cause thrombophlebitis, which may result in the "purple glove syndrome."[62]

Fosphenytoin is a PHT prodrug, which is converted to PHT by phosphatases with a half-life of about 7 minutes. It is prescribed in "PHT equivalents," so the loading dose remains 20 mg/kg. The maximal recommended rate of infusion is 150 mg/min, but it should be started more slowly and increased to this rate if tolerated. Because it is water-soluble, extravasation does not pose the problem of skin and soft tissue necrosis. Hydantoins should not be used in absence SE, as they may worsen the condition.

Barbiturates

PB has long been one of the major anti-SE agents. Some advocate it as a first-line drug,[63] but it is rarely used in this role. It has classically been a third-line agent for control of SE, after a benzodiazepine and PHT. Its utility in SE is diminished by the length of time required to obtain a therapeutic effect in patients for whom treatment with a benzodiazepine and PHT has failed. It remains an important agent in patients with focal motor SE and in preparing patients for withdrawal from high-dose pentobarbital. It is important to note that, although barbiturates also act on $GABA_A$ receptors, they prolong the duration of chloride channel opening, in contrast to benzodiazepines, which increase the frequency of channel opening. Thus their combination should not be discredited, as their collaborative GABAergic actions may assist in terminating seizures.

Pentobarbital and thiopental are commonly reserved for the control of refractory SE, although thiopental is not currently available in the United States. Although these agents are effective if used in large enough doses, side effects often limit their use[64] or may even be fatal.[65] They are important when other rapidly available modalities have failed (see Box 62.3).

Valproate

Intravenous VPA, given in a dose of 20 to 30 mg/kg, has gained popularity for the treatment of SE because it does not produce respiratory depression or marked sedation. It has been successful in case series[66,67] but has not been directly compared to the other available agents. Hypotension may occur with large doses.[68] This drug should be avoided if the patient has an inborn error of metabolism affecting the liver, as it may precipitate fulminant hepatic failure.[69] VPA has a number of drug interactions that limit its utility in the ICU.[70]

Propofol

Propofol has been reported effective in RSE in doses up to 250 μg/kg per minute.[71] It offers more rapid recovery of consciousness after the agent is stopped compared with MDZ therapy, regardless of the duration of infusion.[72] We use it in RSE patients in whom MDZ therapy has failed or those who become resistant to MDZ.[73] A randomized trial found propofol to have the same efficacy as barbiturate therapy for RSE and significantly shorter length of mechanical ventilator days.[74] One should observe for evidence of the propofol infusion syndrome and stop the drug should a metabolic acidosis, hypertriglyceridemia, or evidence of muscle injury develop.

Levetiracetam

Although there are no randomized trials evaluating its efficacy, levetiracetam is frequently used as a second-line agent in seizure control. It is available for IV use, but its role in SE remains to be established. Although some retrospective studies have found it to have a higher failure rate than traditional drugs such as VPA for the treatment of RSE, its lower risk of side effects and drug interactions at times makes it a more desirable medication.[75] Levetiracetam exerts its antiseizure actions via binding of the synaptic vesicle protein 2, decreasing the rate of synaptic vesicle exocytosis in the CNS.[76,77] The effective dose in adults is reported to be between 1 and 6 g/day.[78] Oral administration may be useful for maintenance.[79]

Lacosamide

Lacosamide, which is available for both IV and oral use, is typically started at 200 mg twice daily and may be increased to 400 mg twice daily if needed.[80] Although prior studies with small sample sizes have provided mixed results regarding the benefits of adding IV lacosamide as a fourth-line agent in the treatment of RSE, larger prospective studies have shown a seizure termination rate of up to 76%.[81,82] It should be avoided in patients with atrioventricular block, and electrocardiogram studies should be checked before and after administration to evaluate for PR interval prolongation.

Ketamine

Although only anecdotes and small case series are available, ketamine appears to be a useful agent for the termination of RSE and SRSE.[83] Its NMDA blocking effect distinguishes it from the other agents discussed here, and it carries theoretical advantages in terms of brain protection.[84] Its antagonistic actions on NMDA receptors should be highly considered for the treatment of RSE or SRSE when other GABAergic medications are failing. Its intrinsic sympathomimetic effect makes it a useful choice in hypotensive patients, and it does not markedly impair ventilation. The appropriate dose in SE has not been established; we use a loading dose of 1 to 5 mg/kg, with an infusion rate of 1.5 to 5 mg/kg per hour.

Isoflurane and Desflurane

The inhalational anesthetics isoflurane and desflurane are effective in controlling RSE, but the difficulties involved in delivering the gases (such as the requirement for an anesthesia machine) and the need for a gas scavenging system have essentially confined their use to the operating suite or the recovery area.[85] Advances in delivery systems may make their use in the ICU more reasonable, but long-term use is potentially hepatotoxic.

Immunosuppressants

No etiology for RSE can be found in up to half of patients, for whom the term "new-onset RSE of unknown etiology" has been coined. Up to 37% of these patients are now recognized to have an autoimmune or paraneoplastic cause for their condition.[86,87] Early immunotherapy, unless contraindicated, should thus be considered in patients with new-onset RSE of unknown etiology and should not be delayed pending autoimmune antibody results if the suspicion exists. Although these situations of patients sometimes seem hopeless, it is important to remember that 35% will return to their premorbid level of function.[88]

Hypothermia

The recent HYBERNATUS (Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsant Action after Convulsive Status Epilepticus) study showed that addition of hypothermia to 33°C for 24 hours for the treatment of SE did not improve outcomes when compared to standard of care in French hospitals.[89] However, some experts advise a trial of mild hypothermia (32°C to 36°C) on a case-by-case basis as a therapeutic option for RSE.[90]

Controversial Management Issues

Controversy remains regarding the long-term neurologic consequences of periodic lateralized epileptiform discharges (PLEDs). PLEDs are an EEG phenomenon usually seen in the setting of large acute strokes or rapidly expanding mass lesions (e.g., tumors or abscesses). Less commonly, acute metabolic or toxic disorders will "reactivate" PLEDs in the vicinity of an old lesion. The EEG activity signifies the repetitive, synchronous firing of large numbers of neurons near the lesion; there is occasionally contralateral myoclonic jerking of the hand or face. Expert opinion is divided regarding the possibly epileptic nature of these phenomena. Patients who have clinical seizures (i.e., other than the myoclonic jerks) should receive antiseizure drugs. The myoclonic movements associated with PLEDs are difficult to suppress without resorting to high-dose barbiturates or benzodiazepines.

Another area of contention concerns the epileptiform discharges frequently seen after respiratory or cardiac arrests. Although certain EEG findings can assist with prognostication, multiple studies have now shown that SE (including myoclonus) is not a definite sign of poor prognosis in patients treated with hypothermia and experts recommend that it be treated aggressively when encountered.[91–94]

Prognosis

Wijdicks and Sharbrough reported that 34% of patients experiencing a seizure in any ICU at the Mayo Clinic died during that hospitalization.[20] In our prospective study of neurologic complications in

medical ICU patients,[1] having even one seizure while in the unit for a nonneurologic reason doubled the patient's in-hospital mortality rate. This effect on prognosis appeared to be due to the effect of the cause of the ictus, rather than the seizure itself.

Three major factors determine the outcome of SE: the type of SE, its cause, and its duration. In general, GCSE carries the worst prognosis for neurologic recovery as a consequence of SE itself. Focal nonmotor SE produces some risk of limbic system damage, usually manifested by memory dysfunction. Focal motor SE may produce neuronal damage, but this is difficult to discern from the effect of the lesion that commonly produces this form of SE. At the far end of the spectrum, absence SE does not seem to carry a risk of neurologic deterioration.

Most studies of SE outcome have concentrated on mortality rates in GCSE. Hauser[17] summarized the data available in 1990, showing mortality rates for SE to vary from 1% to 53%. The few studies that attempted to distinguish the mortality rate caused by SE from that of the underlying disease attributed rates of 1% to 7% to SE and 2% to 25% to its cause. The Virginia Commonwealth University population-based studies have analyzed the mortality risks for various aspects of GCSE.[25] SE lasting longer than 1 hour was associated with a 10-fold increase in mortality rate compared with SE lasting less than 1 hour. Other causes associated with marked increases in mortality rate were anoxia, intracranial hemorrhages, tumors, infections, and trauma. Independent factors associated with poor outcome in RSE include age older than 60 years, coma on presentation, and longer duration of anesthetic-induced coma,[95,96] whereas early seizure termination is associated with good outcomes.[97]

Very few findings are available regarding the functional status of GCSE survivors, and none reliably allows a distinction between the effects of SE and its causes. A review of intellectual impairment as an outcome of SE concluded intellectual abilities probably did decline as a consequence of SE.[98] Survivors of SE frequently have memory and behavioral disorders out of proportion to any structural damage produced by the cause of their seizures. This observation is supported by a wealth of experimental data and argues strongly for the rapid and effective control of SE.

The effect of the treatment of SE on the risk of subsequent epilepsy is uncertain. Experimental studies suggest that SE does lower the threshold for subsequent seizures.[99]

Key Points

- Primary generalized seizures arise from the entire cerebral cortex without evidence of focal point.
- SE is defined as 5 or more minutes of continuous seizure activity or seizure activity without return to baseline.
- NCSE should be suspected in any patient with GCSE who does not begin to awaken within 20 minutes.
- In addition to damaging the CNS, GCSE produces serious, often life-threatening, systemic effects that include cardiovascular, respiratory, and muscular systems.
- LRZ is the definitive agent of first choice for terminating SE.
- Hypersensitivity to PHT is the major adverse effect of concern to the intensivist. This allergy may be manifested solely as fever but more commonly includes a rash and eosinophilia. Rarely Stevens-Johnson syndrome occurs.
- Patients who have seizures during ethanol withdrawal will probably not benefit from chronic antiseizure drug treatment, and the administration of PHT will not prevent more withdrawal convulsions during the same episode.
- Errors in the use of medications to terminate SE include (1) use of inadequate doses of potentially effective agents and, conversely, (2) continued administration of drugs that are ineffective in the patient being treated.
- Seizures lasting longer than 1 hour markedly increase mortality risk compared with seizures lasting less than 1 hour.
- Myoclonic SE in the era of postarrest therapeutic hypothermia no longer carries a definite poor prognosis and SE in this setting should be treated aggressively.

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Review Questions

1. A 69-year-old man presents to the emergency department after three witnessed generalized tonic-clonic seizures that began 1 hour before arrival. Although he is no longer having convulsions, the patient has not yet returned to his baseline level of mentation. Which of the following medications should be the first-line therapy for this patient?

a. Diazepam 5 mg IV
b. Levetiracetam 1500 mg IV
c. Lorazepam 0.1 mg/kg IV
d. Phenytoin 20 mg/kg IV

Answer: c. The patient has had three seizures with no improvement in his mentation, meeting criteria for status epilepticus. The Veterans Affairs Status Epilepticus Cooperative Study confirmed lorazepam to be the most effective agent in terminating seizures compared with diazepam or phenytoin. Levetiracetam has not yet been shown as an effective first-line agent in terminating status epilepticus (SE).

2. An 82-year-old female nursing home resident with a history of chronic renal insufficiency, hypertension, and atrial fibrillation has been admitted to the intensive care unit (ICU) for treatment of pneumonia. The patient required intubation on presentation for hypoxemic respiratory failure. She has received 3 days of antibiotics with resolution of fevers, leukocytosis, and she has now been successfully weaned from vasopressor support. On hospital day 3 she has not yet awakened after sedatives have been discontinued for more than 24 hours. Which of the following most significantly increases her risk of nonconvulsive SE?

a. Chronic renal insufficiency
b. Elderly age
c. Administration of vancomycin
d. Septic shock

Answer: d. Although Oddo and colleagues[12] found chronic renal failure to be a risk factor for subclinical seizures in medical ICU patients, multivariate analyses revealed septic shock to be the only independent predictor, with up to 32% of these patients having abnormal continuous electroencephalograms (cEEGs). Antibiotics associated with lowering of seizure threshold include penicillins, carbapenems, and cefepime.

3. A 25-year-old woman has been admitted to the ICU for management of refractory SE. She is otherwise healthy, but she began experiencing personality changes 2 weeks before presentation. She experienced her first generalized tonic-clonic seizure 2 days ago and has progressed to nonconvulsive status epilepticus on cEEG refractory to benzodiazepines, phenytoin, phenobarbital, levetiracetam, and a propofol infusion. Her head computed tomography (CT) scan on admission showed no acute or chronic abnormalities and results of toxicology screens were negative. Which of the following studies should be performed next?

a. Cerebral spinal fluid (CSF)
b. Magnetic resonance imaging (MRI) of the brain
c. CT chest/abdomen/pelvis
d. Psychiatry evaluation

Answer: a. This patient is experiencing new-onset refractory SE of unknown etiology. The preceding psychiatric symptoms suggest a limbic phenomenon. Although an MRI brain scan could show medial temporal abnormalities suggestive of autoimmune limbic encephalitis, it is important to rule out any infectious etiology such as herpes encephalitis before initiating immunosuppressive therapies such as steroids. An autoimmune encephalitis antibody panel should also be sent from the CSF as well as serum, but immunotherapy should not be delayed pending these studies, which can take up to 3 weeks for results.

63

Head Injury

ALAN R. TURTZ AND JAMES C. BARRESE

CHAPTER OUTLINE

Incidence

Diagnostic Approach
- Glasgow Coma Scale
- Computed Tomography

Primary Head Injury
- Skull Fractures
- Epidural Hematoma
- Subdural Hematoma
- Traumatic Subarachnoid Hemorrhage
- Intraparenchymal Contusions and Hematomas
- Hypothalamic-Pituitary Injury
- Diffuse Axonal Injury
- Penetrating Brain Injury

Secondary Head Injury
- Basic Concepts
- Cerebral Blood Volume
- Brain Compartment
- Cerebrospinal Fluid Compartment

Specific Treatment Considerations
- Decompressive Craniectomy
- Management of Intracranial Hypertension
- Anticoagulation
- Seizure Prophylaxis
- Nutritional Support
- Role of Steroid Therapy

Conclusions

In the context of critical care medicine, the management of severe head injuries remains the Achilles' heel of neurosurgery, as borne out by our observations over 25 years of practice in academic Level I trauma centers. The search for neuroprotective and neuroregenerative treatments that can consistently prevent or reverse the devastating cascade of events that leads to irreparable brain damage remains for future investigators as of this writing.

Key to optimizing clinical outcomes has been the recognition that the time from injury to surgery must be as short as possible to minimize the secondary manifestations of serious brain trauma in patients with surgical lesions. The operating room is where patients with significant mass effect and shift are initially managed. The critical care unit is where all patients with severe traumatic brain injury (TBI) are managed, with or without surgery, in an effort to optimize cerebral blood flow (CBF), oxygenation, and metabolism.

The management of serious brain trauma requires specialty teams consisting of experienced neurosurgeons, traumatologists, intensivists, and neurointensivists working together in a dedicated unit equipped and staffed to optimally care for these patients. In the absence of such facilities, outcomes suffer.[1–3]

Throughout this chapter, the 2016 updated guidelines from the Brain Trauma Foundation (BTF) are noted at the time of this writing. These BTF guidelines are intentionally based on the limited studies with relatively high levels of scientific evidence. This approach results in focused conclusions that can be limited by study design and are, therefore, carefully worded to reflect the specific methodology of the study used to support a specific recommendation. Conversely, and equally important, is that the absence of a recommendation is based on the absence of sufficient evidence, so it is important to remember the maxim: absence of proof is not necessarily proof of absence.

Incidence

The Centers for Disease Control and Prevention report the number of patients sustaining a TBI to be at least 2.5 million per year in the United States.[4] Approximately 80% of patients are released from the emergency department, 275,000 are admitted, and 52,000 die. Nearly a third of all traumatic deaths in the United States involve a head injury. The ages most likely to sustain a TBI are children up to 4 years old and adults older than 64 years of age, with adults older than 74 years having the highest rates of hospitalization and death associated with head injury.[5] Teenagers and young adults continue to be at high risk for sustaining TBI, but the age range has decreased over time from between 15 and 24 years to between 15 and 19 years of age.[5,6] The incidence of head injury has been shown to be inversely proportional to economic status[7] and has remained up to three times more common in males in every age group over time.[5,8,9] In the United States, falls are the most common cause of TBI and are responsible for half of children up to 14 years of age who sustain head injuries and 60% of the adults older than 64 years.[5] Although the frequency of head injury related to motor vehicle crashes has decreased over the years to a little less than 20%, these crashes are the second leading cause of head injury in all age groups and result in the largest percentage of TBI-related deaths.[5,10] The incidence of TBI worldwide is difficult to quantify but is estimated to be at least 10 million people a year, with traffic accidents accounting for more than half and falls being the second leading cause[11]; this is the opposite of the distribution seen in the United States.[5] Violence is estimated to cause about

10% of head injuries throughout the world[11] as well as in the United States,[5] but there is significant variability in the specific mechanisms. For example, between 1997 and 2007 in the United States, firearms were related to just over a third of all violent, lethal TBIs compared with a single hospital in South Africa that reported its experience with more than 300 stab wounds to the brain.[12]

Diagnostic Approach

The presenting neurologic condition of patients with head injuries is the primary factor in determining the initial management and prognosis. When a detailed history is unavailable, it is important to keep in mind that loss of consciousness may have preceded and possibly caused the traumatic event, such as aneurysmal subarachnoid hemorrhage (SAH), hypoglycemia, intoxication, or syncope. Level of consciousness is one of the most important neurologic considerations in managing a patient with a head injury. Neurosurgical patients generally have an alteration in level of consciousness from either brainstem or bilateral cerebral hemispheric involvement. This may be secondary to poor perfusion owing to high intracranial pressure (ICP) or brainstem compression, both of which require emergent intervention either in an operating room or an intensive care unit (ICU). Therefore an accurate tool to measure level of consciousness is essential. Many clinical assessment tools are available for use in the critical care setting.[13–25]

Glasgow Coma Scale

Ideally, using the Glasgow Coma Scale (GCS), a nurse, medical student, paramedic, physician assistant, intensivist, trauma surgeon, emergency medicine physician, neurologist, and neurosurgeon all should obtain the same score when assessing a patient. The GCS system is not perfect, but it has proven itself to be, overall, a practical, straightforward grading system that can be used by health care professionals in various fields and at different levels of experience to produce reliable results.[26–31] The GCS has become the most widely used assessment tool and is considered the gold standard for the clinical evaluation of patients with head injuries.[13]

The GCS is a measure of level of consciousness and does not take into account focal deficits. It is based on eye opening (1–4 points), verbal response (1–5 points), and motor response (1–6 points) (Table 63.1). A patient with a normal level of consciousness should have the highest possible score of 15. The lowest score possible is 3, not 0 as might be expected. It is important to identify the score for each observed variable tested: E + V + M = GCS (where E denotes eye opening, V is verbal response, and M is motor response). Commonly, an intubated patient gets a 1 for verbal response and is assigned 1T (for Tube) for the verbal score. However, the American College of Surgeons (ACS) recommends that if a GCS component is untestable because of intubation, sedation, or another confounder, the reason for this should be recorded. The ACS suggests that a score of 1 should not be assigned because differentiation between a "true 1" and an untestable component is relevant.[32]

The GCS attempts to assign a numeric value to level of consciousness; a score of 15 is representative of normal. Therefore it is important to realize the shortcoming of this system in evaluating patients with dementia or aphasia. If a patient from a nursing home who has dementia presents with a normal level of consciousness after a fall but does not know what day it is, the GCS would be calculated as E4 + V4 + M6 = 14. A GCS score of 14 describes a patient with an abnormal level of consciousness but fails to accurately communicate this particular patient's condition. Likewise, clinicians must use caution when applying the GCS to patients with aphasia. Conversely, patients with profound focal deficits and a normal level of consciousness should have a GCS score of 15, illustrated by the case of a quadriplegic patient with a normal level of consciousness who is able to blink the eyes or stick out the tongue to command, thereby achieving a top score of 6 on the motor assessment.

TABLE 63.1 Glasgow Coma Scale

Component	Score
Eye Opening	
Spontaneously	4
To voice	3
To pain	2
No response	1
Verbal	
Oriented	5
Disoriented	4
Inappropriate	3
Incomprehensible sounds	2
No response	1
Motor	
Following commands	6
Localizing to pain	5
Withdrawing to pain	4
Abnormal flexion	3
Abnormal extension	2
No response	1

The GCS has been used to help predict outcome.[33] The motor score itself has predictive value as well.[34] The GCS score is best calculated after initial hemodynamic and pulmonary resuscitation and without sedatives or muscle relaxants, when clinically feasible[35] Aggressive implementation of early sedation and intubation in patients with severe head injuries compromises the ability to determine an accurate GCS score.[36]

Head injuries are typically classified as mild (GCS score 13–15), moderate (GCS score 9–12), or severe (GCS score 3–8), although there is debate that the GCS score of 13 should be in the moderate category.[37]

Computed Tomography

Computed tomography (CT) scanning is the diagnostic imaging study of choice in trauma. Plain x-ray films of the skull are rarely indicated as a screening study for patients with head injuries. Outcomes with the strategy of obtaining CT scans in all patients with head injuries are superior to those with other management strategies. The incidence of missed surgical lesions in patients with mild head injuries by CT scanning is as low as 0.028%.[38–41]

TABLE 63.2 Marshall Computed Tomography Classification

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on computed tomography scan
Diffuse injury II	Cisterns are present with midline shift of 0–5 mm and/or: lesion densities present; no high or mixed-density lesion >25 cm^3; may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift of 0–5 mm; no high- or mixed-density lesion >25 cm^3
Diffuse injury IV (shift)	Midline shift >5 mm; no high or mixed-density lesion >25 cm^3
Evacuated mass lesion	Any lesion surgically evacuated
Nonevacuated mass lesion	High- or mixed-density lesion >25 cm^3; not surgically evacuated

From Marshall F, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *J Neurosurg*. 1991;75:S14–S20.

TABLE 63.3 Prognostic Score Chart for Probability of Mortality in Patients With Severe or Moderate Traumatic Brain Injury by Computed Tomography Characteristics

Predictor	Score
Basal Cisterns	
Normal	0
Compressed	1
Absent	2
Midline Shift	
No shift or shift <5 mm	0
Shift >5 mm	1
Epidural Mass Lesion	
Present	0
Absent	1
Intraventricular Blood or tSAH	
Absent	0
Present	1
Sum Score[a]	+1

[a]The sum score can be used to obtain the predicted probability of mortality (see Table 63.4). The authors chose to add +1 to make the grading numerically consistent with the grading of the motor score of the Glasgow Coma Scale and with the Marshall computed tomography classification.
tSAH, Traumatic subarachnoid hemorrhage.

TABLE 63.4 Computed Tomography Classification by Prediction Score

Score	Mortality Rate (%)
1	0
2	6.8
3	16.0
4	26.0
5	53.0
6	61.0

A useful classification of brain injuries by findings on CT has been devised by Marshall and colleagues. This CT classification, presented in Table 63.2, can serve as a guide in describing scans and has strong predictive power.[36,42] Maas and associates have proposed a scoring system with better predictive power (Table 63.3), with a sum total adjusted to be consistent with the GCS.[36] Table 63.4 presents a mortality prediction chart based on this classification. This scoring system is best used as one piece of data in the overall clinical assessment in considering a patient's prognosis.[43] Severe brain injury outcomes can also be approximated using four variables: age, GCS score on admission (especially the motor score), CT characteristics, and the presence of ischemic and hemodynamic secondary insults. Using these four predictors, numerous investigators have used statistical modeling techniques to predict up to 80% or more of outcomes.[44]

Primary Head Injury

Primary head injury can be defined as the damage that occurs the moment an abrupt force affects the head and can take the form of skull fractures, contusions, lacerations, diffuse axonal injury, or vascular injury.[41] Some authors include the contusions and hematomas that blossom as a direct and immediate effect of the initial trauma as part of the primary injury as well.[45] These hemorrhages may develop significant mass effect requiring surgical intervention.

Management of a primary injury generally involves emergent neurosurgical intervention to limit secondary injury and prevent permanent damage to the central nervous system (CNS) in general and to the reticular activating system in particular. Located in the brainstem, the reticular activating system is what allows a meaningful, awake condition; if it is destroyed, the patient will be in a vegetative state.

The surgical management of patients with head injuries is typically driven by the presence of pathologic masses (hematomas) in anatomic spaces. These spaces are best described by reviewing the anatomic layers.

In most cases of head injury seen in neurosurgical practice, the pathogenic mechanism is an impact. The first layer involved is the scalp, the layers of which are best remembered by the pneumonic SCALP: S for *s*kin, C for *c*onnective tissue, A for galea *a*poneurosis, L for the *l*oose connective tissue layer, and P for *p*eriosteum. The scalp is the thickest skin in the body and absorbs some of the energy delivered to the head during impact. The scalp has a rich blood supply with relatively large blood vessels situated in the space where the connective tissue meets the galea aponeurosis. A large laceration has the potential for heavy blood loss and needs to be managed with local, direct pressure until surgical repair can be accomplished. Care must be taken in applying pressure if there is an underlying depressed skull fracture or defect, as is seen in

missile injuries. It should be noted that an unattended, serious scalp laceration does have the potential for enough blood loss to cause hemodynamic instability. This extracranial hemorrhage should be differentiated from an intracranial hemorrhage. An adult cannot lose enough blood volume from a contained intracranial hemorrhage to cause hypovolemia to the point of hemodynamic instability. Blood clots within the scalp usually are limited to the loose connective tissue layer and are referred to as subgaleal hematomas, which may be a feature of massive injuries or a sign of coagulopathy, but they rarely require treatment other than direct pressure if active bleeding is suspected. A cephalohematoma is a blood clot that expands in the potential space between the periosteum and the skull and is typically limited to neonates.

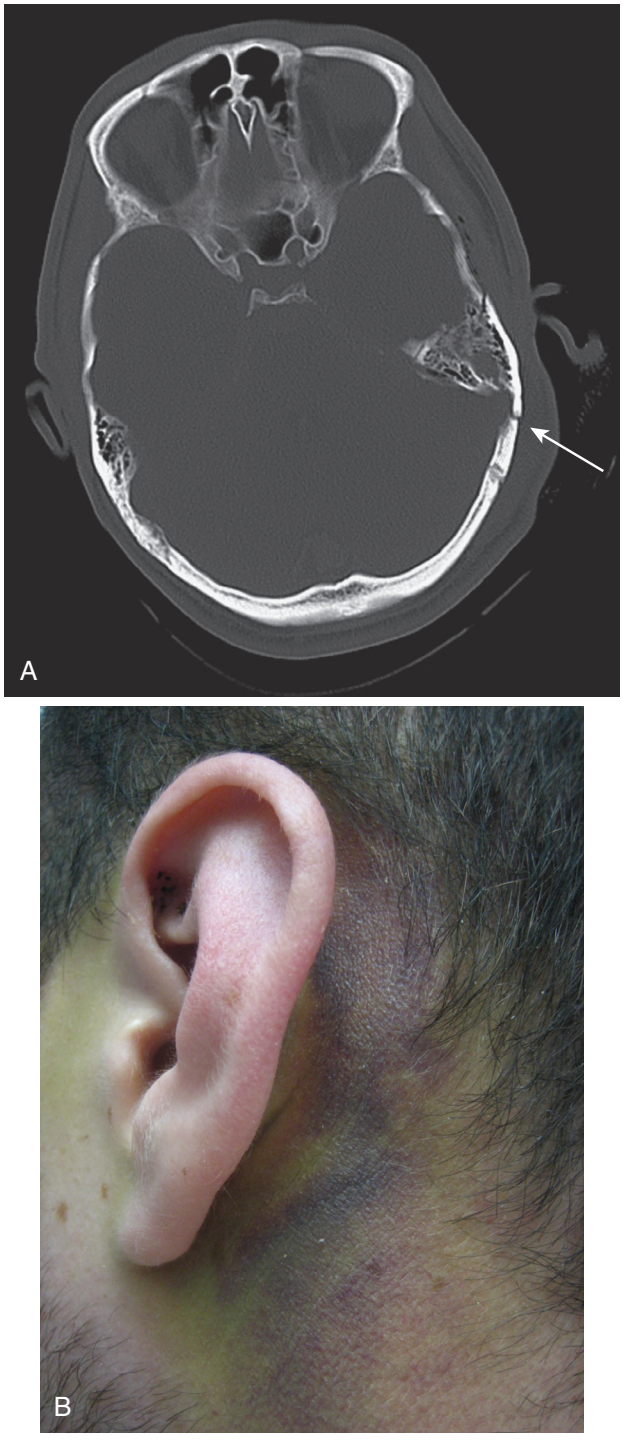
Skull Fractures

The next layer involved in trauma is the skull, composed of outer and inner tables with the intervening vascular diploic space. Skull fractures are best considered as involving the cranial vault or the skull base. Cranial vault fractures are further divided into linear or depressed, and open or closed. In general, closed linear fractures of the cranial vault do not require any specific treatment.

Basilar skull fractures are commonly linear and mostly involve the anterior cranial base and the petrous part of the temporal bone. Approximately 4% of significant head injuries include skull base fractures, with most (90%) the result of closed head trauma and the remainder involving penetrating trauma.[46] These fractures have the potential for an associated dural laceration adjacent to potentially contaminated paranasal sinuses, or the external ear canal if the tympanic membrane is disrupted. This allows the potential for a cerebrospinal fluid (CSF) fistula to develop, as well as meningitis. Clinical signs of a fracture of the petrous portion of the temporal bone include hemotympanum with or without tympanic membrane disruption, hearing loss, CSF otorrhea, and Battle sign. The cranial nerves that course through the temporal bone include the facial, acoustic, and vestibular nerves; therefore associated vestibular dysfunction or facial weakness may be noted (Fig. 63.1). Anterior cranial base fractures may be associated with "raccoon eyes," anosmia, and CSF rhinorrhea. It is important to remember that when a fracture of the floor of the anterior cranial base is suspected, a nasogastric tube should not be inserted because of the risk of intracranial penetration (Fig. 63.2).

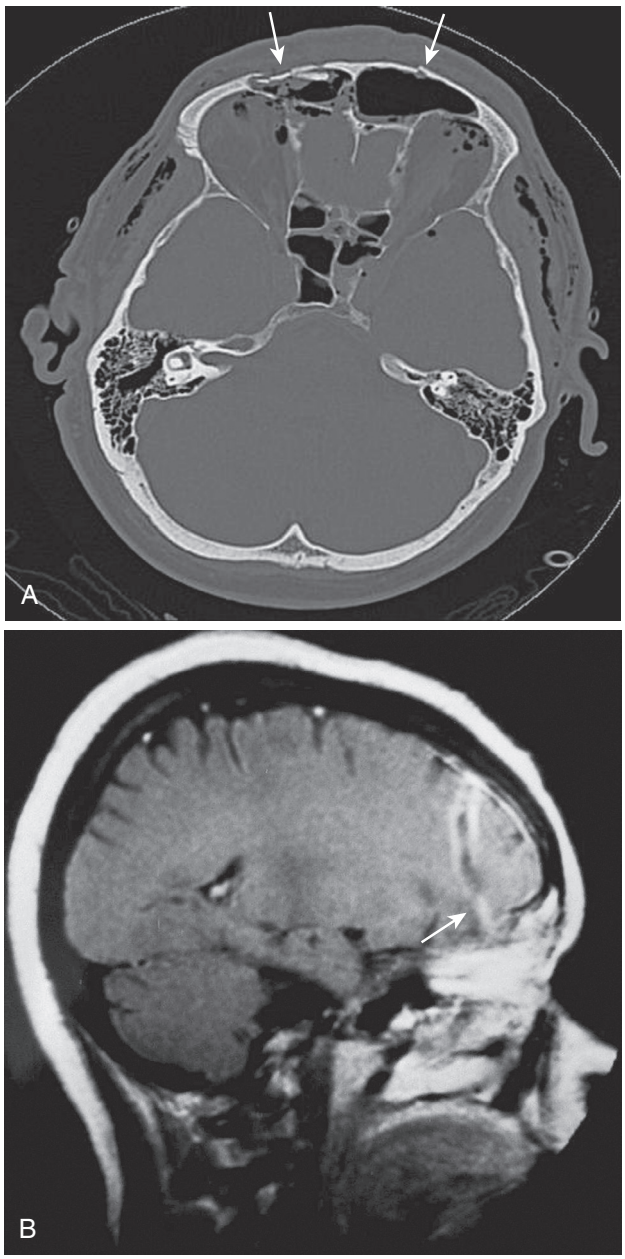
The use of prophylactic antibiotics in basilar skull fractures has been debated but generally is not recommended. A 2016 study of basilar skull base fractures observed associated CSF leaks in 15% and meningitis in less than 4% of patients. All cases of meningitis were in patients with a clinically evident CSF leak. The researchers concluded that there is no indication for prophylactic antibiotics in patients with skull base fractures.[46] When CSF leak does occur, the fistula will usually heal with conservative treatment over the course of a week, unless the defect is very large or a bony spicule is identified. Keeping the patient's head elevated and possibly using external CSF diversion after a few days are reasonable nonoperative methods; however, if the leak persists, surgical repair is indicated.[47]

Most depressed skull fractures occur in men younger than 30 years of age.[48] Despite little literature to support any particular management strategy, closed depressed skull fractures are generally operated on if the extent of depression is greater than the full thickness of the adjacent skull, with theoretical benefits of a decrease in late-onset posttraumatic epilepsy and a reduction in the incidence of persistent neurologic deficit, as well as an improved cosmetic result.[7] Many depressed skull fractures are open[48] (Fig. 63.3), meaning that a scalp laceration with galeal disruption overlying the fracture is present.



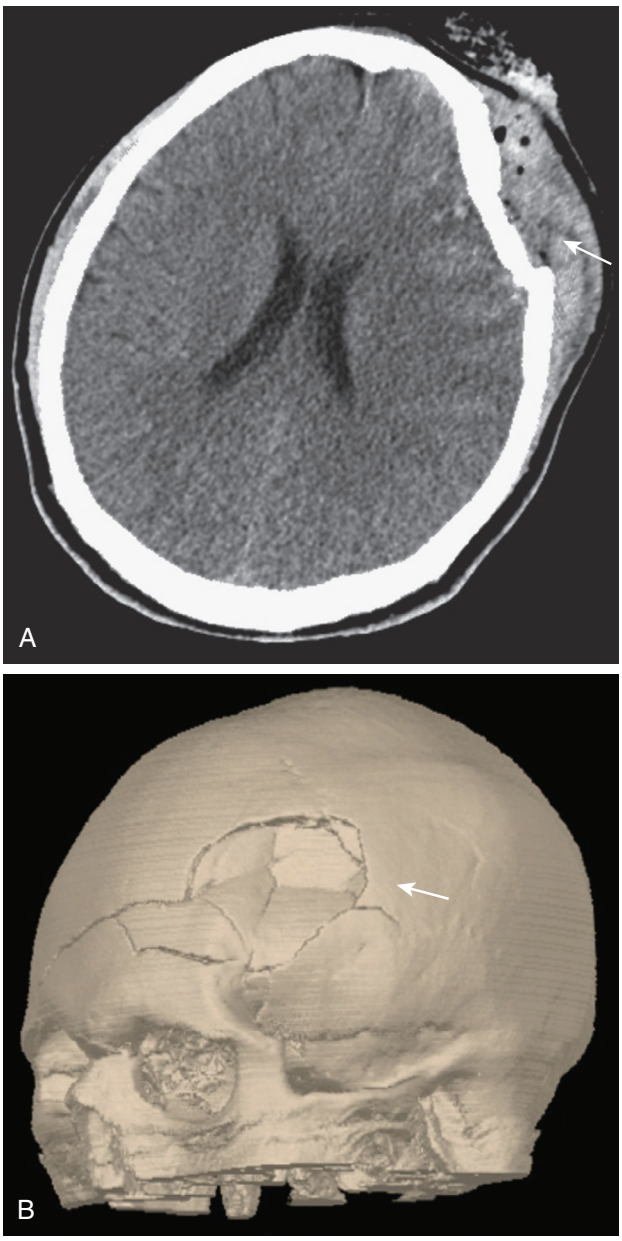
• **Fig. 63.1** A, Axial computed tomography image demonstrating skull base fracture *(arrow)* through the petrous portion of the temporal bone. B, Battle sign.

Open depressed skull fractures may be associated with significant morbidity and mortality.[48,49] Infection rates are reported to be between 1.9% and 10.6%,[49–53] with neurologic morbidity and mortality rates of approximately 11% each[50] and an incidence of late epilepsy up to 15%.[54]



• **Fig. 63.2** A, Preoperative axial computed tomography image demonstrates multiple anterior cranial base fractures involving the cribriform plate and posterior wall of the frontal sinus *(arrows)* in a 50-year-old man who fell off a ladder onto his face. The patient sustained minimal brain injury from the impact because the facial and anterior frontal sinuses absorbed much of the energy, cushioning the brain during impact, much like an air bag. B, Image from a preoperative sagittal T1 magnetic resonance imaging study without contrast demonstrates the tract of a nasogastric tube through the frontal lobe in a 42-year-old woman with an anterior cranial base defect *(arrow)*.

By convention, open depressed cranial vault fractures are treated surgically, with debridement and elevation, primarily to attempt to decrease the incidence of infection. Open depressed cranial fractures may be treated nonoperatively if clinical and radiographic examination reveals no evidence of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination.[50]

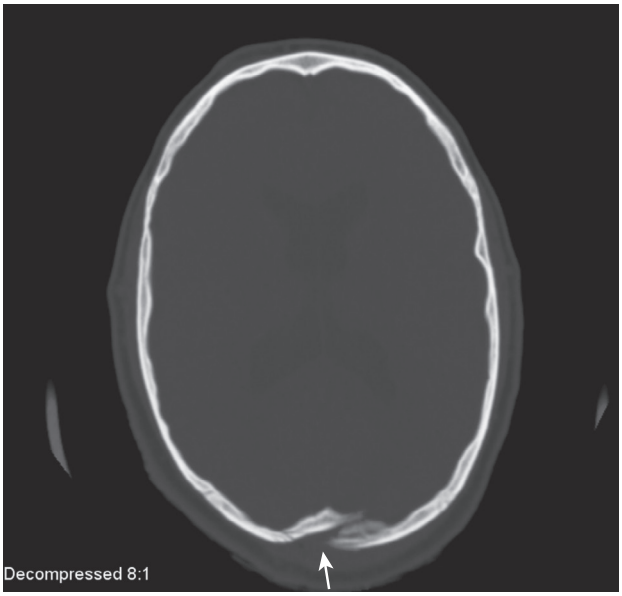


• **Fig. 63.3** Depressed skull fracture. A, Brain window *(arrow)*. B, Computed tomography three-dimensional reconstruction also demonstrates the depressed skull fracture *(arrow)*.

A special type of depressed fracture involves the frontal sinus. Depression of the fracture may require surgery to prevent CNS infection and CSF leak (Fig. 63.4). Another special type of depressed fracture involves a major dural venous sinus (see Fig. 63.4). Under these circumstances, the risks associated with surgery are increased, and elevation of the fracture fragment generally is reserved for significant compromise of venous drainage.[47]

Epidural Hematoma

The next anatomic layer below the skull is the dura, which is the periosteum of the inner table of the skull and, as such, is tightly adherent to the bone. The potential space between the inner table of the skull and the dura is the *epidural space*. Epidural hematomas (EDHs) expand this potential space between the skull and the



A

B

• **Fig. 63.4** Depressed skull fracture requiring urgent decompressive surgery. The patient was a 32-year-old man hit on the back of the head by a metal beam at a construction site who presented with a deteriorating level of consciousness. A, Axial computed tomography scan demonstrates an open depressed skull fracture *(arrow)* at the level of the superior sagittal sinus (SSS) that extended down to the confluence of the transverse and SSS. B, Sagittal magnetic resonance venogram demonstrates occlusion of venous outflow *(arrow)* at the level of the fracture, which necessitated emergency surgical decompression and repair of the SSS.

dura. The most common mechanism for the development of an EDH is a motor vehicle crash (in 53% of the cases), followed by falls (30%) and assault (8%).[55–63] Typically bleeding results from damage to the middle meningeal artery, a dural vessel that runs half in the dura and half through a groove along the inner table of the skull. When a fracture extends across the bony groove of the artery, it can tear and bleed. An EDH also can occur from injury to the middle meningeal vein, diploic veins, or venous sinuses.[63]

EDHs generally occur in the temporal and temporoparietal regions (Fig. 63.5).[55,60,64–67] A useful way to describe the development of an EDH is to follow the clinical events that occur when a patient presents with a lucid interval following a brief loss of consciousness after head trauma. A lucid interval occurs when a patient initially is rendered unconscious from a concussive head injury that causes a linear skull fracture involving the middle meningeal artery with bleeding into the potential epidural space. Because the dura is tightly adherent to the inner table of the skull, significant force is needed to push the dura off the inner table. An arterial hemorrhage generally has enough pressure to strip the dura off the bone, converting the potential epidural space into a mass. The bony attachment of the dura becomes progressively stronger with age; therefore the dura of a younger patient requires less force to push off the bone than would be required in an older patient. Not surprisingly, the mean age of patients with an EDH is between 20 and 30 years of age,[56–58,66–73] and EDHs are unusual in patients older than 50 years.[63]

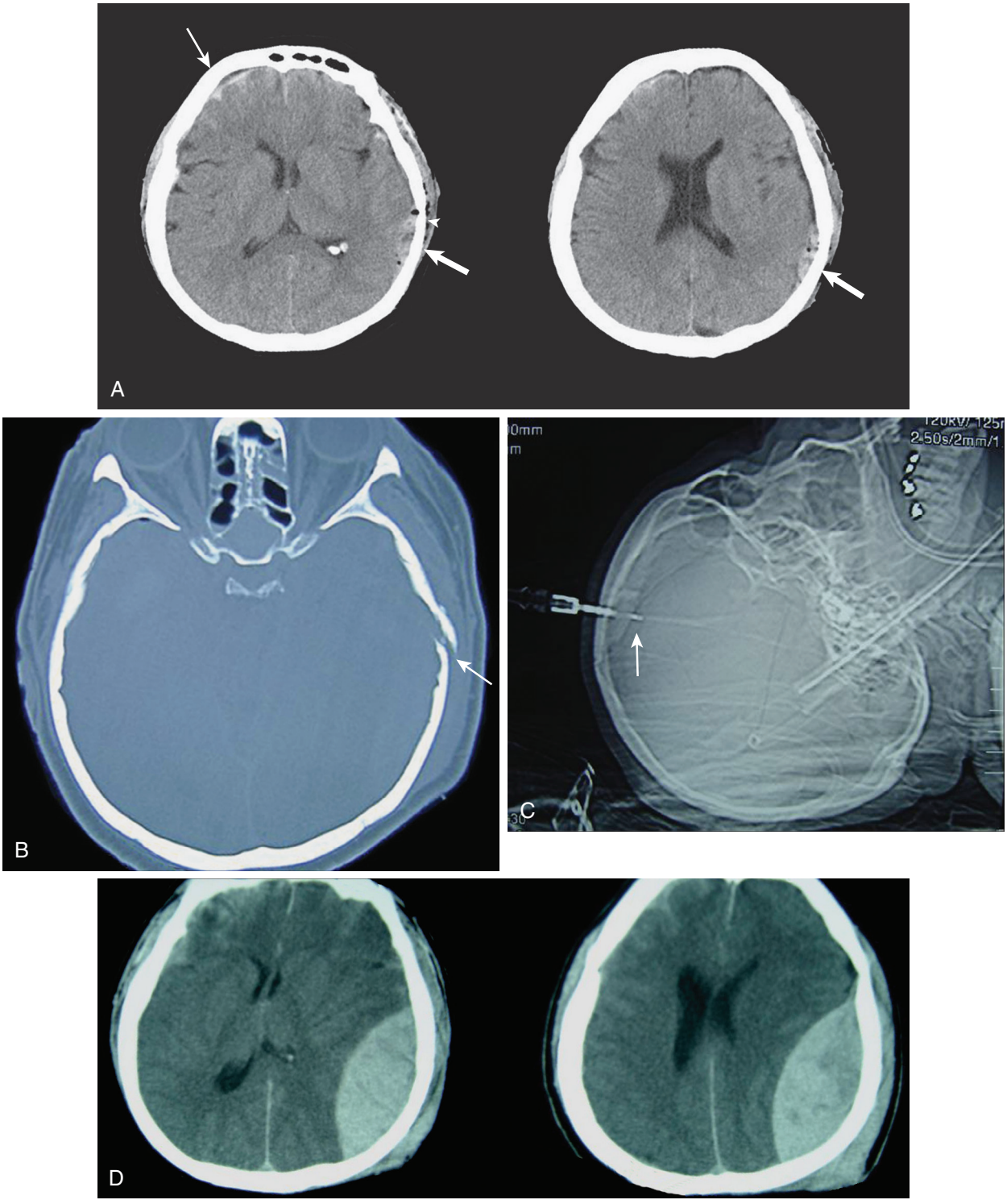
The growing epidural mass commonly compresses the anterior temporal lobe, which usually does not cause a major detectable neurologic deficit early in the course in the emergency department. During this lucid component of the lucid interval, the patient regains consciousness from the concussive injury while the EDH is expanding and compressing the clinically silent anterior temporal lobe. The medial part of the temporal lobe, the uncas, lies just lateral to the brainstem at the level of the third cranial nerve (oculomotor nerve), which runs alongside the tentorial edge. When the EDH enlarges to the point at which it pushes the uncas of the temporal lobe over the tentorial edge, rapid development of a third nerve palsy, along with brainstem compression, is possible. This may cause a contralateral hemiparesis from direct compression of the cerebral peduncle and a decrease in level of consciousness from the effect on the reticular activating system in the brainstem. The classic signs at this point are coma with a dilated pupil ipsilateral to the EDH and a contralateral hemiparesis. Occasionally, instead of directly compressing the ipsilateral cerebral peduncle, the herniating uncas can shift the brainstem itself into the contralateral tentorial edge, a relatively sharp rigid structure. This can damage the brainstem on the side opposite the EDH and cause a hemiparesis ipsilateral to the side of the hematoma. This is known as Kernohan notch phenomenon.

Taking a general view, the patient progresses from unconscious at the time of impact from a concussive injury, to awake, to unconscious again secondary to brainstem compression—hence the term *lucid interval*. The lucid interval is observed in close to half of the patients undergoing surgery for EDH.[a]

Pupillary abnormalities occur in approximately 20% to 30% of patients with surgical EDH.[55,57,62,63,70] Cranial fractures are present in between 70% and 95% of the cases.[b] Associated intracranial lesions are found in 30% to 50% of adults with surgical EDHs,[c] and subdural or parenchymal lesions in association with EDH lower the chance of a good outcome.[63]

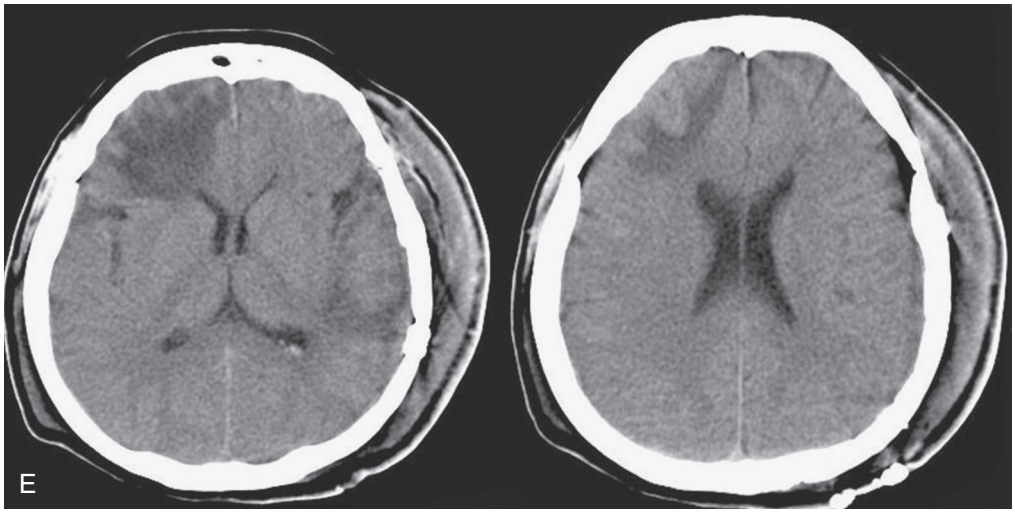
The overall mortality rate (for all ages and GCS scores) is approximately 10%.[d] The time lapse between the onset of pupillary abnormalities and surgery determines outcome,[64,69,83] but the single most important predictor of outcome in patients who undergo

[a]References 55, 58, 63, 68, 72, 74–76.
[b]References 57, 63, 71, 73, 77, 78.
[c]References 55, 57, 58, 60–63, 66–70, 76, 79, 80.
[d]References 57, 58, 67, 68, 71, 75, 76, 81, 82.



• **Fig. 63.5** The patient was a 58-year-old female pedestrian who was hit by a car and unconscious at the accident scene. She was combative on presentation, pharmacologically paralyzed, and intubated in the trauma bay. A, Computed tomography (CT) image shows a small left temporal epidural hematoma without significant mass effect *(large arrow)*. Note the right frontal traumatic subarachnoid hemorrhage *(small, thin arrow)* and the small amount of air *(arrowhead)* from the associated open, linear fracture *(arrow)*, seen in B. There is no significant mass effect, and an intracranial pressure monitor *(arrow)* was placed, seen in C. Intracranial pressure steadily increased shortly after placement, and immediate follow-up CT scans, shown in D, reveal marked expansion of the epidural hematoma with mass effect and shift requiring emergency craniotomy.

Continued



• **Fig. 63.5, cont'd** E, Postoperative CT scans reveal adequate decompression of surgical clot, with subsequent development of edema on the right side of the brain.

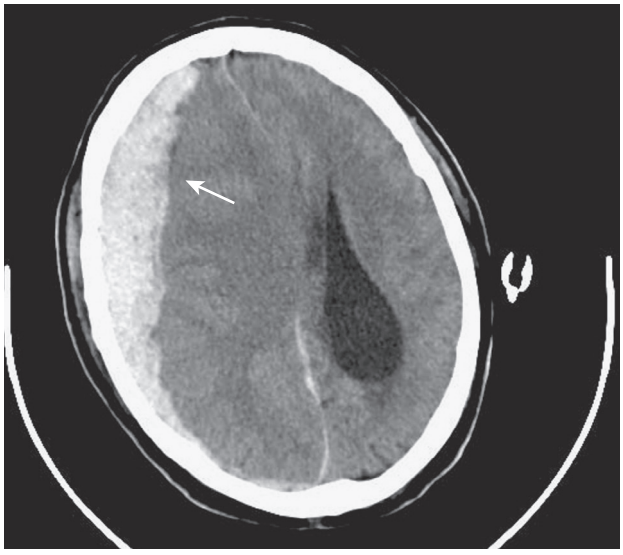
surgery for EDH is the GCS score on admission and before surgery.[55,56,58,64,84–86]

Not all EDHs, however, require surgery. No prospective randomized trials have been conducted to compare surgical treatment with nonoperative management, nor should there be. Available data describe nonsurgical management in selected cases. In one study, approximately 10% of the total number of EDHs were treated nonoperatively. All patients were conscious with a GCS score greater than 11 and a midline shift on CT scan of less than 10 mm. Not one of these nonoperative hematomas was in the temporal region.[87]

Another study reported findings in a group of 57 selected patients treated nonoperatively with an initial GCS score of 10 or higher, with maximum hematoma thickness less than 13 mm, with 5 clots located in the temporal region, but only one patient had a midline shift on CT.[56]

An interesting approach for dealing with thin, acute EDHs in an early stage has been reported in a small, isolated series of patients using endovascular techniques to occlude the middle meningeal artery.[88] Surgical decision making for an acute EDH is based on GCS score, pupillary findings, comorbid conditions, CT findings, age, and, in delayed decisions, ICP. Guidelines for the surgical management of acute EDH published in 2006 recommend surgical evacuation of an EDH greater than 30 mL in volume, regardless of GCS score. Smaller hematomas in patients with a GCS score greater than 8 and without focal deficits, clot thickness less than 15 mm, and less than 5 mm of midline shift may be considered for nonoperative management. Close neurologic monitoring and serial CT scanning are essential if a nonoperative approach is taken. Of importance, a temporal location for an EDH is associated with failure of nonoperative management and should lower the threshold for surgery.[63]

The time between neurologic deterioration and surgery is critical, and the question of whether a patient with an acute EDH should receive treatment at the nearest hospital or be transferred to a trauma center is important. The issue is whether or not a non-neurosurgeon should operate on a patient whose condition is deteriorating from an acute EDH is a true emergency. One suboptimally controlled study reported worse outcomes in a small group of patients who underwent emergency operations by non-neurosurgeons and attributed this mainly to the technical inadequacy of the operation.[62,63] Other studies have documented worse outcomes in patients transferred from outlying hospitals for surgery.[55,76] The take-home message is that EDHs are extra-axial hemorrhages located adjacent to the brainstem that can represent a true neurosurgical emergency, and that rapid, competent decompression makes a difference.



• **Fig. 63.6** Axial computed tomography scan demonstrating a typical acute subdural hematoma *(arrow)*. Note that the hematoma expands the subdural space and follows the contour of the brain as it generates severe extra-axial mass effect and shift.

Subdural Hematoma

Deep to the epidural space, below the dura, is the subdural compartment. Unlike the potential epidural space, the subdural compartment is a real space. It is a compartment that follows the contour of the brain, which is how it appears on a CT scan (Fig. 63.6). Anatomically, bridging veins course through the subdural space from the cerebral hemispheres to the superior sagittal sinus. As the brain accelerates within the skull, these veins can stretch and tear.[89] The source of bleeding can also be from a cortical artery[90,91] or vein.

These hematomas typically form over the surface or between the cerebral hemispheres, over the tentorium, or along the skull base.

Acute SDHs consist of clotted blood, which is fibrous and can be adherent to adjacent tissue. The blood remains clotted for several days. After this time, the clot gradually and progressively lyses, resulting in a mixture of clot and fluid as it transitions to the subacute phase. After several weeks, the clot is fully liquefied and becomes a chronic SDH. Chronic SDHs may manifest weeks or months after what may have been mild or insignificant trauma. Chronic SDHs occur more often in elderly patients and individuals who have more of a subdural space because of cortical atrophy. A membrane often surrounds these hematomas, and the collection of fluid may slowly grow in size because of repeated small bleeds or accumulation of fluid transudate from the membrane.[89]

The incidence of acute SDHs is approximately 20% in severe TBI,[63,92–95] and the mean patient age is between 31 and 47 years, with most patients being men.[63,96–99] The mechanism of injury differs between age groups, with patients older than 65 years more commonly presenting after a fall and younger patients more often being involved in a motor vehicle crash,[63,100–102] which, among comatose patients with acute SDH, is the most common mechanism of injury.[63,93,95,103]

Between 37% and 80% of patients with acute SDH present with a GCS score of 8 or lower,[a] and the overall mortality rate is between 40% and 60%.[b] Mortality rates among comatose patients requiring surgery are somewhat higher, with reported rates between 57% and 68%.[c] Acute subdural hematomas are frequently associated with other brain injuries,[99,104] which is one of the reasons why the mortality rate is relatively high.

A simple acute SDH is a subdural, extra-axial hematoma without any other associated brain injury (Fig. 63.7). A complex SDH is associated with parenchymal injury (Fig. 63.8).[109,110] Fewer than half of acute SDHs requiring surgery are isolated, simple lesions.[63,99,104]

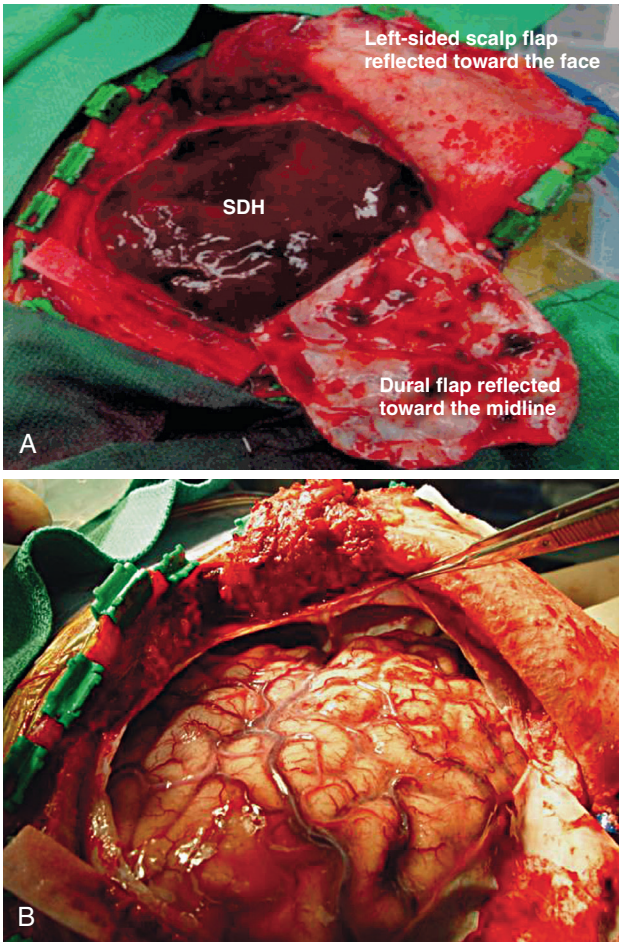
One useful method to identify the presence of associated injury is to measure the thickness of the subdural clot relative to the amount of brain shift on the CT scan. If the amount of shift is directly proportional to the thickness of the extra-axial clot, the injury is likely to be simple and the brain simply compressed. However, if the amount of shift is more than expected as indicated by the size of the hematoma, then additional parenchymal brain injury probably is present under the clot, causing additive mass effect. Not surprisingly, the mortality for complex injuries is higher than that for simple SDHs.[109,110]

In addition to the obvious compressive effects that an SDH generates, the available evidence points to a direct toxic effect of the blood itself on the underlying cortex, potentially compounding the problem.[111,112]

Age is an important factor in acute SDHs. There is a significant increase in poor outcome among patients older than 60 years of age with severe head injury in general.[95,100–103,113,114] Older patients with an acute SDH and a low GCS score do especially poorly.[100–103,113,114]

The decision for immediate surgery is dependent on GCS score, age, pupillary examination, comorbidities, CT findings, and salvageability with respect to the patient's level of injury. In addition to all of these factors, decision making for delayed surgery is dependent on clinical course and ICP.[63]

[a]References 63, 68, 74, 96, 99, and 104.
[b]References 63, 69, 94, 97, 98, and 105–108.
[c]References 63, 79, 82, 93, 94, 103, and 108.



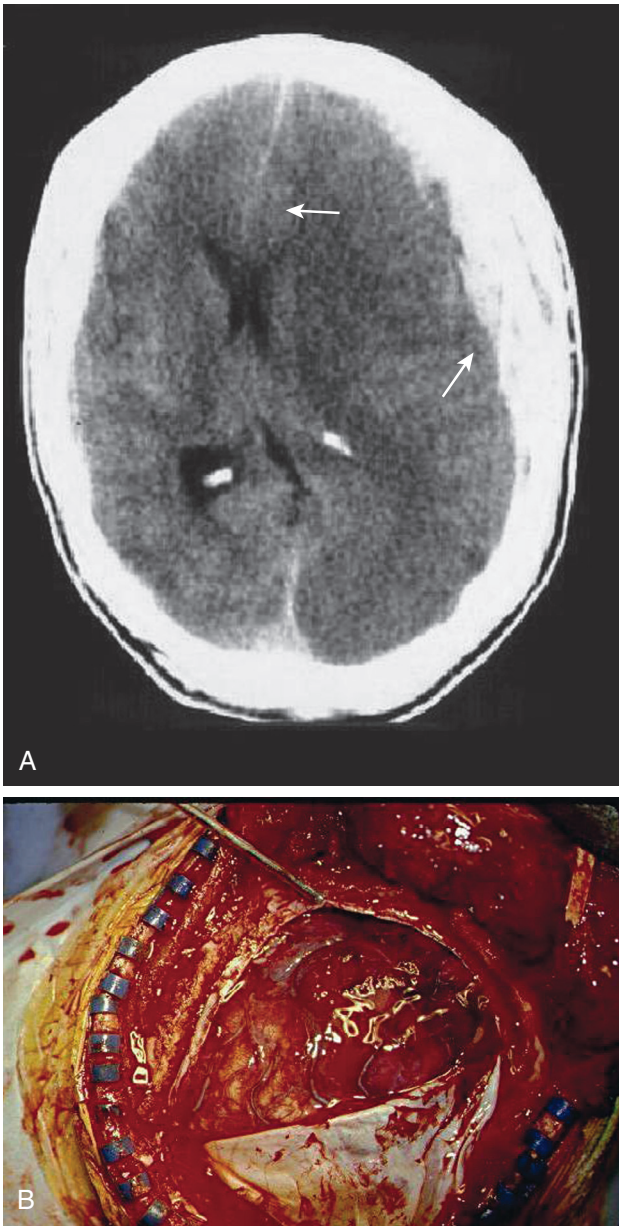
• **Fig. 63.7** A, Intraoperative view of a solid subdural hematoma *(SDH)* on the surface of the brain. B, Decompressed brain with demonstration of evacuated subdural space.

On the basis of a contemporary search of the literature, Bullock and colleagues found that CT parameters of a midline shift greater than 5 mm and/or a clot thickness greater than 10 mm were independent factors requiring surgery in salvageable patients. They also identified a select group of comatose patients with smaller SDHs who could be managed nonoperatively if the patients remained neurologically stable with normal pupils and ICP of 20 mm or less.[63]

Traumatic Subarachnoid Hemorrhage

The subarachnoid space is a CSF-filled compartment within which are the major cerebral blood vessels. The CSF within the subarachnoid space fills the basal cisterns and interdigitates into the cortical sulci. Traumatic SAH can be caused by bleeding of cortical arteries, veins, or surface cerebral contusions.[115]

In contrast with hemorrhages in other locations, SAH is not a discrete surgical clot that requires evacuation. Trauma is the most common cause of SAH, and a ruptured aneurysm is the most common cause of a spontaneous SAH. Aneurysmal SAH generally involves the suprasellar cistern, where the circle of Willis lies. Traumatic SAH can be found as small-volume hemorrhages in the sylvian fissures and interpeduncular cistern. Traumatic SAH also commonly involves the cerebral convexity and can fill cortical



• **Fig. 63.8** A, Computed tomography scan of acute, complex left-sided subdural hematoma (SDH) *(lower arrow)* with mass effect *(upper arrow)* disproportionate to the size of the clot, indicating more than just the effect of an extra-axial compressive mass—that is, intrinsic, parenchymal brain injury with edema. B, Intraoperative photograph of decompressed brain reveals hemorrhagic, inflamed, and edematous brain swelling out through the cranial defect. Compare with the intraoperative photograph of the simple SDH in Fig. 63.7.

sulci, which can sometimes mimic sulcal effacement[116] (Fig. 63.9A). Occasionally, the distribution of the hemorrhage may be hard to differentiate from an aneurysmal hemorrhage. Under this circumstance, a vascular study should be obtained (Fig. 63.9B).

Cerebral vasospasm after aneurysmal SAH is a common, well-described problem with an unclear pathogenesis. In general, traumatic SAH has not been considered a cause of clinically relevant cerebral vasospasm, but increasing evidence suggests that SAH from trauma may cause clinically significant cerebral vasospasm, which may be responsible for ischemia and infarction.[117,118] Clearly the incidence of clinically relevant cerebral vasospasm is less than what is seen in aneurysmal SAH; however, posttraumatic SAH may cause ischemia during the acute as well as the delayed phase.[117,119]

In severe nonpenetrating head injury, the degree of SAH can help predict outcome,[120,121] and although traumatic SAH can be an isolated finding, it is commonly associated with other intracranial injuries.[122] Traumatic SAH can be a marker of severe primary injury, and the amount of blood can also be an independent predictor of the development and progression of intraparenchymal contusions[115] (Fig. 63.9C).

Intraparenchymal Contusions and Hematomas

Traumatic parenchymal mass lesions are common and are reported in 13% to 35% of severe TBI.[123–129] Contusions consist of heterogeneous areas of necrosis, pulping, infarction, hemorrhage, and edema.[130–132] Hemorrhagic contusions are mixtures of blood and edematous cerebral parenchyma that also have a heterogeneous appearance on CT.[130] Contusions commonly occur in the frontal and temporal lobes at the poles and on the inferior surfaces as a result of contact with the rough, bony skull base[133] (Fig. 63.10A).

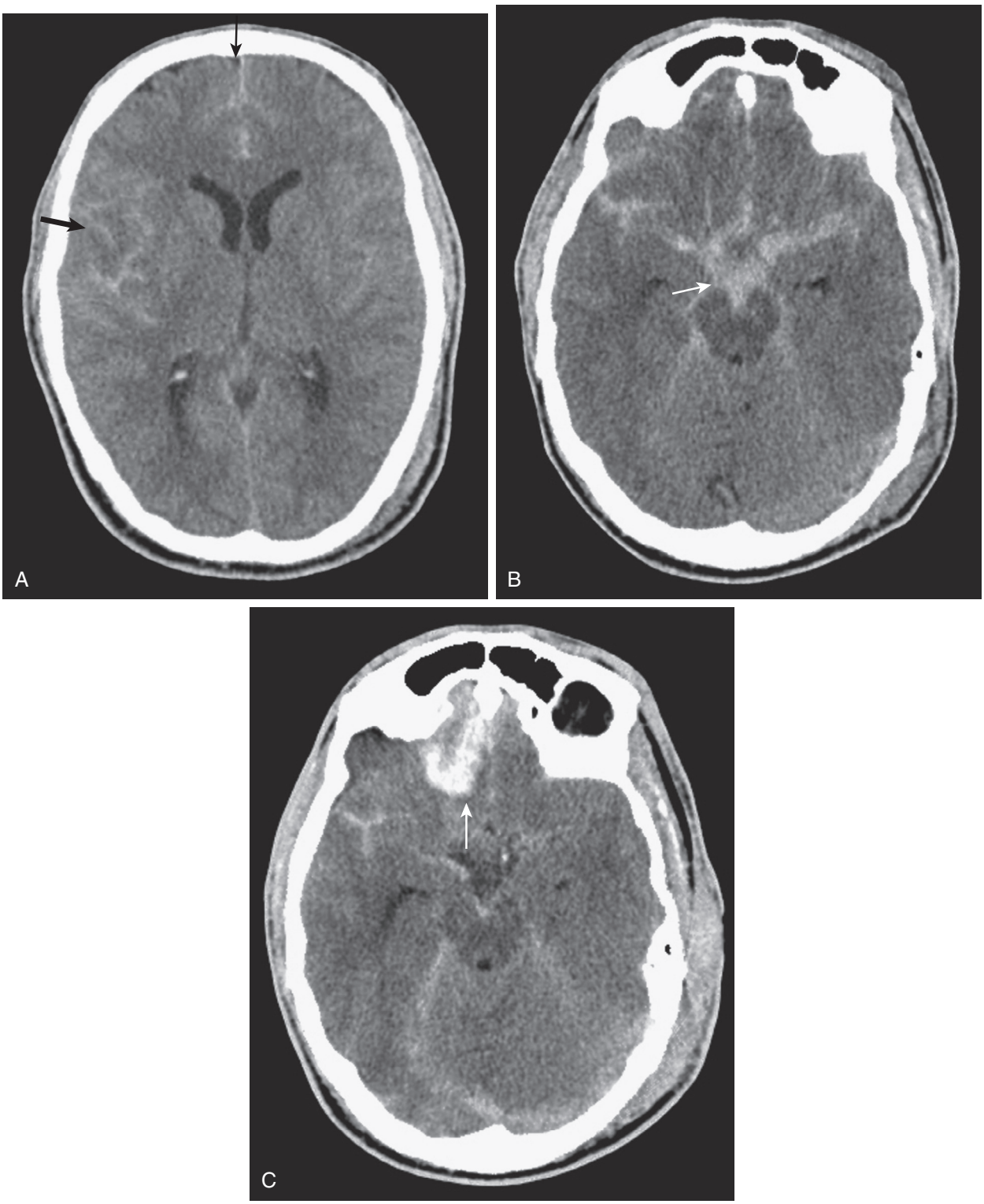
Contusions typically involve the crests of the gyri but in more severe injury may extend into the substance of the white matter. If the pia-arachnoid is torn, contusions are classified as cortical lacerations.[133–135]

Contusions represent one end of a spectrum of injury on which hematomas, which are well-defined, homogeneous collections of blood, are the other end (Fig. 63.10B). The amount of energy delivered may have only been enough to cause failure of small vessels, resulting in contusions. If more energy is delivered, failure of larger vessels may occur, resulting in hematomas. Alternatively, the hemorrhagic component of a contusion may continue to bleed and coalesce into a more discrete hematoma. In general, the most common traumatic parenchymal lesions are contusions,[130] and they tend to evolve.[124,128,129,136,137]

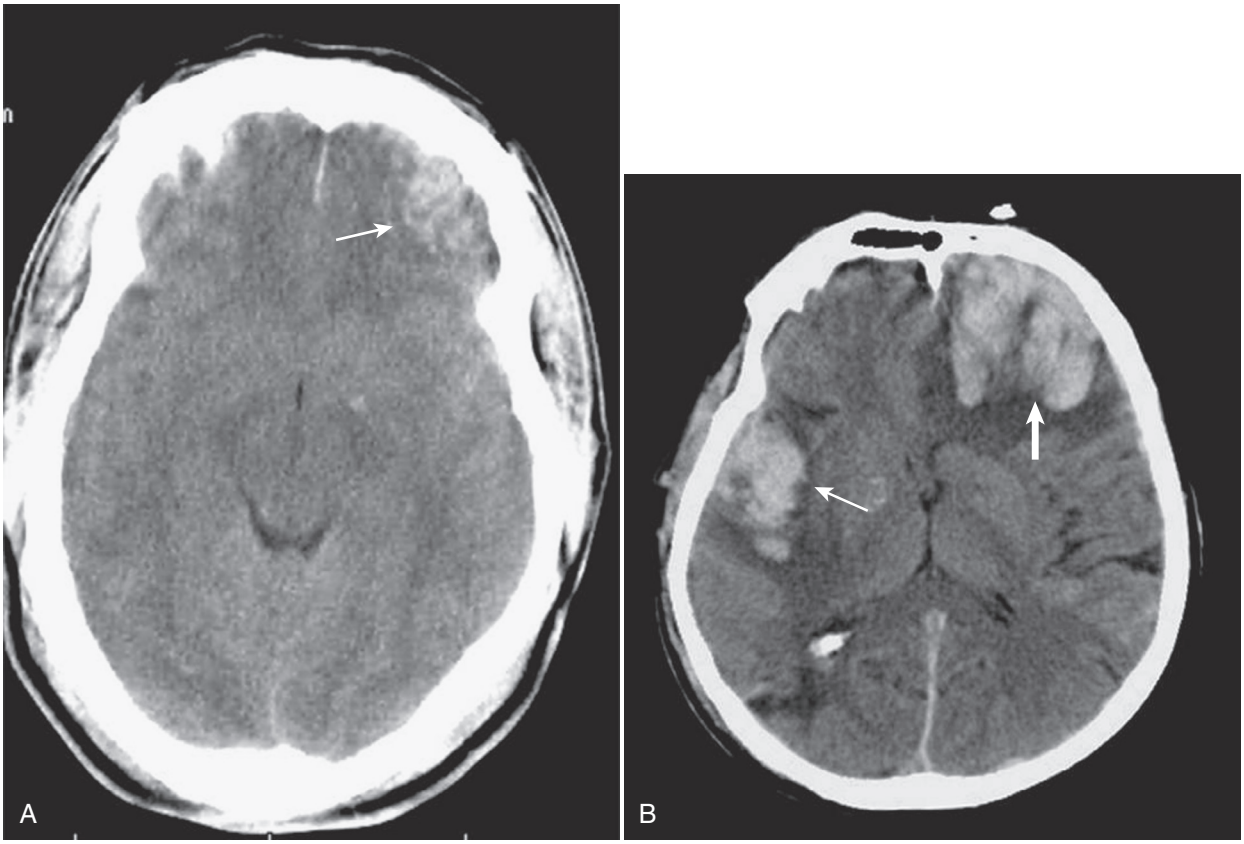
Risk factors for the progression of intraparenchymal hemorrhage include the presence of SAH (see Fig. 63.9C) and subdural hematoma, as well as the size of the clot on the initial CT scan. Enlargement of contusions occurs approximately 40% of the time, which justifies early follow-up CT scanning.[138] In addition to the problem of progressive enlargement of existing contusions is a phenomenon of *d*elayed *t*raumatic *i*ntracerebral *h*emorrhage (DTICH). DTICH is defined as a new hemorrhage identified on a CT scan in an area of brain that was normal on the admission CT scan. These delayed hemorrhages are reported to occur in up to 7% of patients with severe head injuries.[92]

Contusions can be subdivided into two groups. *Coup* contusions occur in the brain tissue under the impact site and are usually associated with an acceleration injury. *Contrecoup* contusions are located away from the point of impact and are usually associated with a deceleration injury.[133,134,139–141]

Understanding the biomechanics of how a contrecoup contusion develops is useful. In general, biologic tissues tolerate strain better if they are deformed slowly rather than quickly. For example, a 150-mL hematoma with accumulation of blood over minutes is likely to be lethal, whereas a 150-mL slow-growing meningioma may have no appreciable effect on the patient's level of consciousness. In trauma, the cause of tissue damage may be any of three types of induced strains: compression, tension, and shear. The skull, brain, and blood vessels will tolerate compression better than tension, and tension better than shear. These strains are induced by contact or inertia (relative to acceleration-deceleration), or both. Contact injuries are a result of impact, which may cause inward



• **Fig. 63.9** The patient was a 25-year-old man who sustained a brain injury in a motorcycle accident. A, Computed tomography (CT) scan immediately after the accident demonstrates traumatic subarachnoid hemorrhage (SAH) in cortical sulci *(thick arrow)* and anterior interhemispheric fissure *(thin arrow)*. B, CT scan at the level of the circle of Willis reveals a distribution of subarachnoid blood *(arrow)* throughout the suprasellar cistern, a pattern similar to that seen with a ruptured aneurysm. Findings on an immediate cerebral angiogram to rule out an aneurysm were normal. C, Follow-up CT scan obtained 8.5 hours later demonstrates an intraparenchymal contusion *(arrow)* that was not seen on the initial study, with rapid clearing of the traumatic SAH in the suprasellar cistern.



• **Fig. 63.10** A, Computed tomography (CT) scan demonstrates a typical left frontal basal contusion *(arrow)* where the brain interfaces with the rough base of the anterior cranial fossa. B, CT scan demonstrates left frontal *(thick arrow)* and right temporal hemorrhagic *(thin arrow)* contusions. The floor of the middle (temporal) fossa also is quite rough. This scan also illustrates the continuum from contusion to hematoma. Note the large, homogeneous areas within the contusions that could be classified as hematomas.

deformation of the skull with local effects, and of shock waves, which can produce remote effects. As a consequence of contact the head is set in motion, which leads to inertial injury. Inertial injuries may cause damage by differential acceleration of the skull and brain. In addition, acceleration-deceleration can independently produce strains in the brain itself. The two clinically relevant types of acceleration are translational (when the brain moves in a straight line) and angular. Most injuries are a combination of both.[142]

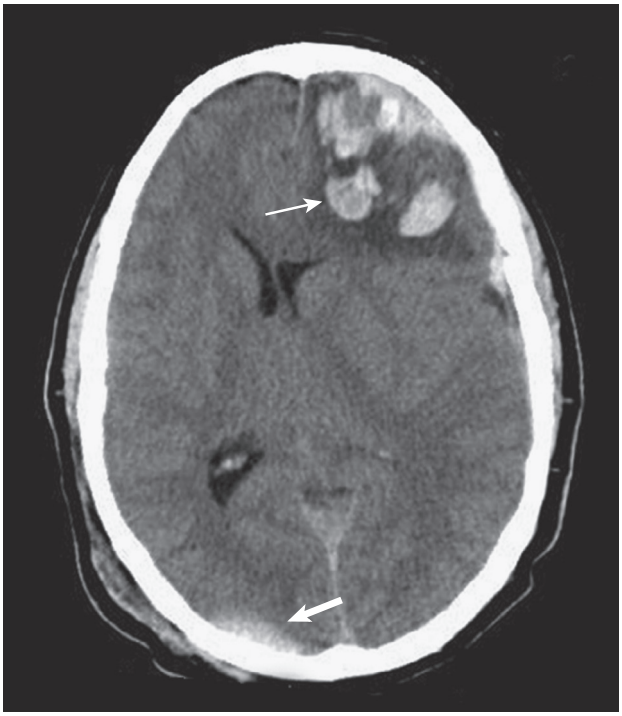
These effects are best illustrated by a case example of a 37-year-old man who falls from a height onto the back of his head and presents with a deteriorating level of consciousness. His CT scan (Fig. 63.11) reveals soft tissue swelling at the point of impact in the right occipital region with a small underlying hemorrhage, as well as a large, hemorrhagic contusion in the left frontal lobe. The mechanism involved is primarily translational (linear) deceleration. The skull stops suddenly as it hits the ground, but the brain continues to move toward the impact site, where compression is induced (Fig. 63.12).

As the brain is moving toward the inner table of the skull at the impact site, it also is moving away from the skull on the opposite side, creating regions of low pressure and tensile strains. Contributing to the extensive tissue damage in the left frontal lobe may also be movement of the brain across the rough surface of the anterior cranial base.[130,142]

The same amount of energy is delivered to the brain in nearly a straight line, with the compressive injury at the point of impact resulting in much less damage than the contrecoup injury caused by tension. In view of the dramatic differential susceptibilities of the brain and blood vessels to compressive, tensile and shearing strains induced in trauma, it is understandable that diffuse injuries can be caused by seemingly less violent trauma when the head undergoes an injury with a large component of angular acceleration-deceleration. This is the motion that can induce shearing strains, which the tissues tolerate poorly (see the Diffuse Axonal Injury section).

Surgical decision making is more straightforward for epidural and subdural types of hematomas, in which the extra-axial mass causing compression is simply on the surface of the brain. Contusions and hematomas, however, are intra-axial masses intimately associated with surrounding regions of brain that may be salvageable. It is one thing to surgically evacuate an extra-axial hematoma *compressing* the dominant frontal lobe, and quite another to operate on a large contusion *within* the dominant frontal lobe.

In 2006 guidelines were published after a thorough review of the relevant but scientifically weak literature. The reviewers reported that patients with parenchymal mass lesions and signs of progressive neurologic deterioration referable to the lesion, medically refractory intracranial hypertension, or signs of mass effect on CT scan should be considered for surgery. Patients with GCS scores of 6 to 8 with frontal or temporal contusions greater than 20 mL in volume with midline shift of at least 5 mm or cisternal compression on CT scan and patients with any lesion greater than 50 mL in volume should be considered for operative treatment. Patients with



• **Fig. 63.11** Computed tomography scan demonstrates a relatively small right occipital hemorrhage *(thick arrow)* underlying the point of impact as confirmed by the overlying soft tissue swelling of the scalp and a large, left frontal hemorrhagic contrecoup contusion *(thin arrow)*.

parenchymal mass lesions who do not show evidence of neurologic compromise, whose ICP is controlled, and who demonstrate no significant signs of mass effect on CT scan may be managed nonoperatively with intensive monitoring and serial imaging. For patients with refractory intracranial hypertension and diffuse parenchymal injury with clinical and radiographic evidence for impending transtentorial herniation, the guidelines also recommended, as treatment options, subtemporal decompression, temporal lobectomy, or hemispheric decompressive craniectomy (Fig. 63.13). With regard to timing of surgery, the literature at one time supported a bifrontal decompressive craniectomy within 48 hours of injury as a treatment option for patients with diffuse, medically refractory posttraumatic cerebral edema and resultant intracranial hypertension,[129] but newer data are less clear cut. In 2016 the BTF released updated guidelines that are less supportive under specific circumstances (see the Decompressive Craniectomy section).[143]

Hypothalamic-Pituitary Injury

Injury to the pituitary and hypothalamus can complicate head injury. A prolonged loss of consciousness often is reported in patients with such injuries. Up to 80% of cases are associated with a fracture through the skull base. Injuries include (in decreasing order of frequency) pericapsular hemorrhage, hypothalamic infarction, posterior pituitary hemorrhage, anterior pituitary infarction, and rupture of the infundibulum.[144–146] Clinically measurable decreases in pituitary hormone production are not seen until at least 75% of the gland is destroyed. Complete loss of production requires destruction of at least 90% of the gland.

Derangements in pituitary function can result in decreased production of any of the pituitary hormones. Of particular clinical significance is impairment of adrenocorticotropic hormone release that can result in secondary adrenal insufficiency. Physiologic stressors such as trauma, surgery, or infection can result in Addisonian crisis, with potentially life-threatening results. Diabetes insipidus has been reported in a significant number of patients with severe head injuries, with a high percentage of cases remaining permanent.[147] Injuries to the pituitary often are not suspected in the acute period, and the diagnosis of hypopituitarism is therefore often delayed (Fig. 63.14).

Diffuse Axonal Injury

The term *diffuse axonal injury* (DAI) describes brain damage in a group of patients who become immediately unconscious or go into coma at the time of the head trauma.[82] Depending on the severity of the injury, patients may have mild, moderate, or severe DAI. A large number of patients with severe head injury will have DAI. Rapid angular acceleration and/or deceleration of the head can induce shearing strains at the gray-white junction, corpus callosum, or brainstem.[134,148] The result can be diffuse tearing of axons and small blood vessels. These lesions initially may be hemorrhagic, but as they become chronic, shrinking, softening, and scarring ensue, often with cyst formation.[41,149] The lesions usually are microscopic but can be large and macroscopic. Although small, focal, petechial hemorrhages may be visualized, the initial CT scan often is normal.[150] Most of the clinical and experimental studies support that the diffuse injury occurs at the time of initial impact and is not the result of other adverse factors, such as decreased brain oxygenation, increased ICP, or brain swelling,[149,151] although these factors tend to accentuate the amount of damage.

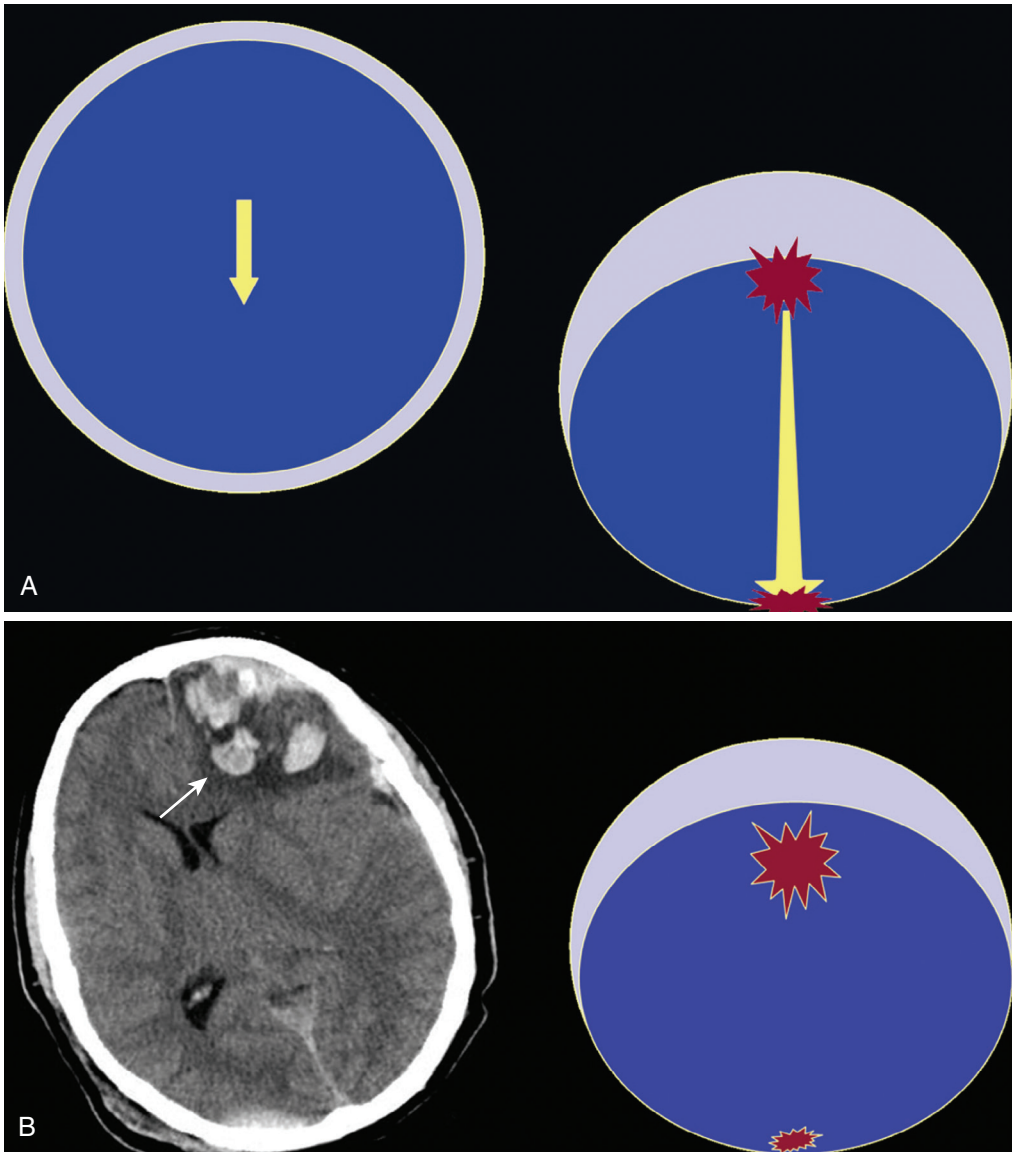
The term *gliding contusions* was originally introduced by Lindenberg and Freytag[152] to describe hemorrhagic lesions in parasagittal white matter; this brain injury concept has been reanalyzed.[153] Gliding contusions frequently are found in association with DAI and acute subdural hematomas. Two mechanisms have been considered in relation to the formation of these contusions. First, during angular acceleration, more movement and displacement of the cortical gray matter occur than of the deep white matter; accordingly, most of the tissue injury occurs at the gray-white junction because shearing strains predominate. The second mechanism involves excessive displacement of the bridging veins during brain acceleration. Patients with severe DAI who survive may be profoundly disabled, but some patients with mild or moderate DAI may recover with mild or no disability.[82] The importance of recognizing DAI in the initial evaluation cannot be overstressed; this will affect the management and outcome. Clinically, these patients will have impaired consciousness secondary to bicortical damage, possibly in association with unremarkable imaging findings and normal ICP.

Penetrating Brain Injury

A penetrating brain injury (PBI) involves an object breaching the scalp, skull, and dura.

Classification

A common classification method for these injuries is by velocity of the penetrating object. Low-velocity PBIs include wounds from nail guns, arrows, and knives and some types of gunshot wounds (Fig. 63.15). Gunshot wounds are divided into low-velocity injuries, such as from civilian handguns and shrapnel, and high-velocity injuries, from rifles and military weapons[154] (see Table 63.1). It is



• **Fig. 63.12** A, Schematic representing the head falling in a straight line. Rapid deceleration of the skull occurs as the brain continues to move toward the impact site. The energy is applied in a linear trajectory, resulting in a compressive strain generated at the impact site and a tensile strain at the opposite point *(right diagram)*. The same energy delivered to the brain results in more damage by tension than compression. B, A comparison of this schematic with that for a similar mechanism of injury would demonstrate why a contrecoup contusion (*arrow* on computed tomography scan, *left*) generally is more severe than the injury sustained as a result of compression at the point of impact.

estimated that between 6000 and 7000 people die each year in the United States from gunshot wounds to the brain.[133–142,154–156]

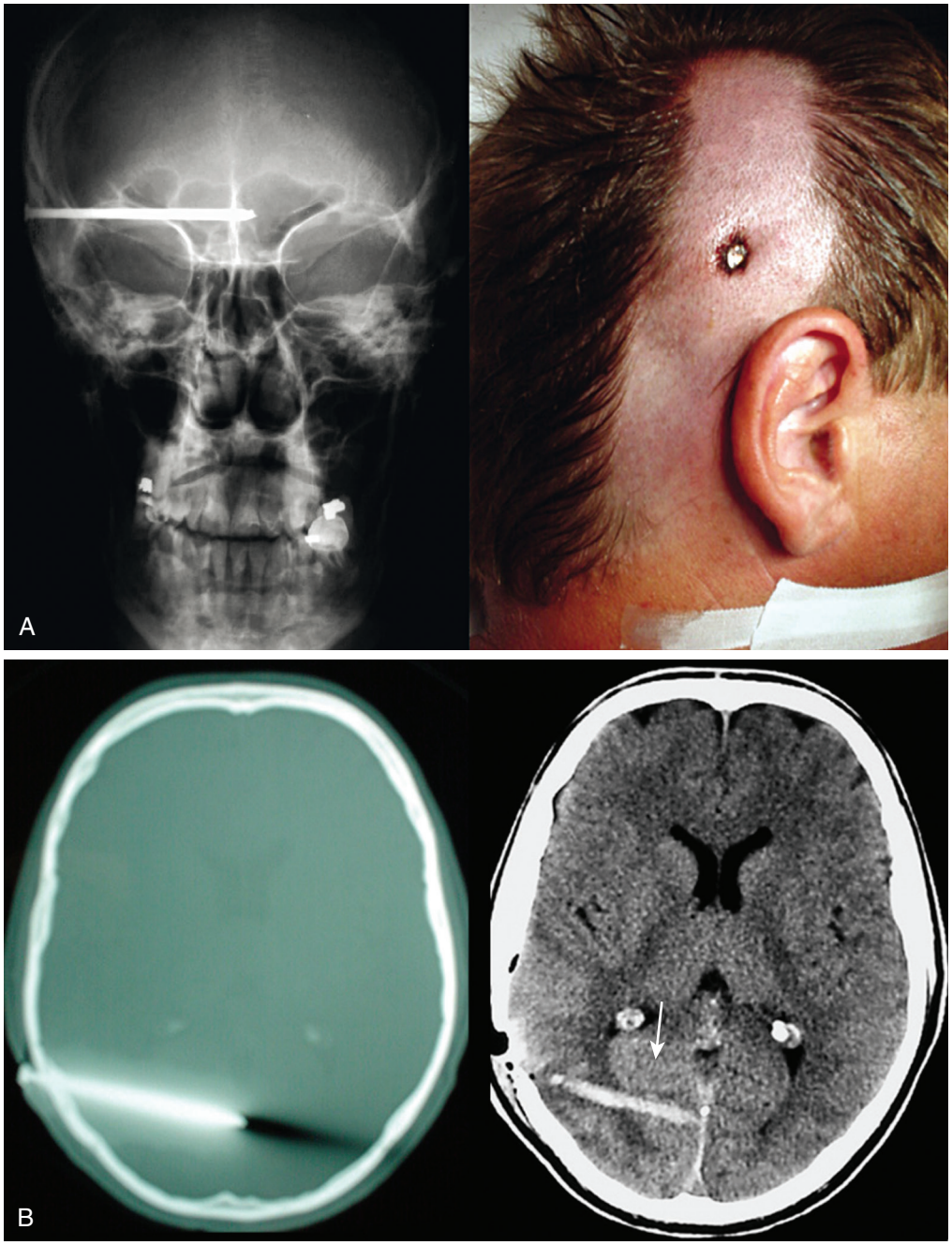
An Israeli report described an intermediate type of injury from spherical bolts whereby the ball bearings used by suicide bombers, having unique ballistics, may cause a type of "stab wound" injury to the brain.[154]

Ballistics

The biomechanics of PBI are important and require an understanding of the dynamics of projectiles—that is, ballistics. Ballistics can be divided into three phases. The first phase, internal ballistics, deals with the source of the projectile and its intrinsic dynamics (e.g., rifle, bomb). External ballistics, the second phase, focuses on the flight of the projectile itself and the deviation of its longitudinal axis relative to the line of flight, referred to as yaw motion. Collision of the projectile with any object during this external phase will change the speed, angle, and yaw. The third phase is referred to as terminal ballistics, which is the physical interaction between the projectile and the body.[154]

As the projectile directly crushes tissue, it forms a permanent cavity, and as surrounding tissue is compressed, a temporary cavity also is formed. As the missile breaks through the skull, secondary projectiles of bone fragments may be generated, causing independent, secondary permanent, and temporary cavities.[154,157–160]

Terminal ballistics are influenced by many factors, such as size, shape, and stability of the penetrating object; however, most authors (but not all) believe that entrance velocity is the most important factor in determining the degree of tissue damage.[154,157,159,161–163] Experimental evidence has demonstrated an immediate increase in ICP with a pressure wave transmitted throughout the cranial



• **Fig. 63.13** A 32-year-old man presented awake and alert after accidental discharge of a nail gun to the head while working at a construction site. A, *Left*, An anteroposterior radiograph of the skull demonstrates the nail. *Right*, On this intraoperative photograph, the head of the nail can be seen indenting the surface of the scalp. B, Preoperative bone-windowed computed tomography (CT) scan *(left)* and immediate postoperative brain-windowed CT scan *(right)* demonstrate the blood-stained tract after removal.

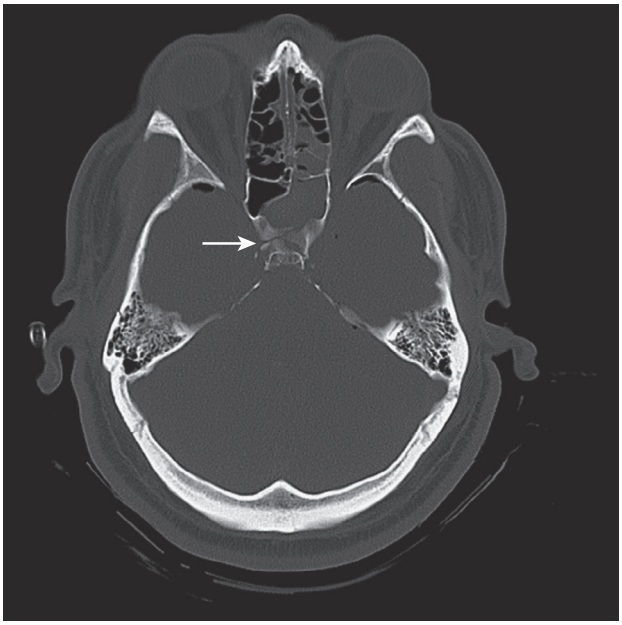
cavity, which probably accounts for the transient respiratory arrest observed in PBI.[154,164] High-velocity injuries (velocity > 320 m/s) cause shock waves that emanate from the front of the missile. These shock waves can reflect off the inside of the skull and summate, producing significant pressure gradients with remote effects.

Initial Resuscitation

In general, initial resuscitation in the trauma bay should be in accordance with current recommendations for patients with head injuries. During this initial resuscitation it is important to recognize that hypotension in PBI either is a terminal event or is related to other injuries. Once resuscitation has been accomplished, a CT scan is essential. Although skull films seldom add to the information obtained from a CT scan,[154] our group has found plain films to be very helpful in PBI, particularly in industrial accidents, in which the shape of the penetrating object may be unknown.

Surgical Management

Most of what is known about the surgical management of PBI comes from the battlefield, beginning with World War I, when

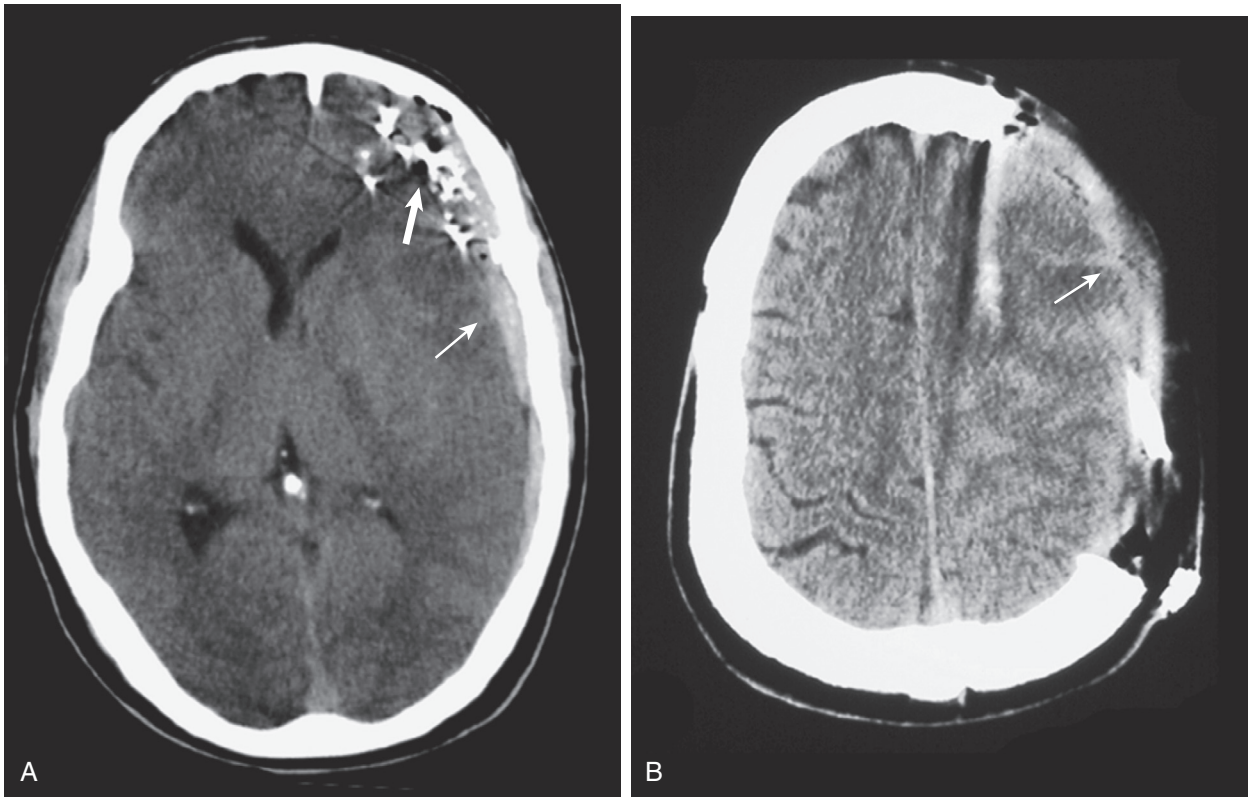


• **Fig. 63.14** Computed tomography scan through the skull base in bone window demonstrating fractures through the sella turcica *(arrow)*.

Harvey Cushing, the father of American neurosurgery, described his technique of en bloc craniectomy under aseptic conditions: thorough debridement of scalp, brain, metal, and bone fragments; and watertight closure of the scalp. Using this management strategy a century ago, in the absence of antibiotics, Cushing reported a significant drop in postoperative mortality from 55% to 28%.[165,166]

Mortality decreased even further in World War II, primarily because neurosurgical personnel were present in forward military hospitals and antibiotics were introduced. The operative approach, however, was largely the same: that of radical debridement. Treatment consisted of four tiers: emergent life-saving maneuvers through hemostasis and cerebral decompression; prevention of infection through extensive debridement; preservation of brain tissue; and restoration of anatomic structures through accurate closure of the dura and scalp. Although untested against other management strategies, this approach became the standard of treatment for PBI by default. Indeed, in the U.S. military, thorough debridement of intracranial bone and metal fragments was official military policy through the Vietnam War.[166]

The overall mortality rate from PBI sustained during relatively modern wartime conditions ranges from 8% to 43% and generally is considered to be in the 20% range.[166–175] The mortality rate from military gunshot wounds has been reported to be 2.5 to 4



• **Fig. 63.15** The patient was a 27-year-old man with a self-inflicted gunshot wound to the head who presented with a deteriorating level of consciousness. The patient put the muzzle of a handgun to the right medial orbital roof. The bullet traversed the frontal sinus and traveled through the left frontal lobe. A, Computed tomography (CT) scan demonstrates bullet fragments *(thick arrow)* and an associated left frontotemporal acute subdural hematoma *(thin arrow),* requiring surgical evacuation and hemicraniectomy for anticipated swelling. B, Postoperative CT scan demonstrates edematous hemisphere herniating out through the cranial defect *(arrow)*. There was damage to the anterior cranial base with contamination secondary to involvement of the frontal sinus. Surgical repair of the skull base was delayed because of the anticipated cerebral edema, and the antibiotic treatment was started. When the cerebral swelling resolved, there was no evidence of cerebrospinal fluid rhinorrhea or infection. The patient never required the delayed repair of the anterior cranial base anticipated. He made an excellent neurologic recovery and returned to work as a professional recruiter several months after replacement of his cranial bone flap.

times more than from shrapnel.[166–169,174] Of interest, mortality rates from wartime PBIs in the U.S. military from World War II through the Vietnam War did not change significantly,[176] which is consistent with the relatively unchanged management strategy of complete removal of intracranial bone or metal fragments, using repeated surgery as necessary.[177]

Aggressive debridement was intended to reduce complications such as infection, epilepsy, and cerebral edema. However, studies reveal that additional surgery to remove retained fragments results in significant morbidity and mortality.[174,178,179] Primary surgery for conservative debridement is now common practice for salvageable patients, with judicious use of decompressive craniectomy when necessary for selected cases.

The use of broad-spectrum antibiotics in recent wars has resulted in data suggesting that retained bone fragments are not independently associated with an increased risk of infection. Therefore aggressive debridement is no longer supported.[166,180] The use of broad-spectrum antibiotics in PBI has now become common practice.[154]

Multiple studies have looked at post-PBI epilepsy and reported an incidence of 22% to 53%.[171,181,182] Several studies suggest that it is not necessary to remove all bone fragments to decrease the chance of developing epilepsy, but the value of removing metal fragments in this regard remains unclear.[166,171,173,181,182] In military PBI, it appears that vigorous debridement is associated with increased morbidity and mortality and is not necessary to prevent infection, has no obvious efficacy in preventing epilepsy, and does not appear to improve survival.[166]

A CSF leak resulting from a PBI is the variable most highly correlated with intracranial infection.[166,170,171,174,183–186] One study found that most CSF leaks appeared within 2 weeks of the injury and less than half of them closed spontaneously. The incidence of infection was approximately 10 times higher in the group with CSF fistulas than in the group without leaks, and the mortality was greater as well.[185] Because CSF leaks are the primary predictor of the development of intracranial infection,[171,173,175] it is important to fix or prevent a CSF leak; therefore a watertight closure of the scalp entry wound is necessary.[185]

To accomplish this objective, various surgical interventions are available. Small entrance wounds without underlying surgical pathology may be cleaned up and closed in the emergency department.[186] Complex entry wounds or those with underlying surgical pathology require more extensive surgical manipulation, which may include extending the incision to allow vigorous superficial debridement; complete excision of devitalized tissues including muscle, fascia, and periosteum; extension and debridement of the bony entry or exit site by craniectomy; and similarly generous debridement of the dural opening with watertight closure, using grafting as necessary.[a]

Predictive Factors

Increased mortality in penetrating head injury is associated with increasing age, suicide attempts, hypotension, coagulopathy (particularly with lower GCS scores), respiratory distress, low GCS score, bilateral fixed and dilated pupils, high ICP, and cisternal effacement on CT scan. Mortality is also increased with traumatic injuries in which a missile tract perforates the skull (through-and-through injury) or with injuries that involve both hemispheres, multiple lobes, or the ventricular system.[166]

[a]References 165, 172, 174, 176, 187, and 188.

In civilian gunshot wounds to the head, a specific vector analysis from Los Angeles County demonstrated a region of involvement that resulted in 100% fatality and is designated as the zona fatalis. This region consists of the midbody of the ventricle, the body of the corpus callosum, and the cingulum.[188]

No effect has been demonstrated for weapon caliber on outcome, independent of total kinetic energy, and no relation between midline shift and outcome has been established.[166] Using predictive factors, Harrington and Apostolides have proposed a treatment algorithm for patients with gunshot wounds to the head. Patients with lesions causing mass effect and a postresuscitation GCS score of 7 or greater undergo surgery, and patients with a GCS score of 3 or 4 with bilaterally fixed pupils after resuscitation receive no treatment beyond wound closure. In patients with GCS scores of 5 or 6, treatment should be individualized, depending on pupillary findings and other conditions.[189]

Special Problems

Special problems that may be encountered with PBI include those associated with craniofacial entrance wounds: an increased incidence of hematoma formation, direct vascular injury, extensive contamination owing to paranasal sinus involvement (see Fig. 63.15), and CSF fistulas.[154]

Other special problems include dural venous sinus involvement, tangential wounds, and traumatic aneurysms, with 0.4% to 0.7% of all intracranial aneurysms being caused by penetrating trauma.[190]

In PBI, mechanical loading of the cerebral vasculature, by either the contact forces of the projectile or the shearing forces of a pulsating temporary cavity, may cause partial or complete transection of an arterial wall. Such damage can result in SAH or formation of intracerebral and intraventricular hematomas.[166,191,192]

Damage to the arterial wall also may cause the development of a traumatic intracranial aneurysm. These aneurysms are primarily false aneurysms, which could heal or change in size over time, but they are especially vulnerable to rupture and can lead to delayed traumatic intracerebral hematoma, SAH, or both.[190,193–195]

Patients with an increased risk of vascular injury include those in whom the trajectory passes through or near the sylvian fissure, supraclinoid carotid, cavernous sinus, or a major venous sinus. The development of substantial and otherwise unexplained SAH or delayed hematoma also should prompt consideration of a vascular injury.[166]

Cerebral angiography (CTA or conventional) remains the usual technique to detect intracranial aneurysms.[192,194,196] Because a majority of traumatic intracranial aneurysms are not true aneurysms, excluding the aneurysm by surgical clipping may not be possible and may require trapping between clips on the parent vessel[166] or endovascular management.

Course in the ICU

Not surprisingly, intracranial hypertension is common after PBI.[185,197–199] Early ICP monitoring should be considered when the ICU clinician is unable to assess the patient's neurologic status accurately; if the need to evacuate a mass lesion is unclear; or if CT scanning results suggest elevated ICP.[166] Another practical use for ICP monitoring is ongoing assessment of a patient with a depressed level of consciousness to look for an early sign of progressive intracranial pathology, which may require repeated imaging and surgical decompression.[185,197,199]

Cerebral autoregulation may be defective after PBI[185,197,199] and cerebral edema can appear rapidly, contributing to medically

refractory intracranial hypertension. Systemic hypertension may exacerbate intracranial hypertension after PBI.[166]

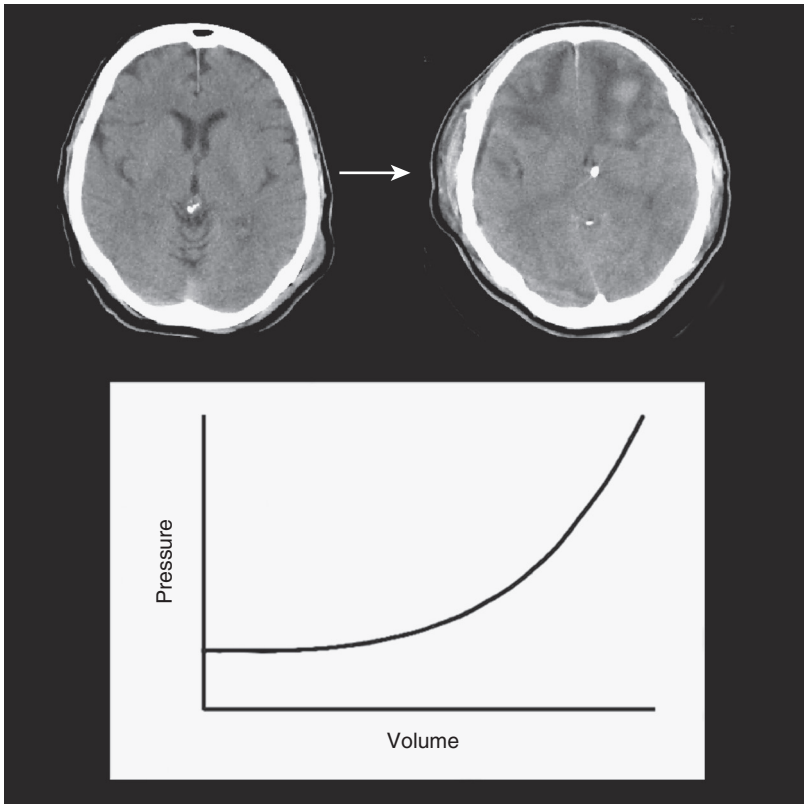
Treatment is not necessarily futile, and some patients with intracranial hypertension can be managed successfully and survive with acceptable morbidity.[185,197,199,200] However, the literature does not clearly relate successful treatment of intracranial hypertension after PBI to an improved outcome. Insufficient good data are available to guide management strategies for intracranial hypertension after PBI. It cannot be assumed that the intracranial pathology is the same as in nonpenetrating TBI. Because of the paucity of data, however, treatment in the ICU generally follows the methods for nonpenetrating TBI as outlined in Guidelines for the Management of Severe Traumatic Brain Injury.[166,201]

Secondary Head Injury

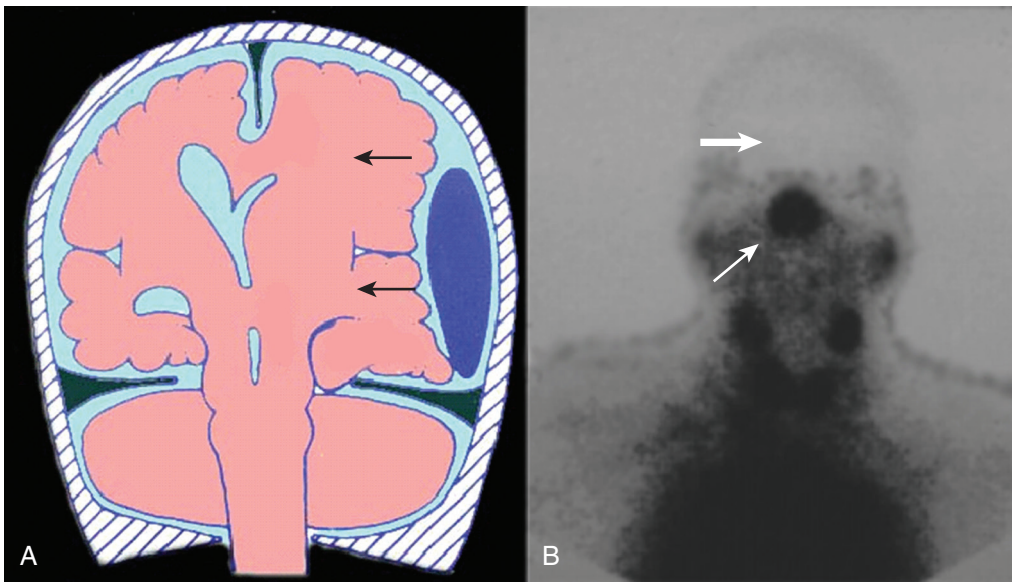
Basic Concepts

Management of primary head injury may require surgical intervention driven by the presence of pathologic masses (hematomas) in anatomic spaces. Management of secondary head injury generally involves nonsurgical interventions driven by pathologic derangement of physiologic processes.

The three functional volumetric compartments in the head are blood, brain, and CSF. The volumes of these three functional compartments are approximately 1200 mL for brain, 150 mL for CSF, and roughly 150 mL for the variable blood compartment. The total volume of the intracranial compartment is relatively fixed and relatively incompressible. Therefore if volume is added to one of these three compartments, a compensatory loss of volume from another compartment will occur; otherwise, ICP will rise. To illustrate this point, a pressure-volume curve for the intracranial compartment is shown in Fig. 63.16. Initially, as volume is added to the system, no significant change in pressure occurs. With cerebral edema, for example, as the brain compartment increases in volume, venous capacitance vessels collapse, which moves blood volume out of the system; therefore overall net volume does not change and ICP remains stable. As the brain continues to swell and increase in volume, the ventricles compress, which moves CSF out of the system, again keeping overall net volume and ICP relatively stable. At some point the system loses this buffering capacity, and as more injury-related volume accumulates, ICP starts to rise. The rise in ICP is gradual, progressive, and nonlinear. As the system continues to be stressed with additional volume, it progressively loses compliance and, in effect, gets stiffer. The result is that increasingly smaller volumes introduced into the system result in higher changes in ICP. Using MRI methods to study cerebral edema, Marmarou and colleagues noted a rise in ICP when edema was only 1% higher than the normal water content of brain tissue. These investigators also showed that when water content increased in a



• **Fig. 63.16** Pressure-volume curve of the intracranial compartment using cerebral edema as an example (see text). The computed tomography (CT) scan above the graph on the *left* is an image of a normal brain. The CT scan on the *right* demonstrates severe cerebral edema in a trauma patient with obliteration of most of the subarachnoid space, reducing cerebrospinal fluid (CSF) volume to make room for the swelling brain. Initially, as CSF moves out of the system, overall net volume does not change significantly. This part of the process is represented by the flat part of the curve toward the *left* and reflects the buffering capacity of the brain to respond to gradual increases in volume.



• **Fig. 63.17** A, Increased intracranial pressure can be associated with hematomas causing mass effect, shift, and possibly herniation. The resultant pathostructural changes from such unbalanced forces *(arrows)* usually are managed surgically. With increased intracranial pressure, cerebral perfusion may be impaired, resulting in ischemia—the ultimate secondary injury. Intractable intracranial hypertension and inadequate perfusion can lead to brain death, as demonstrated by the nuclear flow study shown in B. Note the absence of flow to the brain *(thick arrow),* compared with the overly generous blood supply to the face, sometimes referred to as the "hot nose sign" *(thin arrow)*.

contused hemisphere, ICP increased exponentially. These findings demonstrate the importance of small changes in intracranial volume, particularly when the buffering capacity of the system has been exhausted.[202]

Increased ICP may be associated with mass effect secondary to hematomas causing direct mechanical compressive damage to intracranial structures that requires surgical decompression in the operating room. Increased ICP also may result in inadequate perfusion, requiring medical management in the ICU (Fig. 63.17).

The heart delivers blood at a given mean arterial blood pressure (MABP), the systemic perfusion pressure, to the base of the skull. The blood pressure then has to overcome whatever pressure is inside the head for blood flow to get in, and whatever is left over will be the pressure that perfuses the brain—that is, cerebral perfusion pressure (CPP). Simple in concept and calculation, CPP is defined as the MABP minus ICP (CPP = MABP − ICP). It is the physiologic variable that defines the pressure gradient driving CBF and metabolic delivery and is therefore closely related to ischemia.[203,204]

Technically, the MABP should be measured as the mean carotid pressure with the arterial line transducer zeroed at the level of the foramen of Monro (as opposed to the right atrium),[205] but this approach is not common in clinical practice. Normal values generally are considered to be 60 to 80 mm Hg for CPP and approximately 10 mm Hg or less for ICP.

The ultimate cause of secondary injury is typically ischemic, and the fundamental goal in dealing with severe TBI is to ensure adequate CBF relative to the metabolic demand of the brain. It is, however, impractical to continuously measure CBF at the bedside. Fortunately, CBF is dependent on CPP—which can easily and continuously be measured at the bedside. Therefore a fundamental management strategy for treating a patient with a head injury is to maintain adequate CPP by lowering ICP, accomplished by reducing intracranial volume.

Surgical methods for reducing intracranial volume include evacuating an intracranial hematoma, removing part of the frontal or temporal lobe, and placing a ventriculostomy to drain CSF. Other methods for reducing intracranial volume are applicable in the ICU setting, where management strategies are directed at treating volume in the blood and brain compartments.

Cerebral Blood Volume

In discussing cerebral blood volume (CBV), it is useful to divide this topic into the arterial and venous compartments.

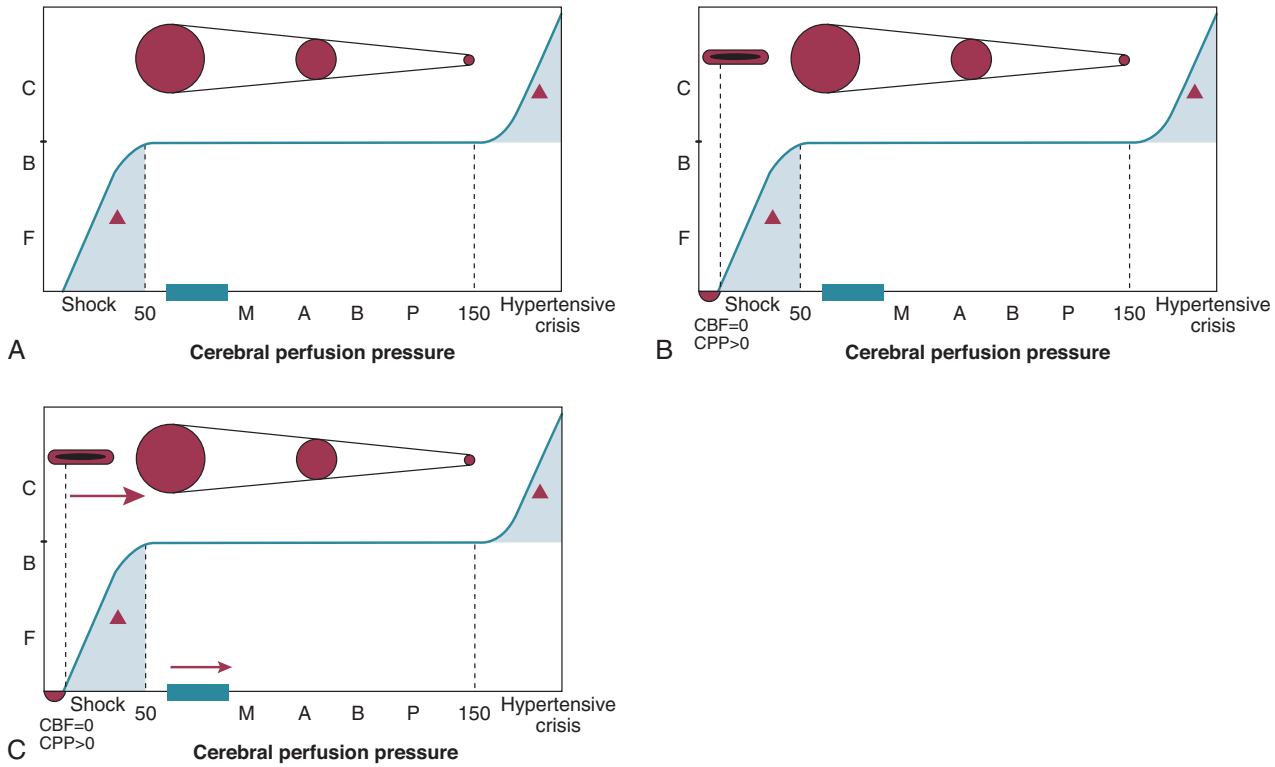
Arterial Blood Compartment

Blood Pressure

Systemic blood pressure has a direct effect on arterial CBV. Normally, CBF will remain relatively constant over a wide range of perfusion pressures as cerebrovascular resistance (CVR) automatically adjusts. The autoregulation curve (Fig. 63.18) demonstrates the relationship among CBF, perfusion pressure, and CVR. As MABP goes up, CVR increases to maintain a stable CBF.

The CVR increases by vasoconstriction, which reduces the volume of blood in the brain. Conversely, as MAPB drops, CVR goes down by means of vasodilation, which increases the volume of blood in the brain. This is a very powerful system; a cerebral arteriole has the ability to change its diameter by up to 200%. It also is quite fast, responding to sudden changes in pressure within 3 to 5 seconds.

Most people have had the experience of suddenly jumping out of bed after having been recumbent for several hours and then feel the "lights going out" as the cerebral vasculature rapidly dilates as it tries to keep up with the even faster, sudden drop in perfusion pressure. CBF transiently falls off the autoregulation curve for the time it takes (3–5 seconds) for cerebrovascular resistance to adjust to the lower perfusion pressure.



• **Fig. 63.18** A, The autoregulation curve demonstrates how the brain maintains a relatively constant cerebral blood flow *(CBF)* over a wide range of perfusion pressures by changing the caliber (resistance) of the cerebral vasculature, which necessarily leads to changes in intracranial volume. Under normal circumstances, when intracranial pressure (ICP) is negligible, the MABP is equivalent to cerebral perfusion pressure (CPP); however, when ICP is elevated, it is the CPP that is "read" by the brain. CPP will drive CBF, causing changes in cerebrovascular resistance, unless overridden by other superimposed processes such as hyperventilation, which may be pathologic or intentionally altered for a therapeutic effect. Although we have the ability to autoregulate over a wide range of perfusion pressures, the normal range is at the lower end of the curve *(horizontal blue bar)*. B, The normal resting state of the cerebrovasculature is collapsed. These vessels have critical opening and closing pressures that are slightly different from each other. With the vessel open, it typically will collapse at a slightly lower pressure than is required to open it from a collapsed state. C, After a significant injury, the potential exists to increase the critical closing pressure, which could shift the autoregulation curve to the right. *MABP,* Mean arterial blood pressure.

A normal MABP range for a young, healthy adult is approximately 70 to 90 mm Hg, and a normal ICP generally is considered to be approximately 10 mm Hg or less, which is consistent with the normal range of CPP values between 60 and 80 mm Hg. Normal ranges are at the low end of the autoregulation curve, which maintains normal CBF between MABPs ranging from approximately 50 to 150 mm Hg. It is clear from the autoregulation curve that CBF becomes a direct, linear function of MABP when outside the ability of the cerebrovascular bed to maximally dilate (MABP < 50 mm Hg) or constrict (MABP > 150 mm Hg).

The normal range of 50 to 150 mm Hg is not rigidly fixed, and individual variations are common. A hypotensive patient with an MABP of 20 mm Hg is clearly in shock, but a 21-year-old athlete with an MABP of 45 mm Hg after minor surgery may still be autoregulating. A clinical assessment is necessary in borderline situations, and one of the most important indicators of shock is a change in mental status. In this example, if the athlete demonstrates a change in mental status, he is likely to be off his autoregulation curve and in shock.

At the other end of the spectrum is chronic hypertension. Is a 74-year-old patient with long-standing hypertension who presents with an MABP exceeding 150 mm Hg by a few points having a hypertensive emergency? Again, a change in mental status may be the indicator that autoregulatory capacity has been exceeded, and the patient may be diagnosed with hypertensive encephalopathy.

CVR is often increased by trauma. At the beginning of the autoregulation curve, CBF is zero at a perfusion pressure greater than zero. A measurable pressure in the vessel exists, yet no blood flow occurs, indicating vascular collapse (see Fig. 63.18). The cerebrovasculature in its resting state is collapsed; it takes a certain amount of energy (pressure) to open the vessels. These vessels each have critical opening and closing pressures. After a head injury, free radicals can be released, which tend to make biologic tissues less compliant. This in turn may make it more difficult for the vessels to stay open—that is, more pressure is required to keep the vessels from closing, which could shift the autoregulation curve to the right (see Fig. 63.18).[206–209] This is the theoretical basis for the studies that led to the earlier recommendations to keep the minimum CPP in patients with head injuries above normal minimal values—that is, at 70 mm Hg or greater.[210]

Cerebral Perfusion Pressure

A low perfusion pressure jeopardizes ischemic regions of the brain. Increasing intravascular hydrostatic pressure by increasing CPP

can help improve cerebral perfusion. Although CPP can be manipulated and enhancement of CPP may help to avoid both global and regional ischemia, the level at which CPP is best maintained is not entirely clear,[210] and considerable interest has been directed toward attempts to determine the optimum CPP for a patient with a head injury. Some studies suggested that increasing CPP to greater than 70 mm Hg leads to improved outcomes.[211]

A combination of studies of TBI in which CPP was actively maintained at approximately 70 mm Hg in patients with a GCS score less than 8 reported a mean mortality rate of 21%, which was substantially less than the 40% mortality rate reported for similar patients in the Traumatic Coma Data Bank (TCDB). Good recovery and moderate disability rates were 54% in the patients whose CPP values were maintained in the 70-mm Hg range, compared with the 37% reported in the TCDB. However, it could not be concluded that the improved outcomes in these studies were a result of CPP management because none of the reported studies was a randomized, prospective trial of this treatment[204,209,212–216]; and in some studies, another treatment was actually the focus of the study.[212,213]

In a prospective study of 21 patients with severe TBI in whom brain tissue partial pressure of oxygen ($BtiO_2$) was monitored, ischemic episodes during the first week after injury were associated with unfavorable neurologic outcomes. Elevation of the CPP improved $BtiO_2$, but raising CPP above 68 mm Hg did not cause a further increase in $BtiO_2$. In the investigators' analysis, a CPP greater than 60 mm Hg emerged as the most important factor determining a sufficient $BtiO_2$.[204,217]

Another prospective, controlled trial of 189 adult patients with a motor GCS score of 5 or lower within 12 hours of head injury randomly assigned patients to an "ICP-targeted protocol" in which CPP was kept above 50 mm Hg or to a "CBF-targeted protocol" in which CPP was kept above 70 mm Hg. The investigators in this study found no significant difference in outcome. In this trial, the mean CPP for patients managed in the CBF-targeted protocol was 76 mm Hg and for those in the ICP-targeted protocol, 72 mm Hg. These differences were small but statistically significant.[218]

Contant and associates used data from this trial to examine risk factors for acute respiratory distress syndrome (ARDS) and consequences of its development. The risk of ARDS was five times greater among patients in the CBF-targeted group than in those in the ICP-targeted group and was associated with a more frequent use of epinephrine and a higher dose of dopamine.[203,219] Patients in whom ARDS developed were two and a half times more likely to develop refractory intracranial hypertension[219] and almost three times more likely to be in a vegetative state or dead at 6 months after injury.[219,220] These outcomes may be a direct consequence of ARDS and the related therapeutic limitations of treating raised ICP and low CPP in the presence of ARDS.[203]

Analysis of data from a study investigating the value of a neuroprotective agent in 427 patients with severe TBI revealed that the critical CPP threshold was 60 mm Hg. Although CPPs persistently less than 60 mm Hg were associated with a significant decline in outcomes, no effect on neurologic outcomes was observed for patients who had CPPs that were higher, and specifically no difference was observed among those whose CPPs averaged 60 mm Hg and those at 70 mm Hg or higher.[203,221]

In 1995 and 2000, the BTF in cooperation with the American Association of Neurological Surgeons and the Joint Section for Neurotrauma and Critical Care published guidelines for the management of severe head injury. From the data available, based on the theoretical need to increase the minimum CPP because of a change in critical opening pressures (see Fig. 63.18), the guidelines recommended maintaining a minimum CPP of 70 mm Hg or greater—10 mm Hg above the accepted norm. In 2003 this group updated the recommendation for CPP management and published a guideline that CPP should be maintained at a minimum of 60 mm Hg. In the absence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors should be avoided because of the risk of ARDS.[203] In 2007 the recommendations were again modified with a level 3 recommendation to target CPP values within the range of 50 to 70 mm Hg.[204] In 2016 the guidelines stated that CPP values should be between 60 and 70 mm Hg.[143] Clearly, guidelines change as new data become available and readers are strongly advised to check for the most up-to-date recommendations.

Carbon Dioxide

Carbon dioxide is a powerful regulator of cerebrovascular resistance. At any given physiologic perfusion pressure, the partial pressure of arterial carbon dioxide ($PaCO_2$) can act rapidly and severely to affect CBF in a linear fashion by vasodilating or vasoconstricting the cerebrovascular bed. For every 1-mm Hg change in $PaCO_2$, a 3% change in CBF can occur.[222]

Allowing the $PaCO_2$ to rise to levels between 60 and 80 mm Hg can result in a doubling of CBF, through vasodilation with a concomitant increase in CBV. Conversely, aggressive hyperventilation of a patient down to a $PaCO_2$ of 20 mm Hg or less can result in cutting CBFs in half, along with a reduction in CBV. Hyperventilation was a mainstay in the therapeutic management strategy of treating patients with head injuries because it had such immediate and measurable effects on ICP. Lowering $PaCO_2$ causes rapid vasoconstriction, resulting in reduced CBV, which translates to reduced intracranial volume, which lowers ICP and increases CPP. However, hyperventilation reduces ICP by taking blood *away* from the brain, when the goal is to prevent ischemia. As seen on the autoregulation curve, the cerebrovasculature is fine-tuned to the existing perfusion pressure, providing a normal level of CBF. Aggressive hyperventilation can override the normal effect of MABP and cause a marked increase in CVR to the point at which a very high perfusion pressure would be needed to match the degree of severe vasoconstriction induced to maintain a normal level of CBF. This is the mechanism involved when a normal person hyperventilates, vasoconstricts, and becomes lightheaded as CBF falls. It is important to recognize that this individual has a normal MABP, ICP, and CBF before the $PaCO_2$ decreases.

Despite the fact that hyperventilation lowers ICP, the degree of vasoconstriction can be disproportionate relative to the enhancement in CPP. For example, at an MABP of 80 mm Hg with an ICP of 30 mm Hg and a CPP of 50 mm Hg, aggressive hyperventilation could reduce ICP to 15 by reducing intracranial volume, thereby improving CPP to 65. But aggressive hyperventilation can cause severe vasoconstriction. At maximal vasoconstriction, the cerebrovascular bed would need an MABP of 150 mm Hg with a normal ICP to maintain a normal CBF.

The data on CBF in patients with severe head injuries indicate that phases of CBF change over time after TBI, with hypoperfusion occurring in the first 24 hours.[222] Multiple studies have identified brain ischemia in up to 35% of serious head injuries within the first 12 hours.[204,222–228] It appears that this reduction happens almost immediately. Mean CBF values measured less than 4 hours after head injury in adults were 32 mL/100 g per minute in survivors and 20 mL/100 g per minute in nonsurvivors (normal CBF averages

approximately 55 mL/100 g per minute).[228] Low CBF, to ischemic levels (<18 mL/100 g per minute), was observed in 31% of patients with severe head injury measured an average of 3 hours after trauma.[204,229]

Because of the consistent data regarding reduced CBF early after trauma, attempts at further reductions using hyperventilation have come under close scrutiny. Some evidence suggests that hyperventilation carries a particular risk of causing cerebral hypoxia when $PaCO_2$ is 30 mm Hg or less, or within the first 24 hours[230,231] because of a further reduction of an already low CBF.[229] It has become clear that hyperventilation decreases $BtiO_2$ because of decreased CBF in most patients, which negates the perceived benefit of improving intracranial and cerebral perfusion pressures.[217,230–236]

The 2016 BTF guidelines recommend that chronic prolonged hyperventilation therapy (partial pressure of carbon dioxide [PCO_2] ≤25 mm Hg) should be avoided after severe TBI. However, they recognize the potential need for hyperventilation as a temporizing measure.[143]

Oxygen

Within a normal physiologic range, oxygen causes little or no change in CBF (Fig. 63.19). Beyond a partial pressure of arterial oxygen (PaO_2) of approximately 300 mm Hg, CBF can begin to wane. Oxygenation does become very important at PaO_2 levels considered to be hypoxic. Below a PaO_2 of 60 mm Hg in most patients with head injuries, the cerebrovasculature can vasodilate rapidly, causing an increase in CBV with poorly oxygenated blood, with an attendant increase in intracranial volume and pressure.

With careful clinical monitoring, our group has observed sudden ICP spikes as a result of acute oxygen desaturation that occur seconds before the pulse oximeter reading starts to deteriorate. With a moderate degree of clinical certainty, the BTF has recommended that hypoxia, defined as apnea or cyanosis in the field or a PaO_2 less than 60 mm Hg, must be scrupulously avoided or corrected immediately. Therefore in contrast with $PaCO_2$, manipulation of PaO_2 is not a useful tool for medical management of a patient with a head injury, and hypoxia must be avoided.[204]

In view of the powerful effects of hypoxia and hypercarbia, early intubation in significant head injury is important if gas exchange is compromised.

Metabolism

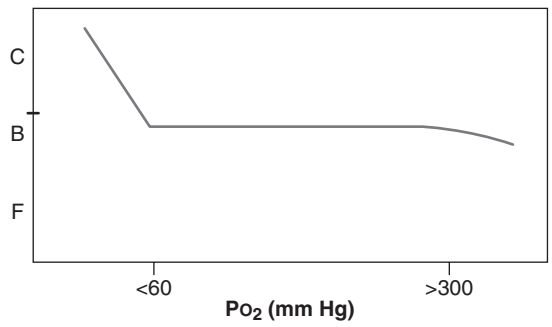
Under normal circumstances, the cerebral metabolic rate of oxygen ($CMRO_2$) is directly related to CBF; this is referred to as a coupled relationship. As metabolic demand increases, the cerebrovasculature will vasodilate to supply an appropriate increase in CBF; and conversely as $CMRO_2$ decreases, the cerebrovasculature will vasoconstrict to maintain a coupled relationship between supply and demand. As demand exceeds supply and the ability of the brain to extract more oxygen wanes, ischemia develops. Therefore as the $CMRO_2$ increases, there will be an appropriate vasodilatory response in the brain with its attendant increase in CBV and, potentially, ICP, with a resultant decrease in CPP. Clearly, if the primary event is an increase in demand and the end result is a reduction in supply, the gap between supply and demand increases, and with it the potential for ischemia. Under physiologic conditions whereby the $CMRO_2$ is coupled to CBF, various clinical states will demonstrate an appropriate balance of the two. For example, a comatose patient will have low $CMRO_2$, and a patient having a generalized seizure will have a high $CMRO_2$.

The metabolic state of the brain is sensitive to changes in temperature; lower temperatures lower $CMRO_2$, and vice versa. Recognition of this relationship has led to interest in using hypothermia as a therapeutic tool in severe head injury, both as a way to lower ICP and as a neuroprotective strategy by reducing demand in the face of limited supply. Although hypothermia can be a useful adjunct to standard treatments for controlling elevated ICP, it is difficult to find good data to prove a benefit in outcome. Clifton and associates found that ICP was lower in patients managed with hypothermia, but no improvement in outcome was observed, and the complication rate was higher than in a normothermic group. These investigators concluded that lowering body temperature to 33°C within 8 hours after injury was not effective in improving outcomes in patients with brain injuries.[237] A Cochrane review of therapeutic hypothermia for head injury studied 14 trials with more than 1000 participants and found no evidence that hypothermia is beneficial in the treatment of head injury, and that it increased the risk of pneumonia nearly twofold.[238] A different meta-analysis, using clinical trials of moderate or poor quality, identified preliminary findings suggesting a greater decrease in mortality risk when target temperatures are maintained for more than 48 hours, as well as an association with better outcomes.[239,240] The 2016 BTF guidelines state that early (within 2.5 hours), short-term (48 hours after injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.[143]

Although it is not clear that hypothermia is helpful, hyperthermia is believed to be harmful to a patient with a severe head injury.[241] As the temperature rises, so does the $CMRO_2$, with a concomitant increase in CBV. If the patient has lost enough compliance, then small changes in intracranial volume can result in large changes in ICP (see Fig. 63.16) and CPP can fall.

A frequent scenario is development of a fever in a trauma patient with a high ICP and poor compliance who is barely meeting metabolic needs. Metabolic requirements increase as CBV and ICP increase and CPP decreases, widening the gap between supply and demand, resulting in ischemia.

Another consideration in the management of $CMRO_2$ is drug effect. Pentobarbital is the gold standard drug for reducing cerebral metabolism and can be used in cases of refractory intracranial hypertension to induce a barbiturate coma. A condition of burst suppression is achieved, meaning that the continuous EEG recording demonstrates periods of an isoelectric tracing (straight line) interrupted by bursts of cortical electrical activity. This therapy results in vasoconstriction appropriate for the degree of reduction in metabolism, with an attendant decrease in ICP. This has the



• **Fig. 63.19** Graph demonstrating the relationship of cerebral blood flow *(CBF)* to oxygen (partial pressure of oxygen *[Po_2]*). Within a physiologic range, oxygen is of no use as a therapeutic tool. The cerebral vasculature will vasodilate under hypoxic conditions, so hypoxia must be avoided.

theoretical advantage of improving supply to a brain with reduced metabolic demands. However, despite the evidence for cerebral protection in experimental models, little clinical evidence is available to suggest that induced barbiturate coma improves outcome after severe head injuries in humans. Other drugs that reduce the $CMRO_2$ and CBF are other barbiturates such as thiopental, as well as the substituted phenol propofol, the hypnotic agent etomidate, and the water-soluble short-acting benzodiazepine midazolam.[241]

According to the 2016 BTF guidelines administration of barbiturates to induce burst suppression measured by EEG as *prophylaxis* against the development of intracranial hypertension is not recommended. The guidelines also state that high-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment, but hemodynamic stability is essential both before and during barbiturate therapy. Finally, the BTF guidelines state that although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes, and caution is required as high-dose propofol can produce significant morbidity.[143]

Viscosity

When autoregulation is intact, lowering the blood viscosity improves flow dynamics and results in an appropriate increase in CVR to maintain a constant, normal CBF.[242–246]

This vasoconstriction reduces intracranial volume. From a rheologic standpoint, there is an advantage to lowering viscosity by hemodilution, but this is at the expense of oxygen-carrying capacity. Reducing the hematocrit from 45% to 30% can theoretically double CBF, and oxygen-carrying capacity would be reduced by only a third. By generalizing experimental and clinical data involving ischemia and hematocrit, it is reasonable to consider an optimum hematocrit of approximately 30% to 35%.[247]

A common mechanism for lowering viscosity in traumatic head injury is the use of mannitol, which causes an immediate influx of extravascular water, leading to hemodilution. The vasoconstriction resulting from this reduction in viscosity allows the same CBF and oxygen delivery to be maintained by means of smaller vessels and with a lower intracranial volume (see the Hyperosmolar Therapy section). In addition, mannitol will dehydrate the red blood cells themselves by about 15%, which further improves blood flow dynamics.[247]

Venous Blood Compartment

In general, vascular organization of most organ systems is anatomically similar—for example, the renal artery travels with the renal vein. The brain, however, has two entirely different anatomic systems for arterial supply and venous drainage. The paired carotid and vertebral arteries provide the arterial supply to the brain but have no corresponding venous counterparts. Blood leaves the brain through cortical and deep draining veins that empty into the superior sagittal, transverse, and sigmoid sinuses. These dural sinuses are open, semirigid structures that empty into bilateral jugular veins, which communicate directly with the right heart through the superior vena cava. There are no valves in this entire venous system. This means that right heart pressures are in direct continuity with the superior sagittal sinus within the intracranial compartment. When measured with the patient lying supine, ICP cannot be lower than central venous pressure. Of more importance, right heart pressures will be directly transmitted to the intracranial compartment, a relevant dynamic involved with a Valsalva maneuver.

During a Valsalva maneuver, intrathoracic pressure increases and venous return to the right heart decreases. Decreased venous return means decreased venous outflow from the brain. This results in a rapid, instantaneous increase in CBV as the arterial side continues to supply the brain with blood that is not draining out on the venous side. A Valsalva maneuver also will decrease cardiac output along with a decrease in venous return, but it is a disproportionate change. A common neurosurgical practice is to have the anesthesiologist induce a controlled Valsalva maneuver toward the end of a brain procedure during the final stages of hemostasis, just before beginning the closure. Intrathoracic pressure is elevated to approximately 30 mm Hg for 10 seconds as the surgeon looks for any areas of bleeding while the brain immediately swells as it engorges with blood. An intrathoracic pressure of 30 mm Hg will overcome a normal central venous pressure and essentially interrupt venous outflow from the brain. The concomitant decrease in cardiac output with a pressure of 30 mm Hg will have much less of an effect than on the venous side; therefore a relatively large volume of arterial blood will continue to fill the brain. Even a normal brain with normal compliance will immediately be affected by decreased venous outflow with a Valsalva maneuver because it happens faster than the buffering capacity of the brain can react (see Fig. 63.16). In fact, one mechanism the brain uses to buffer increases in volume is to collapse venous capacitance vessels, which in the case of decreased venous outflow from the brain, cannot occur.

Other common ways in which venous outflow from the brain can be compromised is with anything that interferes with jugular venous drainage such as a tight-fitting rigid cervical collar or thrombosis from an internal jugular line. It is not uncommon to have dominant venous outflow on one side and, following head rotation to that side, increased resistance to venous outflow. Gravity also has a role, with head elevation enhancing venous outflow from the brain. We generally keep our patients with the head elevated at 30 degrees, neck straight and free of lines, with a good-fitting cervical collar that is not too tight.

Brain Compartment

Another functional volumetric compartment is the brain itself. One of the consequences of TBI is an acute increase in total brain water.[248]

The volume of the brain parenchyma can be affected by therapeutic dehydration induced with the use of osmotic agents. These agents can be used to treat cerebral edema in an effort to remove a pathologic accumulation of fluid. Dehydration also can be used to manipulate the volume status of an otherwise normal but threatened brain compartment to emergently manage an increase in ICP as a temporizing measure before surgery, such as with extra-axial hematoma or hydrocephalus. The agents most commonly used to effect these changes are mannitol and hypertonic saline solution.

Cerebral Edema

By definition, brain edema is an abnormal accumulation of fluid within the brain parenchyma that produces a volumetric enlargement of the brain tissue.[202] The three types of cerebral edema are vasogenic, neurotoxic, and cytotoxic. Vasogenic edema occurs when the blood-brain barrier opens, resulting in movement of vascular fluid into the extracellular spaces of the brain.[249] Neurotoxic edema involves astrocytic and dendritic swelling secondary to the neurotoxic effects of excitatory amino acids, particularly glutamate, seen with

reperfusion.[202] Cytotoxic edema results from retention of water within swollen cells, most commonly found in stroke, in which interruption of energy supply leads to pump failure and an intracellular increase in sodium and water.[202]

It is ischemia, associated with energy failure at the level of mitochondria, that contributes to cytotoxic brain edema and intracranial hypertension.[248–256] Earlier studies led to the general acceptance that traumatic brain swelling was primarily a result of vascular engorgement, which caused increased ICP.[257–261] Although opinions differ, more recent work has demonstrated that cerebral edema may be primarily responsible for brain swelling, not vascular engorgement.[237,262] Marmarou and colleagues have used sophisticated MRI techniques to demonstrate that traumatic brain edema is predominantly a cellular phenomenon in both focal and diffuse brain injury.[202]

Although cellular edema predominates, it is likely that edema formation in head injury is complicated, with time-dependent contributions of both vasogenic and cytotoxic mechanisms. Experimental evidence points to transient compromise of the blood-brain barrier occurring immediately after injury, with resultant vasogenic edema. Studies indicate early closure of the blood-brain barrier, after which cytotoxic, cellular edema predominates.[202,263–265]

Hyperosmolar Therapy

Mannitol

Mannitol, an inert six-carbon alcohol of the corresponding sugar mannose, causes cellular dehydration by increasing serum osmolarity. The use of mannitol to lower ICP in patients with head injuries is based on two mechanisms of action of this drug. It establishes an osmotic gradient across the blood-brain barrier to reduce water content,[266,267] and it causes cerebral vasoconstriction through rheologic effects that decrease blood viscosity and enhance CBF and MABP (see the earlier Viscosity section).[247,268,269] This vascular mechanism of action has a strong, independent effect, such that CBF can be enhanced even when ICP is not substantially reduced.[270,271]

With patients with head injuries, mannitol is used in two clinical scenarios. The first is that of a patient with signs of herniation secondary to a surgical clot, when mannitol is given on the way to the operating room to buy time until emergent decompression is accomplished. Generally, higher doses of up to 1.2 to 1.4 g per kg can be given in this situation.[272,273]

The second clinical scenario is one of cerebral edema, when mannitol is given to control ICP. Unlike with its use for emergency surgical clots, there is no consensus on the optimal dosing regimen of mannitol in the ICU to manage ICP. Doses ranging from 0.25 g per kg to 1.0 g per kg may be effective. Mannitol can be given in response to high ICP, or it can be used prophylactically regardless of ICP, using serum osmolarity as an endpoint of treatment,[274] although some evidence indicates that it is most effective when used in the presence of high ICP or low perfusion pressure.[269,275]

Regardless of how mannitol is used, it is intended to induce a hyperosmolar, normovolemic state. Therefore because of its osmotic diuresis, replacement of urinary water and electrolyte losses is critical to avoid hypovolemia and hypotension. Mannitol typically is given as a bolus at a rate not to exceed 0.1 g/kg per minute to avoid hypotension.[274] Caution should be exercised in patients with a propensity toward congestive heart failure, because the early effects of bolus administration cause intravascular volume expansion[274] Because of its strong diuretic effect, the use of an indwelling urinary catheter is necessary.

Mannitol can extravasate into the interstitium of the brain, with breakdown of the blood-brain barrier, which may be a cause of cerebral edema. This is thought to be less of an issue with bolus dosing as opposed to continuous infusion.[276] Because of this particular concern with mannitol toxicity, many clinicians prefer to use the smallest doses of mannitol necessary and to administer it only for proven intracranial hypertension.[277]

Another concern is renal failure, which is a rare complication of mannitol therapy. It is generally believed that the kidneys are at risk above a serum osmolarity of 320 mOsm/L[278,279]; however, kidney damage may in fact be due to high serum concentrations of mannitol itself, as opposed to high serum osmolarity. It is suggested that keeping the osmolar gap (measured serum osmolarity minus calculated serum osmolarity) below 55 mOsm/kg H_2O may be better than using serum osmolarity alone to direct mannitol therapy.[274,279]

To summarize, mannitol therapy in the ICU is effective given as boluses for elevated ICP while keeping the patient normovolemic and hyperosmolar with an osmolar gap less than 55 mOsm/kg.

Furosemide, a loop diuretic, has some effectiveness for removing extracellular fluid from the brain. Although it does not work as fast as mannitol, furosemide commonly is used in conjunction with that agent because of a synergistic effect on ICP.[280]

Hypertonic Saline Solution

In many ICUs, hypertonic saline solution is being used with increasing frequency for the treatment of raised ICP in patients with TBI.[281] It is known that patients with hypotension after severe TBI have twice the mortality rate of normotensive patients[282]; therefore aggressive resuscitation with IV fluids is recommended in the guidelines for the management of patients with severe TBI.[283] However, the important concern for the development of cerebral edema is reason enough to limit the amount of free water available to the injured brain during this early period. The use of hypertonic saline solution, both to increase mean arterial pressure and to decrease ICP, is a logical approach to limit secondary injury and improve neurologic outcome.

The rapid infusion of a small volume of hypertonic solution originally was designed for the prehospital treatment of hemorrhagic shock,[284–287] and a trial found a trend toward a reduction of ICP in a double-blind, randomized, controlled trial of prehospital fluid resuscitation using hypertonic saline solution in comatose and hypotensive patients with head injuries (although no improvement in outcome was demonstrated).[288]

The rapid infusion of small volumes of hypertonic solution leads to an osmotic gradient that mobilizes parenchymal fluid into the vascular compartment,[289,290] resulting in hemodilution, endothelial shrinkage, and improved blood flow in the microcirculation,[291,292] as well as improved cardiac output.[284,285,293] Hypertonic saline solution has been shown to reduce brain bulk and ICP[294–297] and to be effective in lowering ICP both in bolus form and as a maintenance fluid.[298–300]

It is widely believed that the mechanism of action of both hypertonic saline solution and mannitol in reducing ICP is their hyperosmolar properties, although additional mechanisms are likely to be in play. Some authors have found hypertonic saline solution to be more effective than mannitol in selected patients.[301,302]

Concerns about central pontine myelinolysis and acute renal failure appear to be unfounded on the basis of clinical experience; however, a rebound effect may occur in some patients.[303] A trial also reported no episodes of acute anemia or hypokalemia associated with 23.4% saline solution administration, nor were there any

episodes of convulsions, congestive heart failure, or coagulopathy after the administration of hypertonic saline solution.[301]

In the United States, 3% sodium chloride is readily available. An initial dose of 1.5 to 3.0 mL/kg with a target for a serum sodium concentration of approximately 155 mEq/L is reasonable,[297] although 23.4% saline solution has been shown to be safe and effective in the treatment of intracranial hypertension.[301] As with hyperosmolar therapy for mannitol, it is important to maintain a normovolemic state at all times during treatment.

The 2016 BTF guidelines state that although hyperosmolar therapy may lower ICP, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe TBI.[143]

Cerebrospinal Fluid Compartment

CSF is produced mostly by the choroid plexus located in the ventricles. CSF flows from the lateral ventricles (first two ventricles) through the foramina of Monro into the third ventricle, and from there the fluid moves through the aqueduct of Sylvius to the fourth ventricle. From the fourth ventricle, CSF moves out of the ventricular system through the foramen of Magendie in the midline and the foramina of Luschka laterally. CSF then enters the subarachnoid space, circulates around the surface of the cerebellum, brainstem, and spinal column, then up through the tentorial hiatus forming basal cisterns. The clear and colorless fluid migrates over the cerebral hemispheres toward the midline where, through a semiactive process, it is transported from the subarachnoid space into the superior sagittal sinus by the arachnoid granulations.

CSF is made at a continuous rate of approximately 0.3 mL/min. With a total volume of approximately 150 mL (roughly 10% of intracranial volume), the entire CSF volume is replaced three times a day. A little less than one-third of the total volume is in the ventricular system.

In severe head injury, CSF can be displaced from the intracranial compartment as pressure differences between the superior sagittal sinus and the intracranial compartment increase (see Fig. 63.16). The spinal CSF compartment also is an important physiologic sink, and this contribution of CSF flow to ICP is another justification for nursing patients with TBIs with the head elevated.[302]

A standard way of managing the CSF compartment in the trauma patient is by draining CSF through an indwelling ventricular catheter (ventriculostomy). This has proved to be a relatively safe and effective tool in lowering intracranial volume and pressure, although ventricles in younger trauma patients commonly are smaller and harder to access and have less CSF to drain.

Specific Treatment Considerations

Decompressive Craniectomy

Decompressive craniectomy is an alternative to the medical and direct surgical methods for reducing intracranial volume. This is a surgical strategy for managing a dangerous increase in intracranial volume by expanding the size of the intracranial compartment and converting it from a semi-rigid to an elastic container. The necessary expansion is accomplished by removing a large portion of the skull and opening the dura (see Fig. 63.13). Craniectomy can be used on one side for a swollen hemisphere causing unilateral midline shift, or bilaterally for diffuse intracranial hypertension without significant midline shift.

Intractable intracranial hypertension despite maximal medical therapy is associated with a high risk of morbidity and death.[303–305] In one multicenter trial, an 86% mortality rate was found among patients whose condition failed to respond to an induced pentobarbital coma[306]—the last line of defense in medical management. Similarly, a significant relationship has been recognized between an ICP higher than 25 mm Hg and a poor outcome.[307]

Because of these ominous facts, craniectomy to increase the space available for the swollen brain has been used to lower ICP, although early outcome studies of hemicraniectomy yielded poor results.[308–310] More contemporary experiences, however, have achieved better results. In 2006 Aarabi and colleagues reviewed 10 reports published since 1988, with a total of 323 patients treated with decompressive craniectomy for posttraumatic brain swelling and intractable intracranial hypertension, and calculated a collective mortality rate of 22.3%, with good outcomes in 48.3%, with the rest of the patients (29.4%) remaining severely disabled or in a vegetative state.[250] These results compared favorably with six previous reports in which the mortality rates ranged from 42% to 100% when ICP greater than 20 mm Hg remained refractory to medical management. Reported complications included subgaleal collections, which resolved over the course of weeks to months; delayed wound healing; bone flap resorption and infections; increased swelling and hemorrhagic contusions; and parenchymal lucencies, possibly caused by ischemia.[a] Despite the reported complications, contrast-enhanced ultrasonography used to assess cerebral perfusion after decompressive craniectomy found an average fivefold improvement in microvascular blood flow.[321,322]

Despite the apparent reduction in mortality over the years, craniectomy has not consistently been shown to improve functional outcomes. A trial published in 2011 was a multicenter, randomized, controlled Decompressive Craniectomy (DECRA) trial to test the efficacy of bifrontotemporoparietal decompressive craniectomy in adults with TBI. The authors found that in patients with severe diffuse TBI and increased ICP that was refractory to first-tier therapies, the use of craniectomy, compared with medical management alone, decreased the mean ICP and the duration of both ventilatory support and the ICU stay. However, the patients who had craniectomy had a significantly worse outcome at 6 months, as measured by the score on the extended Glasgow Outcome Scale.[323] The DECRA trial was followed by the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial in 2016, which was designed using methods more consistent with common clinical practice. Compared with medical management, this trial demonstrated that surgery resulted in fewer deaths at the expense of more vegetative survivors and patients surviving with lower severe disability. However, compared with medical management, at 12 months there was a higher rate of upper severe disability, defined as independent in the home, which may be an acceptable outcome to some patients and their families. These trials have further reinforced the mortality benefit of decompressive craniectomy and highlight important issues regarding the quality of life afterward.

The poor outcomes of decompressive craniectomy reported in these trials may result from choice of surgical approach, patient selection, and/or timing of the procedure. All of the patients in the DECRA trial and nearly two-thirds of the patients in the RESCUEicp trial had bifrontotemporoparietal craniectomies. When a unilateral craniectomy is performed, it must be large enough to prevent damage to the edges of the brain herniating out into the

[a]References 11, 221, 289, 303, 307, 311–320.

cranial defect. Several recent studies support the use of a large unilateral craniectomy (12 cm × 15 cm) to optimize outcomes.[324–327] The timing of surgical decompression may also be important, as some studies suggest that early craniectomy (within 24 hours of injury) is associated with better outcomes, especially for younger patients with higher GCS scores on presentation.[325,328,329]

The BTF released specific guidelines in 2016 before the publication of the RESCUEicp study and made the following level IIA recommendation:

> Bifrontal decompressive craniectomy is not recommended to improve outcomes as measured by the Glasgow Outcome Scale–Extended (GOS-E) score at 6 months post-injury in severe TBI patients with diffuse injury (without mass lesions), and with ICP elevation to values >20 mm Hg for more than 15 minutes within a 1-hour period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the intensive care unit.[143]

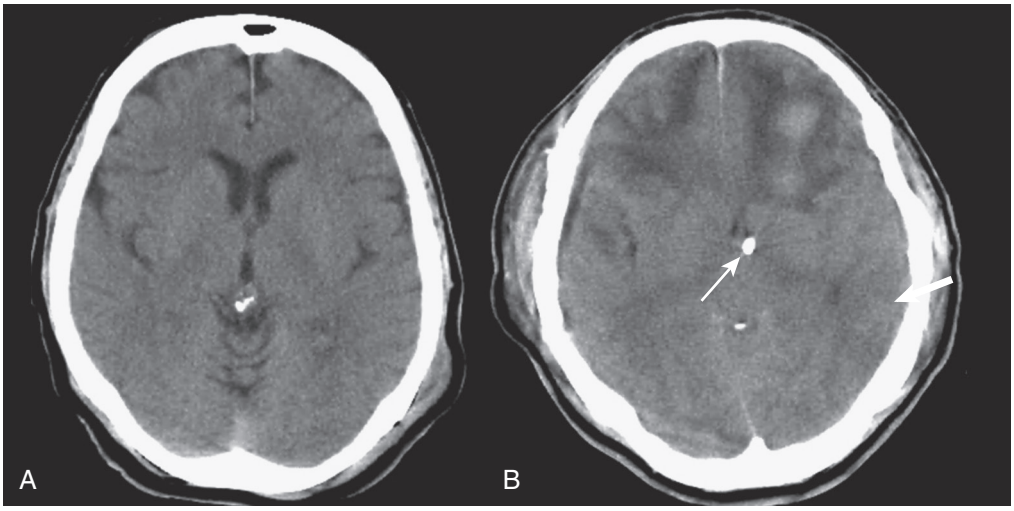
Management of Intracranial Hypertension

Acute, severe TBI is a dynamic process with the potential for dangerous changes that can evolve over hours to days; therefore all patients need to be observed closely. Ideally, ongoing assessment by neurologic examination should be at least hourly. In most patients with a GCS score of 8 or less, however, airway protection mechanisms will be impaired, necessitating intubation and, therefore, sedation, which makes an accurate neurologic assessment problematic. An ICP measuring device is usually needed at this point to adequately monitor the patient, in lieu of a reliable examination (see Chapter XX).

The medical management of intracranial hypertension in the ICU generally occurs after surgical decompression of hematomas, and in patients presenting without a surgical lesion. The threshold for treating intracranial hypertension has historically been 20 mm Hg[330]; however, a 2016 update of the BTF guidelines for the management of severe TBI made a specific level IIB recommendation to treat ICP above 22 mm Hg because values above this level are associated with increased mortality.[143] The management strategy generally is divided into tiers of therapy. The first tier is sedation, analgesia, and intubation without hyperventilation, keeping the head elevated and the neck straight and uncompressed. The routine use of paralytic agents may increase the risk of pulmonary complications; therefore muscle relaxants should be used for ICP control when sedation is inadequate.[331] If ICP exceeds targeted thresholds despite these maneuvers, moving to the next level of care is indicated, which includes CSF drainage if a ventriculostomy is being used, mannitol, or hypertonic saline solution. Beyond the first 24 hours, mild hyperventilation to keep P_{CO_2} in the mid-30s can be used. Throughout the clinical course it also is necessary to maintain an adequate CPP of at least 60 mm Hg by ensuring normovolemia and a safe MABP. If ICP is refractory to these treatments, the next step is use of decompressive hemicraniectomies or barbiturate coma (or both). Historically, surgical decompression has been reserved as a radical, end-of-the-line treatment after the patient has failed to respond to burst-suppression barbiturate coma; however, craniectomy in selected patients is moving up in the treatment algorithm of most centers, despite the literature that remains unclear (Fig. 63.20).

When ICP increases, it is important to understand why and then try to correct th underlying problem if possible. In any given patient with a head injury in whom the brain has lost its buffering capacity and compliance, small increases in intracranial volume can cause a significant rise in pressure. When ICP rises, CPP falls. If autoregulation is intact, this will usually result in a decrease in CVR and vasodilation, with its attendant increase in CBV and increase in intracranial volume. This, of course, leads to a further increase in ICP, and the cycle perpetuates itself. This is the mechanism of a plateau wave, a sustained elevation of ICP.[247]

In managing these patients, it is critical to try to determine the source of the problem. Perhaps the patient became hypovolemic and the blood pressure dropped, or a ventilator change caused hypercarbia or hypoxia. Maybe the patient is inadequately sedated or having an unrecognized seizure while pharmacologically paralyzed. The problem may be as simple as a high fever or a rigid cervical collar compressing the jugular veins. Whatever is driving this process must be corrected to break this dangerous plateau wave.



• **Fig. 63.20** A, Computed tomography (CT) image of a normal brain. B, CT scan of the brain of a patient with severe traumatic brain injury and medically intractable intracranial hypertension. Between the poorly controlled cerebral edema and the indwelling ventriculostomy, almost no cerebrospinal fluid can be identified on the scan, which shows complete obliteration of cortical sulci *(thick arrow)* and basal cisterns *(thin arrow)*. Given the absence of shift, bilateral hemicraniectomies were required.

If the cause cannot be determined, a new CT scan may be needed, and therapeutic maneuvers should be used to help turn things around, such as increasing sedation, further head elevation, ventricular drainage, administration of mannitol or hypertonic saline solution, pressors when needed, and brief periods of cautious hyperventilation.

Anticoagulation

It is intuitive that severe coagulopathy is associated with increased mortality after head injury.[332–340] Penetrating or blunt brain injury can be associated with the massive release of thromboplastin from neuronal tissue, thereby initiating the coagulation process, which evolves to an exaggerated fibrinolytic response and disseminated intravascular coagulopathy (DIC).[333] This brain injury–induced coagulopathy may lead to significant secondary injury and delay the invasive monitoring necessary for the aggressive management of intracranial hypertension.[341] The criteria for the diagnosis of DIC include abnormal results of clotting studies, thrombocytopenia, low fibrinogen, and, in some cases, elevation in levels of products of fibrinolysis (D-dimer or fibrin degradation products).[342] The DIC caused by head trauma is relatively common and frequently is detected by a prolonged prothrombin time and elevated international normalized ratio (INR). Its presence may be an indication for more intense clinical observation and follow-up CT scanning. An important component of DIC is coagulation; however, in the setting of active bleeding, anticoagulation is not indicated. The therapeutic focus is on hemostasis and replacement of diluted or consumed blood elements and components.[337,338]

Typical treatment of coagulopathy may consist of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) administration; however, there can be a variable effect on brain injury–induced coagulopathy. Recombinant activated factor VII (rFVIIa) may improve coagulopathy in patients with head injuries.[335] Originally developed for the treatment of individuals with hemophilia, rFVIIa also may be helpful in reversing the effects of anticoagulants and antiplatelet drugs.[335,339–349] It is a vitamin K–dependent glycoprotein, similar to the human plasma-derived factor VIIa, which appears to promote hemostasis by activating the extrinsic pathway of the coagulation cascade.[350] Its mechanism of action is not fully understood but includes interaction with platelets or tissue factor to augment thrombin generation and platelet activation.[339,341,343,344] Factor VIIa seems to be the bottleneck, the critical factor most depleted when patients are profoundly anticoagulated.[351] The use of rFVIIa to correct a coagulopathy before neurosurgical intervention was reported in 1998 in a hemophiliac patient with an EDH requiring craniotomy for evacuation.[352] Although not specifically evaluated for use in DIC, rFVIIa has been administered to neurosurgical patients in whom DIC was likely to be present.[338,347] Recombinant FVIIa has been used in the absence of hemophilia for neurosurgical emergencies such as EDH and SDH, SAH and intracerebral hemorrhage (ICH), tumor resection, and during placement of ICP monitors.[342,345,347,39] A retrospective study found improved outcomes, without complications, when rFVIIa was used for coagulopathic patients requiring urgent neurosurgical intervention.[353] The incidence of thrombosis after rFVIIa is low, but thrombosis is an extremely important potential complication[343,347,348,354,355] and is of particular concern in DIC.[337] The risk of thrombosis should be carefully considered in patients with a premorbid risk of thrombosis to avoid unintended consequences, such as ischemic stroke or myocardial infarction. Precise dosing for conditions other than hemophilia has not been confirmed[341]; the U.S. Food and Drug Administration has approved rFVIIa only for use in hemophilia; other uses are considered off-label.

In addition to the coagulopathy induced by a brain injury, neurosurgeons and intensivists often are faced with managing patients with traumatic ICH who are taking pharmacological anticoagulants. The use of these drugs is expected to increase as the population ages.[338] These patients must have normal coagulation rapidly restored to prevent further bleeding and to make surgical intervention possible.

Warfarin is a common anticoagulant that works as a vitamin K antagonist. Reversal can be achieved by vitamin K, FFP, PCC, or rFVIIa. Although all of these options reduce the INR, their efficacy, timeliness, and safety vary. It takes about 4 days to normalize coagulation if warfarin is stopped. With IV vitamin K, full reversal begins 4 to 6 hours after administration but may take up to 24 hours to lower the INR.[356] FFP contains vitamin K–dependent factors and is effective at reducing the INR within several hours; however this may take up to 30 hours, depending on the degree of anticoagulation. Additionally, FFP administration may cause pulmonary edema, intravascular volume overload, and transfusion-related reactions.[357] Active intracranial bleeding can be rapidly fatal and faster reversal agents are often required. PCCs contain variable amounts of factors II, VII, IX, X; proteins C, S, and Z; and heparin. Four-factor PCCs (e.g., Kcentra) are distinguished from three-factor products by the inclusion of appreciable amounts of factor VII. Several studies suggest that PCC use leads to faster INR reversal, less hematoma expansion, and similar or better mortality rates and functional outcomes compared with FFP.[358–361] rFVIIa results in rapid INR reversal similar to that of PCC; however, there are limited data to support improved hemostasis, mortality, or functional outcomes compared to other reversal strategies.[357] rFVIIa has also been associated with a slightly higher arterial thrombosis rate.[362] The INR is particularly sensitive to factor VII levels and INR correction may occur despite inadequate levels of factors II, IX, and X that are required for hemostasis. In addition, rFVIIa is expensive compared with other reversal strategies.[357] Considering all these factors, the Neurocritical Care Society and Society of Critical Care Medicine published guidelines in 2016 that recommend immediate administration of IV vitamin K (10 mg) and four-factor PCC (weight- and INR-based dosing), with FFP reserved for situations when PCC is not available. They recommend against rFVIIa use for warfarin reversal in patients with ICH.[357]

In hospitalized patients receiving unfractionated heparin, reversal occurs approximately 60 minutes after an IV infusion is stopped. If reversal needs to be faster, protamine sulfate is recommended. Protamine is dosed at 1 mg for every 100 units of heparin given in the previous 2 to 3 hours with a maximum single dose of 50 mg. Subcutaneous heparin is usually not reversed.[338] With low–molecular-weight heparin, a partial thromboplastin time is variably altered and not a reliable measure of its effect. Reversal of low–molecular-weight heparin LMWH is recommended for patients receiving therapeutic doses in the setting of ICH.[338] rFVIIa may be used a second-line agent.[357]

A common situation is the presentation of a patient with a head injury who is taking an antiplatelet agent such as aspirin or other nonsteroidal antiinflammatory drug (NSAID). Acetylsalicylic acid (ASA) inhibits platelet aggregation for the life of the affected platelet, which is approximately 10 days. This occurs even at the lowest dose of 81 mg/day. A period of 5 to 6 days typically is needed after stopping aspirin to replace approximately half of the circulating platelets (10% per 24 hours). The effect of ASA on platelets is complete and irreversible. If treatment is necessary, platelet transfusion should ideally be administered after three to

five terminal half-lives of the ASA to avoid pharmacologic inhibition of the transfused platelets. A 2013 trial found that platelet transfusion reduced the rate of postoperative hemorrhage, average postoperative hemorrhage volume, disability rate, and mortality rate in ASA-inhibited patients with acute hypertensive basal ganglia hemorrhage undergoing craniotomy.[363] In contrast to the positive results in surgical patients, several studies in nonsurgical patients with ICH have shown that platelet transfusions were associated with an increase in adverse events, such as hypotension, fever, cardiac and respiratory events, and decline in neurologic status.[364–366] Platelet transfusion is also associated with serious risks, including transfusion-related acute lung injury, thrombosis, DIC, hemolytic transfusion reactions, and transfusion-associated sepsis. As a result of these findings, the Neurocritical Care Society and Society of Critical Care Medicine recommend platelet transfusion only for ASA-inhibited patients with ICH if they undergo neurosurgical intervention.[357] The guidelines were published before publication of the 2016 PATCH (Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage) trial, which unexpectedly found an increased risk of death or dependence with platelet transfusion for ICH patients using ASA.[367] The findings of the PATCH trial will likely serve to reinforce the recommendation that platelets should not be transfused for patients with an ICH who are taking ASA unless operative intervention is required.

Desmopressin (DDAVP) may secondarily improve platelet adhesion to endothelial defects and is therefore also recommended to overcome aspirin-induced platelet dysfunction. The recommended dosage of DDAVP is a single administration of 0.4 μg/kg IV. Other NSAIDs have various anticoagulant effects. If significant NSAID use has occurred before a neurosurgical emergency, the same interventional strategy may apply but is not formally recommended.[357] Data confirming efficacy of DDAVP in counteracting an antiplatelet effect are not available.[338]

Other antiplatelet agents include adenosine diphosphate receptor inhibitors (e.g., clopidogrel, ticlopidine) and glycoprotein receptor-blocking agents (e.g., abciximab, eptifibatide, tirofiban). Abciximab, clopidogrel, and ticlopidine irreversibly alter platelet aggregation[368–371] through a mechanism that is additive to the antiplatelet effects of aspirin. The platelets are permanently affected; once the drug is stopped, recovery of normal platelet function requires about a week until new platelets are produced. Rapid correction requires platelet transfusion, and DDAVP also may have a beneficial short-term effect.[338] Eptifibatide and tirofiban are highly effective in generating 80% to 95% reversible inhibition in platelet aggregation.[368,369,371–374] Stopping the medication allows return of normal platelet function within approximately 48 hours for abciximab and within 4 to 8 hours for the others. Platelet transfusion increases the proportion of unaffected platelets and is the primary intervention.[338]

Fibrinolytic and thrombolytic agents disrupt formed clots.[374–376] These drugs have a prolonged half-life and frequently are used in combination with heparin or other agents to ensure continued therapeutic anticoagulation. Because circulating fibrinogen is decreased during thrombolysis, cryoprecipitate, a source of concentrated fibrinogen, is the basis for reversing treatment.[338] When cryoprecipitate is contraindicated or not available in a timely manner, antifibrinolytic agents such as tranexamic acid (10–15 mg/kg IV over 20 minutes) or ε-aminocaproic acid (4–5 g IV) may be used.[357] Although fibrinolytic and thrombolytic agents have well-recognized applications for cardiac[377] and neurologic[378,379] problems, their use generally is not seen in patients presenting with head injury.

Additional anticoagulant classes include the factor Xa inhibitors and direct thrombin inhibitors. Factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban) exert their anticoagulant effect by preventing factor Xa–dependent conversion of prothrombin to thrombin and they are reversed with four-factor PCC. Direct thrombin inhibitors such as bivalirudin, desirudin, argatroban, and lepirudin are also reversed with four-factor PCC. Dabigatran is a direct thrombin inhibitor with a specific antidote, idarucizumab. Activated charcoal is also recommended to aid in the reversal of both anticoagulant classes.[357]

Hypothermia also is known to cause and worsen coagulation abnormalities,[341,380] the treatment for which is rewarming. Certain medical conditions also may affect coagulation, and therefore may be important as underlying factors in patients with a head injury. DDAVP increases the release of factor VIII and von Willebrand factor and is used to treat mild hemophilia A, von Willebrand disease, and chronic renal and liver disease, as well as acquired and congenital platelet disorders.[380–384]

DDAVP has a significant antidiuretic effect and will increase free water reabsorption in the kidney, potentially leading to overhydration and hyponatremia. This may cause serious problems in a patient with a severe head injury with cerebral edema, poor compliance, and high ICP.

Unintended, iatrogenic worsening of coagulopathy may result with use of hetastarch solutions, which may be administered to increase intravascular volume. These solutions may lower von Willebrand factor levels and alter platelet function. Low–molecular-weight hetastarch preparations are available that may cause less severe changes; however, if the patient requires correction of a coagulation abnormality, these solutions should be avoided if possible.[384–387]

Seizure Prophylaxis

A well-known complication of moderate to severe TBI is post-traumatic seizure (PTS). PTS can be divided into two subgroups. Seizures occurring within the first 7 days after brain injury are classified as early PTS. Those occurring more than 7 days after injury are classified as late PTS.[388] In patients with severe TBI, the rate of clinical PTS may be as high as 12%, whereas that of subclinical seizures detected on EEG may be as high as 25%. Nonconvulsive electrographic seizures can also occur, leading to cerebral metabolic crisis, delayed increases in ICP, and worse clinical outcome.[389] The risk factors for early PTS include GCS score of 10 or lower; immediate seizures; posttraumatic amnesia lasting longer than 30 minutes; linear or depressed skull fracture; penetrating head injury; subdural, epidural, or intracerebral hematoma; cortical contusion; age 65 years or younger; or chronic alcoholism.[390] PTS occurs as a result of multiple mechanisms, depending on whether the TBI is penetrating or nonpenetrating. Penetrating TBI results in gliosis, or scarring of the cerebral cortex, whereas nonpenetrating TBI may result in focal contusions or intracranial hemorrhages. Hemoglobin breakdown products may have toxic effects on neuronal function and lead to PTS. A series of stepwise changes occurs in the neuronal network after an epileptogenic insult. Early changes include new gene transcription and modification of neurotransmitter receptors and ion channel proteins. Late changes are anatomic and include axonal sprouting and dendritic modifications.[390,391] These late changes may lead to posttraumatic epilepsy (PTE), which is defined as recurrent seizures more than 7 days after injury.[392]

Several population-based studies have shown that rates of PTE are substantially higher than the risk of developing epilepsy in the general population. The overall incidence of PTE is approximately 1.5% to 4.5% and in patients with severe TBI it is even higher, approximately 13% to 37%.[393,394] Those most at risk for PTE are

individuals who have have the following: severe TBI and early PTS; acute intracerebral hematoma or cortical contusion; post-traumatic amnesia lasting longer than 24 hours; age younger than 65 years; or premorbid history of depression.[395]

Seizure prophylaxis refers to the practice of administering anticonvulsants to patients with TBI to prevent the occurrence of PTS. The rationale for routine seizure prophylaxis is that there are potential benefits to preventing seizures after TBI, such as limiting hypoxia, increased intracranial pressure, increased metabolite production, and higher metabolic demands, as well as preventing the development of PTE.[396]

Historically, phenytoin has been the drug of choice for post-traumatic seizure prophylaxis. Numerous studies have shown that phenytoin reduces the incidence of early PTS, but it has no effect on the incidence of late PTS.[390,397–400] The drug, however, is associated with several disadvantages. It has a narrow therapeutic window and requires regular serum level monitoring. There is a well-established side effect profile that includes IV site reactions, exfoliative dermatitis, granulocytopenia, permanent B-cell immunodeficiency, and fatal phenytoin hypersensitivity syndrome. Phenytoin-associated hypotension is also an important consideration for polytrauma patients in shock.[401] There are data to suggest that phenytoin has negative neurobehavioral effects, especially with prolonged use.[402] It may also negatively affect cognition, particularly involving tasks with significant motor and speed components.[403] Phenytoin is metabolized through the cytochrome P450 system and thus can cause numerous drug interactions.[401] These concerns regarding the side effects of phenytoin have prompted the search for a safer alternative.

Levetiracetam is a drug that has rapidly gained in popularity owing to its demonstrated efficacy and favorable side effect profile.[404] It has a greater than 95% bioavailability, does not require regular serum monitoring, and has few drug interactions.[405] Multiple groups have studied the effectiveness of levetiracetam compared to phenytoin in the prophylaxis of PTS. No statistically significant difference between the two drugs has been found.[401,406–409] One study found that levetiracetam, as compared with phenytoin, was associated with better long-term neurologic outcomes.[408] This finding adds to earlier data suggesting that levetiracetam has a neuroprotective effect.[410,411] A subsequent report, however, found that long-term functional outcomes in patients with TBI were not affected by treatment with phenytoin or levetiracetam. The only significant difference these researchers found is that patients treated with phenytoin had a higher incidence of fever during hospitalization.[407]

Older antiepileptic drugs such as phenobarbital, valproate, diazepam, and carbamazepine have not been as extensively researched and available results are mixed. Given their side effect profiles and pharmacodynamic properties, there is no clear advantage to using these agents over phenytoin.[390,398]

In conclusion, the 2016 BTF guidelines state

> Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS. Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is felt to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes. At the present time there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity"[143]

Nonetheless, levetiracetam is commonly used in trauma centers to decrease the incidence of early PTS.

Nutritional Support

TBI causes the release of inflammatory mediators and alters cellular signals, resulting in hypermetabolism, hypercatabolism, hypoalbuminemia, refractory nitrogen wasting, and immunosuppression.[412] Hyperglycemia is also a component of the stress response to head injury. It is both a significant indicator of the severity of injury and a significant predictor of outcome from head injury.[413] It follows that the goals of nutritional support after TBI are to provide sufficient calories to satisfy the body's increased metabolic needs, maintain nitrogen balance, control blood glucose levels, and prevent immunosuppression. The timing and method of feeding are also important considerations.

The general consensus among researchers is that 25 to 30 kcal/kg per day is probably an appropriate feeding regimen, although indirect calorimetry is preferred.[414,415] A protein intake of approximately 1.5 g/kg per day should be appropriate for TBI patients to improve synthesis of protein and preserve lean body mass.[416,417]

With regard to the timing of feeding, lower mortality rates were found when patients were fed during the first 5 to 7 days after a TBI. Patients with TBI who were not fed within 5 days of injury were twice as likely to die compared with patients who were fed. Patients with TBI who were not fed within 7 days had a four times greater likelihood of death.[418] Additionally, early and aggressive parenteral nutrition administration to patients with severe TBI increases total CD4 count and T-lymphocyte responsiveness.[419]

The 2016 BTF guidelines recommend feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day after injury to decrease mortality. They also recommend transgastric jejunal feeding to reduce the incidence of ventilator-associated pneumonia.[143]

Role of Steroid Therapy

On the basis of class 1 evidence originating from a prospective randomized trial comparing dexamethasone and placebo in 300 patients with head injuries, dexamethasone was found to be ineffective in improving outcome or reducing ICP in patients with severe brain injury.[3,314] Methylprednisolone, when given in high doses to patients with moderate and severe head injuries, is associated with increased mortality.[420] Therefore the use of steroids is not recommended in their management. Accordingly, the 2016 BTF guidelines did not recommended steroids for improving outcome or reducing ICP. In fact, for patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.[143]

Conclusions

The management of TBI will remain a major medical and surgical challenge for the foreseeable future. Despite concentrated basic research directed at elucidating the metabolic factors that mediate the transition from primary to secondary tissue damage, nothing has been found that might have clinical efficacy. As the percentage of the population older than 70 years of age continues to rise, ICU physicians will face an ethical dilemma when dealing with brain hemorrhages in this age group. At present, physicians are left with the application of best protocol-driven critical care management, supported by timely neurosurgical intervention, and a societal commitment to protective and preventive programs.

Key Points

- The management of severe head injuries remains a major challenge to neurosurgeons.
- Timely surgical intervention is important.
- Hyperventilation, although very effective in reducing high intracranial pressure (ICP), must be used judiciously; otherwise, it may become more harmful than helpful. Glucocorticoids have no significant therapeutic benefit in managing severe head injuries.
- A simple-to-use, reproducible neurologic status scoring system, the Glasgow Coma Scale, enables meaningful and consistent multidisciplinary communication from the accident scene through intensive care and beyond.
- Mannitol and hypertonic saline solution can be useful in patients with head injuries to lower ICP.
- Decompressive craniectomy can be used to increase the space available for the swollen brain, thereby lowering ICP. Patient selection and realistic expectations are important in surgical decision making.

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Review Questions

1. A colleague reports to you that a patient's Glasgow Coma Scale (GCS) score is E (eye opening) 3, V (verbal) 4, M (motor) 5. How would you interpret this?
   a. Eyes open to pain, oriented, withdraw from painful stimuli
   b. Eyes open spontaneously, oriented, follow commands
   c. Eyes open to voice, confused, withdraw from painful stimuli
   d. Eyes open to voice, confused, localize to painful stimuli
   e. Eyes open spontaneously, speech is inappropriate, withdraw from painful stimuli
   Answer: d. See the Glasgow Coma Scale section and Table 66.1.
2. Which of the following treatment options is recommended for the reversal of warfarin in patients with a traumatic intracerebral hemorrhage?
   a. Recombinant factor VIIa (rFVIIa) and platelets
   b. Vitamin K and protamine sulfate
   c. Vitamin K and prothrombin complex concentrates (PCC)
   d. rFVIIa and desmopressin
   e. PCC and idarucizumab
   Answer: c. See the Anticoagulation section.
3. Cerebral perfusion pressure can be defined as which of the following? Abbreviations are MABP (mean arterial blood pressure), CVR (cerebrovascular resistance), ICP, intracranial pressure.
   a. MABP − CVR
   b. MABP + ICP
   c. (MABP − ICP)/CVR
   d. MABP − ICP
   Answer: d. See the Secondary Head Injury section.
4. The 2016 Brain Trauma Foundation guidelines recommend which of the following goal values in severe traumatic brain injury?
   a. ICP < 20 mm Hg and CPP > 70 mm Hg
   b. ICP < 22 mm Hg and CPP 60 to 70 mm Hg
   c. ICP < 20 mm Hg and CPP 60 to 70 mm Hg
   d. ICP < 22 mm Hg and CPP > 70 mm Hg
   e. ICP < 22 mm Hg and CPP 50–60 mm Hg
   Answer: b. See the Cerebral Perfusion Pressure and Management of Intracranial Hypertension sections.
5. Antiepileptic drugs such as phenytoin and levetiracetam have been shown to reduce the incidence of early posttraumatic seizures. This effect has not been found to extend beyond what time frame?
   a. 12 hours
   b. 1 day
   c. 1 week
   d. 1 month
   e. 1 year
   Answer: c. See the Seizure Prophylaxis section.

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Critical Care of the Severely Burned

KEVIN K. CHUNG AND BRUCE C. FRIEDMAN

CHAPTER OUTLINE

Introduction
Epidemiology
Phases of Burn Care
Initial Assessment and Triage (Phase I)
  Prehospital Evaluation
Primary Survey
  Secondary Survey
Fluid Resuscitation: The First 48 Hours (Phase II)
  Resuscitation Morbidity
Optimizing Burn Wound Coverage (Phase III)
  Surgical Management
Critical Care (Phase III Continued)
  Neurologic
  Cardiovascular
  Pulmonary
  Gastrointestinal
  Nutrition and Metabolism
  Renal
  Hematologic Considerations
  Infectious Complications
Rehabilitation (Phase IV)

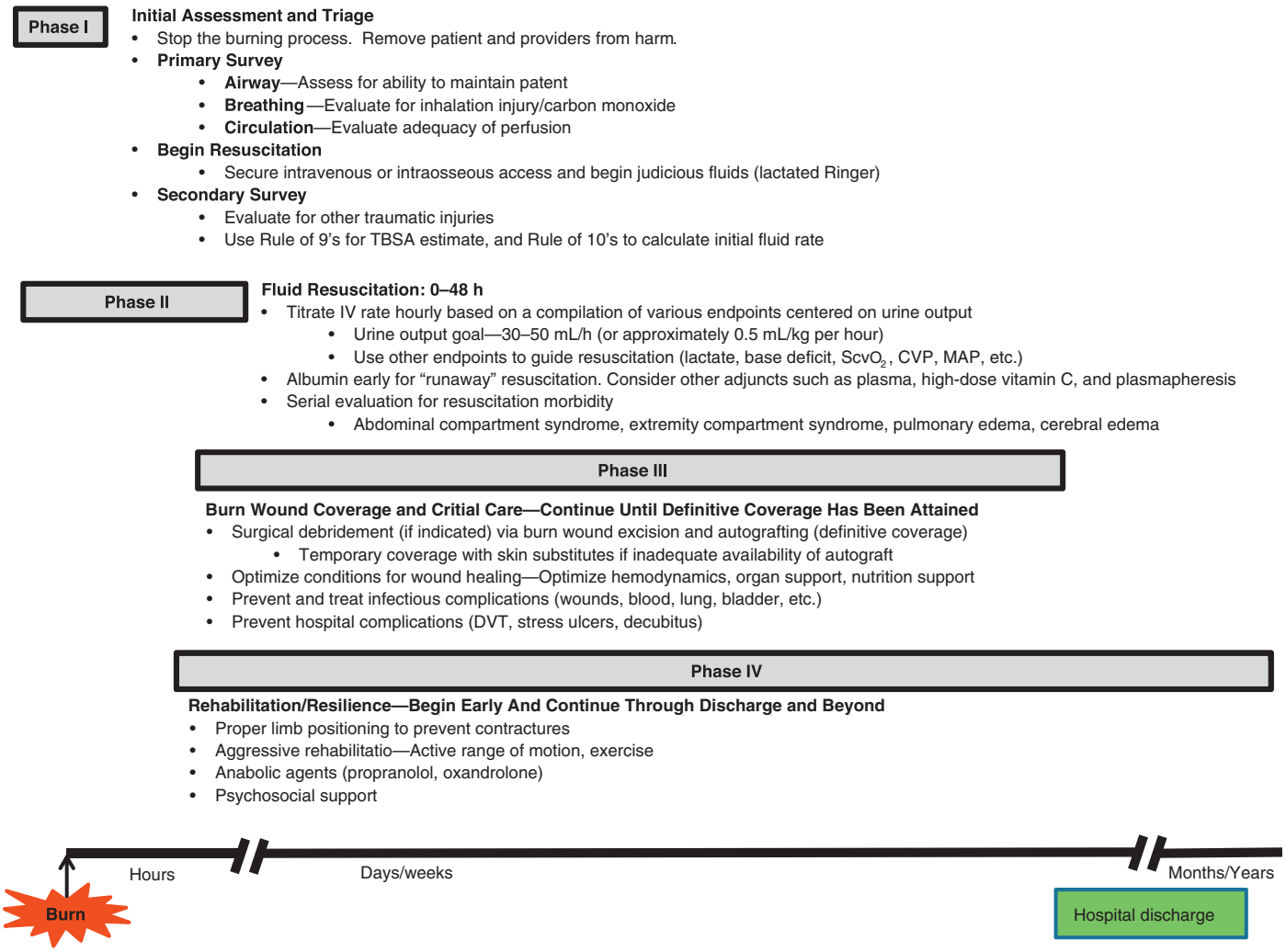
Introduction

Care of the critically ill burn patient is among the most challenging in critical care medicine. Although many fundamental principles of critical care remain similar to the care of other populations, other aspects of burn care make it very unique. For example, the first 24 to 48 hours after severe burn is characterized by a profoundly augmented and dysregulated host response that is only seldom observed in the worst categories of acute illness. Concomitant smoke inhalation injury or trauma only adds to this exaggerated response. Massive fluid resuscitation, generally prescribed to prevent multiple-organ failure and death, can be viewed as an additional insult to injury, particularly if not monitored closely. Severely burned skin then must be removed in the form of surgical burn wound excision, which typically occurs within the first week after the burn is sustained, and replaced with autograft harvested from areas of unburned skin. This procedure can only be described as controlled massive hemorrhage as intraoperative blood loss can be as high as 4 L for burns involving greater than 40% total body surface area (TBSA). For these patients, it may take multiple staged surgeries to achieve the goal of 100% definitive coverage as donor skin becomes a precious and unavailable commodity and may need to be reharvested after sufficient healing. The patient's intensive care unit (ICU) course is characterized by a high risk of bloodstream infections (BSIs) as well as a high risk of pneumonia for those with smoke inhalation injury. When these complications occur, an exaggerated host response can be expected with subsequent organ failure and high risk of death. Even if the patient can overcome the first infectious complication, recurrence is highly likely and will continue until 100% definitive autograft skin coverage has been achieved. All the while, the patient remains in an intensive care setting, subject to all the common ICU-related complications that can accumulate during a prolonged ICU stay. Simply put, burn patients face all the same issues that other critically ill populations typically face. However, unlike most other populations, fighting and overcoming the first, second, or even third insult or ICU complications is only the beginning. It is akin to a war of attrition. The goal of any good intensivist is to help preserve as much organ function as possible during this stage of care where patients are at risk of a near-perpetual barrage of physiologic insults in the form of repeated surgeries, blood loss, and infectious, iatrogenic, and other common ICU complications. At the same time, careful attention must be paid to optimize the conditions of wound healing with adequate nutrition while optimizing acute rehabilitative care to minimize the inevitable hypercatabolic muscle wasting as well as debilitating scar contractures that occur downstream.

This chapter provides intensivists a comprehensive expert review of the most state-of-the-art care of critically ill burned adults. Many principles from recent advances in critical care are extrapolated from studies from the general ICU population where appropriate. In other areas, advances specific to the critical care of burn patients are emphasized.

Epidemiology

Throughout the world, approximately 11 million people annually sustain burns severe enough to seek medical attention, ranked fourth among all injuries. Of these, 300,000 die yearly as a result. In the United States, approximately 5 to 16 per 100,000 per year sustain burns large enough to require hospital admission historically.[1] In 2011, burns were listed as a primary diagnosis in approximately 486,000 emergency department visits across the United States, and approximately 10% of patients required hospital admission.[2] The annual death rate caused by fire and burn has dramatically decreased over the past four decades. In 1981, the age-adjusted



• **Fig. 64.1** The four major phases of burn care. Initial assessment and triage (phase I); resuscitation (phase II); burn wound coverage and critical care (phase III), and rehabilitation (phase IV). *CVP,* Central venous pressure; *DVT,* deep vein thromboses; *IV,* intravenous; *MAP,* mean arterial pressure; *$ScvO_2$,* central venous oxygen saturation.

fire- and burn-related death rate was 2.99 per 100,000. This decreased to 1.39 per 100,000 in 1989.[3] In 2015, the death rate was a near 40-year low of 0.89 per 100,000.[4] This remarkable decrease in the death rate likely represents the combined impact of major advances in burn prevention and management. It should be seen as no coincidence that a relative explosion in peer-reviewed burn-related research occurred in 1980s and 1990s that correlated with many scientific medical advances.[5] Even still, there is much more work to be done. According to the American Burn Association (ABA) National Burn Repository, which contains more than 200,000 entries from major burn centers in North America from 2005 to 2015, the overall mortality among the entire spectrum of burn sizes was 3.1%. However, more than 75% had a burn size less than 10% TBSA; among these the mortality was 0.6%. Among those with greater than 10% TBSA, the mortality was 11%, whereas among those with burns greater than 40% TBSA, the mortality was 47%.[6] Although big burns (>40% TBSA) represent less than 4% of all reported burn admissions, the proportional clinical load required to care for these patients is significantly skewed. As a result, patients with greater than 40% TBSA burns have an average hospital stay that is 8-fold higher with a resultant cost that is 15-fold higher than smaller burns.[6] Hence, much of critical care in burns specifically involves this category of patients.

Phases of Burn Care

Burn care can be compartmentalized into four main phases: initial assessment and triage (phase I); resuscitation (phase II); burn wound coverage and critical care (phase III); and rehabilitation (phase IV) (Fig. 64.1).

Initial Assessment and Triage (Phase I)

Prehospital Evaluation

The main principle of prehospital care is to remove the patient from the site of injury, render a rapid systematic care to identify and treat immediately life-threatening conditions (such as airway compromise), and triage the patient appropriately to the best available medical care. Fortunately, the systematic approach applied in the care of burn patients as adopted by the ABA and taught in Advanced Burn Life Support courses throughout North America

is aligned with the Advance Trauma Life Support program developed by the American College of Surgeons (ACS) Committee on Trauma.[7]

Primary Survey

The main principles of systematically assessing a patient's condition, resuscitating, and stabilizing them, and arranging for interhospital transfer to ensure optimal care are identical. This systematic evaluation begins with the primary survey, which prompts the provider to rapidly evaluate, identify, and address immediately life-threatening conditions (airway, breathing, circulation).

Initial Assessment and Management of Inhalation Injury

Initial assessment of burn patients must always include an evaluation of the possibility of inhalation injury. The Advanced Burn Life Support course categorizes inhalation injuries into three distinct entities: upper airway, lower airway, and poisoning.[8] Inhalation injury can present as supraglottic injury, chemical injury to the respiratory tract, toxicity owing to agents such as carbon monoxide (CO) and cyanide, or a combination of all of the above. These are discussed separately in the following text.

Indications for Intubation

For the most part, indications for intubation during the acute prehospital setting are no different than those for the general trauma population. Generally, these include inability to protect the airway and inability to maintain adequate gas exchange. Inability to protect the airway secondary to alterations in mental status is the most frequent reason for intubation in the field. It should be noted that mental status alterations are not typically present owing to burns alone. In fact, many patients with extensive burns are able to maintain an adequate airway and carry a normal conversation. An altered mental status should alert the provider of the possibility of poisoning (see the "Poisoning: Carbon Monoxide and Cyanide" section) or an acute intracranial process. It should be noted that evidence of facial burns alone should not be reason to prophylactically intubate a patient in the prehospital setting. One large retrospective study determined that up to one-third of patients intubated by prehospital providers are done so owing to prophylaxis as an indication.[9] Most of these intubations may be unnecessary, especially if transport times to the regional burn center are relatively short (<1 hour). As a result, there has been widespread interest in the burn community to develop educational and training strategies to decrease the number of unnecessary intubations. Once it is ensured the airway is patent or secured, breathing is controlled, and circulation is adequate, intravenous (IV) or intraosseous access is achieved and judicious fluids initiated (see the "Fluid Resuscitation: The First 48 Hours (Phase II)" section).

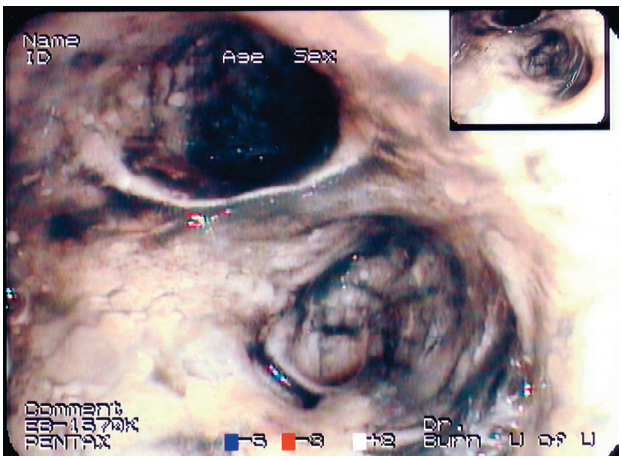
Upper Airway Injury

Upper airway injury as it relates to burns often has a true thermal component.[8] In most cases, the mechanism is a flash flame burn to the face whereby direct thermal injury has occurred to the oropharynx. Less commonly, steam, scald, or chemical burns can involve the upper airway. Flash flame burns are often seen in a flash fire from pouring gasoline on a hot grill or smoking while using oxygen. Additionally, the most severely burned patients who have extensive and deep burns to the face can also present with this type of injury. The typical physical findings of facial burns—singed nasal and facial hair and denuded oral mucosa—are present. Those who have vocal cord involvement and present with hoarseness should be considered to have severe injury. Acutely, there is a high risk of progressive airway occlusion from pharyngeal and supraglottic edema. Over the 24 hours after the burn, edema of the face and tongue can be extreme, also contributing to airway challenges (Fig. 64.2). Hence, these patients must have close follow-up and be intubated early if there are any clinical concerns of impending airway compromise.

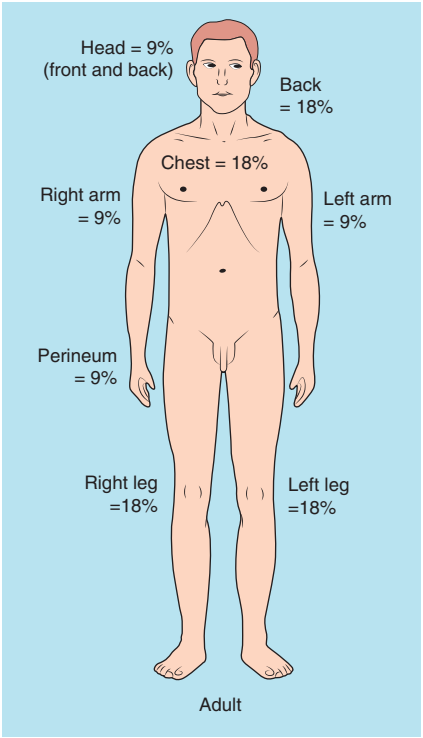
• **Fig. 64.2** This young man was burned playing with matches and gasoline, sustaining burns to 60% total body surface area, including his entire face. On presentation, he was alert and breathing comfortably. Arterial blood gas values (including carboxyhemoglobin) and chest x-ray findings were normal. Based on the extent and location of his injuries, elective nasotracheal intubation was performed. Six hours later the patient displays massive facial edema. Eyes are swollen shut, and oral excursion is severely restricted. If he lost his endotracheal tube at this point, his airway could not be maintained. Note that the tube is tied around his head securely, not taped in position. He will need to remain intubated for at least 3 to 5 days until most of this edema resolves.

Lower Airway Injury: Smoke Inhalation

Involvement of the lower airways (below the glottis) is predominantly a chemical injury.[8] This occurs as a result of patients repeatedly inhaling the toxic by-products of combustion in an enclosed space. This injury typically involves the mucosa of the entire tracheobronchial tree and is best detected by direct visualization under a fiberoptic bronchoscopy (Fig. 64.3). Clinical manifestations of this injury occur over time as the chemical irritation to the tracheobronchial mucosa causes increased secretions owing to



• **Fig. 64.3** Bronchoscopic appearance of the carina of a man who was dragged unconscious from a burning house. Carbonaceous deposits are apparent in his trachea, and more extensively in the mainstem bronchi. This finding is diagnostic of inhalation injury.



• **Fig. 64.4** The rule of nines.

increased production from goblet cells combined with obliteration of the ciliated pseudocolumnar cell lining the mucosa, resulting in inability to clear airways. These patients are at high risk for developing mucous plugs and pneumonia. Over a few days, mucosal sloughing can occur, which complicates the problem as blood and fibronacious debris mix with abundant mucous and further increase the risk of mucous plugs. Deeper into the hospitalization, patients develop tracheomalacia and bronchiectasis. Finally, involvement of the small airways can manifest as small reactive airways disease with the potential for asthma-like symptoms. Diagnosis and ICU management of inhalation injury are discussed later in this chapter.

Poisoning: Carbon Monoxide and Cyanide

Poisoning caused by CO most often occurs concomitantly in patients burned in an enclosed space.[8] CO has an affinity for hemoglobin of more than 200 times greater than oxygen and exposure results in hypoxia and ischemia. CO acts to displace oxygen from hemoglobin (forming carboxyhemoglobin [COHb]) and decreasing oxygen delivery. Symptoms of CO toxicity include confusion, stupor, coma, seizures, and myocardial infarction is diagnosed using a CO-oximeter. The mainstay of initial treatment of CO poisoning remains delivery of supplement 100% oxygen, which shortens the half-life of COHb to about 45 minutes. Hyperbaric oxygen therapy (HBO) has been used to treat CO poisoning and can further reduce the COHb half-life to about 20 minutes.[10] In those who are able to undergo therapy, HBO appears to reduce the risk of long-term cognitive neurologic sequelae.[11] However, in burns, logistical challenges have limited the wide use of HBO as acute care of severe burn is very resource intensive. Unless an HBO chamber is easily accessible and does not interfere with the comprehensive acute care, this will continue to limit wider adoption. Hopefully, continued advancements in HBO technology combined with increased ICU accessibility with ICU- and ventilator-compatible monochambers may result in increased application.

Evidence of CO toxicity should alert clinicians about the possibility of hydrogen cyanide (HCN) toxicity. HCN is a by-product of thermal combustion of various household nitrogen-containing products, such as wool, silk, paper, nylon, and polyvinyl chloride. The significance of HCN and thus the need to treat it has been controversial in the burn community.[10] Previous reports have suggested that significant HCN exposure is rare in flame burns as it is rapidly consumed because of a low flash point.[12] Hence, it is consumed as rapidly as it is produced. Regardless, it is important to look for evidence of HCN toxicity as the prevalence is not zero.[13] The clinical challenge is the lack of a rapid and reliable test to detect cyanide poisoning. A lactate elevation disproportionate to the degree of shock combined with the confirmed presence of COHb should trigger a high level of suspicion and rapid treatment. The current standard of care is to administer 5 g of hydroxocobalamin (Cyanokit, Meridian Medical Technologies, Inc., Columbia, MD) intravenously over 15 minutes.[10] This B_{12} vitamin binds to HCN to form a nontoxic cyanocobalamin that is excreted in the urine. A second dose of 5 g may be administered in patients with persistent clinical deterioration. The advantage of erring on the side of treatment is that this therapy comes with very little risk. The traditional treatment for HCN toxicity, sodium nitrite and sodium thiosulfate, should be avoided in burns as the methemoglobinemia it deliberately induces can be fatal in the setting of CO toxicity.

Secondary Survey

Next a secondary survey is conducted to evaluate for other traumatic injuries while also determining the depth and size of the burn. The rule of nines is recommended for use in the prehospital setting to quickly estimate the percent TBSA involvement (Fig. 64.4). Of note, only second- and third-degree burns (partial- and full-thickness burns) are incorporated into the TBSA estimate. For those who are severely burned or deemed to require specialty care because of anatomically challenging burns, optimal care is typically delivered at a center specializing in burn care. The ABA has published specific burn center referral criteria to aid in the appropriate triage of patients in the prehospital setting.[8] These criteria are listed in Box 64.1.

• BOX 64.1 American Burn Association Referral Criteria

1. Second-degree burn over 10% TBSA
2. Burns to face, hands, genitalia
3. Perineum, crossing joints
4. Any third-degree burn
5. Inhalational injury
6. Electrical or chemical burn
7. Concomitant trauma
8. Comorbid conditions

Concomitant Trauma

The presence of concomitant trauma in the setting of a major burn occurs in a variety of settings to include fires involving motor vehicles, aircraft, explosions, electrical injury, and trauma sustained while escaping fires. Historically, combined injury involving burn and trauma has been reported to be relatively low at 5% to 7% in the civilian setting.[14] The prevalence of concomitant trauma among military burn admissions has been reported to be much higher compared with civilian burns during wartime. Authors at the United States Army Institute of Surgical Research (USAISR) Burn Center reported that 37% of all military burns had additional nonburn injuries compared with just 11% of civilian burns ($P < 0.0001$).[15] Clearly, concomitant trauma is associated with an additive risk of death among patients with burns and should be taken very seriously.[14] During the secondary survey, it is important follow the systematic head-to-toe evaluation as advocated by the Advance Trauma Life Support program.[7] It is important for burn providers to appreciate that burns themselves are not immediately life-threatening while a missed traumatic injury can be. Necessary operations (i.e., thoracotomy, laparotomy, bone fixation) and other lifesaving procedures (i.e., chest tubes, ventriculostomy) should not be delayed by the presence of burn. Intensivists must also appreciate the complexity that trauma will add in the acute care of these patients. Care must be individualized and the various principles of critical care applied accordingly. Optimal care of the patient with combined burn and trauma is delivered by a multidisciplinary team with close coordination between the burn and trauma services.

Fluid Resuscitation: The First 48 Hours (Phase II)

Care of a severely burned patient during the first 48 hours can only be described as an extreme and sustained presentation of distributive shock encountered in only a few critically ill populations. Extensive capillary leak, which can last up to 72 hours after the burn, results in systemic extravasation of proteins, electrolytes, and plasma into the interstitial tissue, depleting the intravascular plasma volume substantially. This often feeds into a near-perpetual spiral of decreased end-organ perfusion, cell death, and shock typical of distributive shock-like states. The magnitude of the host immune-inflammatory response is directly proportional to both the extent (TBSA) and depth (partial vs. full thickness) of tissue damage that has occurred as a result of the burns themselves. Other concomitant insults such as smoke inhalation injury and trauma add to the magnitude of the response. Additional variables that complicate the presentation include overall premorbid physical condition, age, preexisting chronic medical conditions, drug or alcohol intoxication, and timing of presentation to receive medical aid. Finally, other presentations unique to burns include exposure to electricity or an endless variety of chemical compounds. The numerous premorbid conditions, mixed and matched with various types of burn injuries (flame, scald, chemical, electrical) and other burn-related insults (inhalation, trauma from blast), create a vast variety of presentations that make each patient presentation very unique and challenging. Thus an individualized approach is necessary to optimally care for these patients against the backdrop of applying key fundamental critical care principles.

• BOX 64.2 Traditional Resuscitation Formulas

Evan Formula (1952)

First 24 h: NS at 1 ml/kg per % TBSA burn + colloids at 1 mL/kg per % burn + plus 2000 mL glucose in water

Second 24 h: One-half the first 24 h of crystalloid and colloid requirement + the same amount of glucose in water as in the first 24 h

Brooke Formula (1953)

First 24 hours: LR at 1.5 mL/kg per % TBSA burn + colloid at 0.5 mL/kg per % TBSA burn

Second 24 h: Switch to D5W 2000 mL

Parkland Formula (1974)

First 24 h: LR at 4 mL/kg per % TBSA; give half in first 8 hours and the remaining over next 16 hours

Second 24 h: Colloid at 20%–60% of calculated plasma volume to maintain adequate urinary output

Modified Brooke formula (1979)

First 24 h: LR at 2 mL/kg per % TBSA burn, one-half in the first 8 h and half in the remaining 16 h

Second 24 h: Colloid at 0.3–0.5 mL/kg per % TBSA burn + D5W to maintain urine output

D5W, *5% Dextrose in normal saline solution;* LR, *lactated Ringer solution;* NS, *normal saline solution;* TBSA, *total body surface area.*

Adapted from Bacomo FK, Chung KK. A primer on burn resuscitation. J Emerg Trauma Shock. *2011;4:109–113.*

Over the past half century, various fluid resuscitation formulas have been proposed and used to guide burn providers. These formulas each estimate the amount each patient may require during the course of a 24- to 48-hour resuscitation postburn period (Box 64.2).[16] The goal is to maintain optimal end-organ perfusion during this time with volume replacement at the lowest physiologic cost. Underresuscitation results in decreased end-organ perfusion, resulting in cell apoptosis, organ failure, and death. On the other hand, overresuscitation is just as morbid, leading to compartment syndromes (extremities, abdomen, and orbits) as well as pulmonary and brain edema. This constellation of complications can be labeled as "resuscitation morbidity" and has been associated with death.[17]

The ABA practice guidelines suggest that the most common resuscitation formulas used to derive the initial fluid rate estimate a crystalloid requirement of 2 to 4 mL/kg per % TBSA in the first 24 hours.[18] A recent international survey study of burn shock resuscitation practices revealed a large variation in practice among 101 respondents from all over the world.[19] Still the Parkland formula was preferred in nearly 70%. However, in a study comparing those patients whose care was initiated with a standardized resuscitation

strategy with the initial rate derived using the modified Brooke formula compared with those who had the initial rate derived using the Parkland formula, the modified Brooke formula resulted in significantly less fluid without any difference in outcome.[20] The formulas also estimate that 50% of the total 24-hour volume is to be infused over the first 8 hours while it is expected that the remaining 50% will be infused over the remaining 16 hours. These are mere estimates and predict how an ideal resuscitation should be delivered over the first 24 hours. Patients are far from ideal and uniform. Thus the fluid rate is not arbitrarily decreased by half at the 8-hour mark. Clinicians should titrate IV fluid rates based on how the patient responds. Ultimately, these formulas are used to derive a starting point (i.e., initial fluid rate). This starting point matters very little, provided it is within the boundaries of an initial rate that would have been derived by formulas that estimate 24-hour estimated volumes between 2 and 4 mL/kg per % TBSA. The traditional formulas require a minimum of four computations to derive the fluid rate. This was identified as a potential reason that prehospital providers were not using a formula to initiate burn resuscitation in the field.[21] The most recent version of the Advanced Burn Life Support course recommends a flat initial rate of 500 mL/h for all adults in the prehospital setting.[8] This may be more than what is needed for a relatively small burn and not high enough for large burns. A better method for this setting is desired.

The Rule of 10

The (USAISR) Rule of 10 consists of three steps and only one simple computation in most cases (Box 64.3). The first step is to estimate the burn size (% TBSA) to the nearest 10. Second, that number is multiplied by 10 to derive the initial fluid rate in milliliters per hour. For every 10 kg above 80 kg, add 100 mL/h to this rate.[22] This quick calculation enables providers to rapidly derive the initial fluid rate in adults (>40 kg) and allows the emphasis to be placed, appropriately, on the resuscitation itself. The rule of 10 was recently validated in an in silico analysis of 100,000 simulated "patients" as it calculated a reasonable starting point for a wide range of burn sizes and weights in adults.

Once fluid resuscitation is initiated, the crystalloid rate should be titrated up or down on a regular basis (e.g., hourly) while targeting a compilation of endpoints centered on maintaining a urine output around 0.5 to 1.0 mL/kg per hour in adults. Various algorithms and clinical protocols have been proposed.[17,23,24] One such algorithm is depicted in Fig. 64.5. The goal of burn resuscitation is to provide adequate fluid necessary to avoid end-organ failure while avoiding "fluid creep."[25] Again, we must emphasize the importance of applying an individualized approach while adhering to basic critical care principles as the response to fluid therapy varies based on a number of variables. One fundamental critical care principle to keep in mind is the importance of optimizing perfusion and oxygen delivery to the end-organs until cellular dysoxia has been reversed and the underlying pathologic state is controlled. The compilation of endpoints to assess the adequacy of end-organ perfusion and oxygen delivery is no different than the various endpoints used while resuscitating patients with conditions such as sepsis and hemorrhage. The only difference in patients with burns is the expectation that the pathologic state driving the circulatory and distributive shock will persist up to 48 to 72 hours in most cases.

• BOX 64.3 The Rule of 10

1. Estimate burn size to the nearest 10
2. % TBSA × 10 = Initial fluid rate in milliliters per hour (for adult patients weighing 40–80 kg)
3. For every 10 kg above 80 kg, increase the rate by 100 mL/h

TBSA, *Total body surface area.*

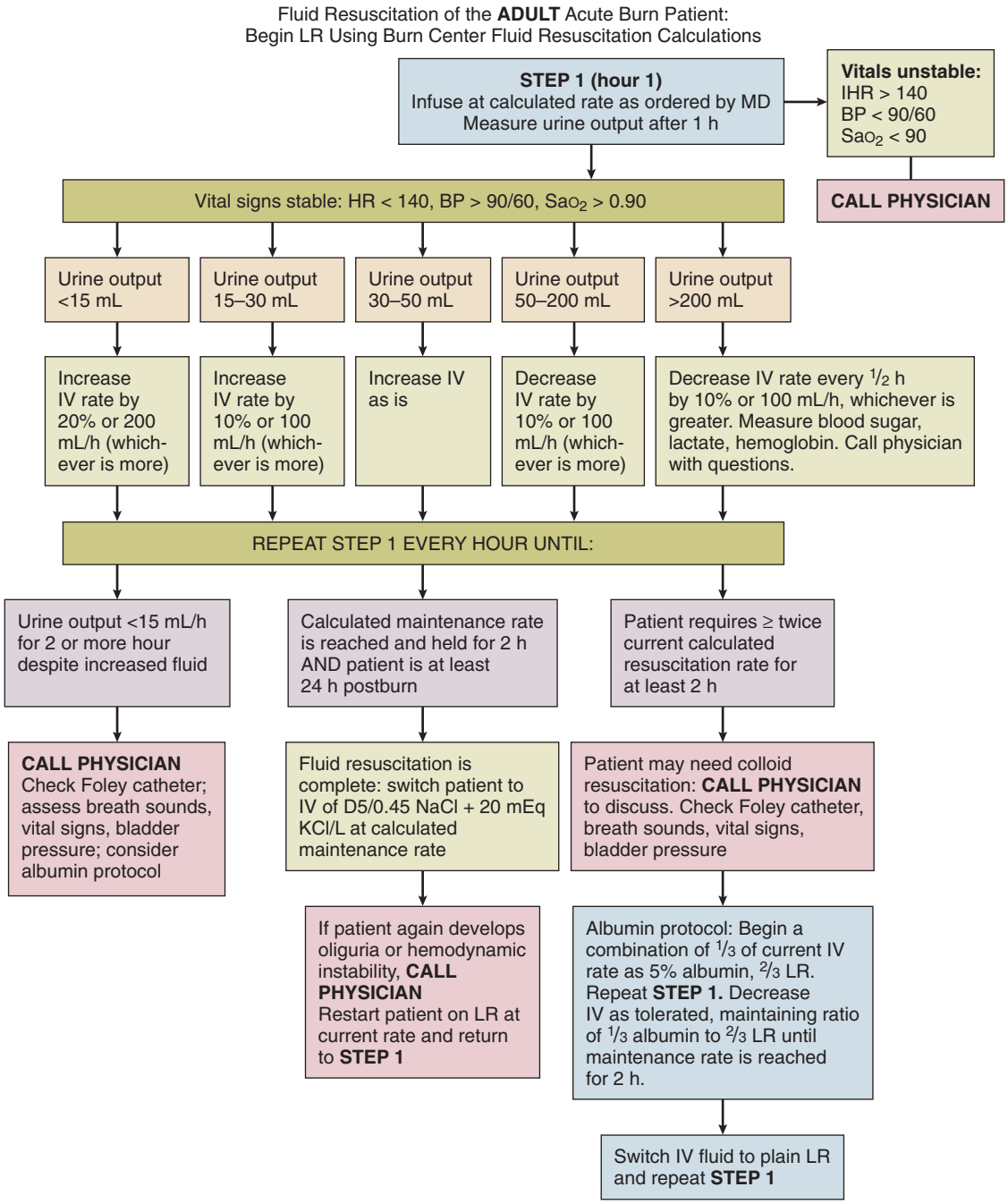
Runaway Resuscitation

During the course of resuscitating a patient with severe burns, it is important for providers recognize the point at which resuscitative adjuncts may be necessary to prevent resuscitation-related morbidity. Box 64.4 lists the different types of complications that can occur as a result of overresuscitation. A resuscitation volume greater than 250 mL/kg in a 24-hour period is often used as a benchmark and is otherwise known as the Ivy index.[26] In this study, exceeding this volume was associated with the development of abdominal compartment syndrome. Thus at any point during the first 24 hours of burn resuscitation, if the projected 24-hour volume exceeds the Ivy index, we recommend the addition of adjuncts listed in Box 64.5. This 24-hour projection is typically done at 8 to 12 hours after the burn injury to determine the need for adjuncts. Albumin is the first adjunct we recommend.

Colloids: Albumin or Plasma

Rescue therapy in the form of colloid infusion with albumin has been described a "colloid rescue."[24] A recent meta-analysis concluded that existing evidence, although somewhat limited, demonstrates improvement of burn shock resuscitation outcomes with albumin.[27] The military's Joint Trauma System Clinical Practice Guidelines recommend that 5% albumin should be initiated as early as 8 hours after a burn if certain conditions are met. These conditions include the hourly IV fluid rate exceeds 1500 mL/h or the projected 24-hr total fluid volume approaches 250 mL/kg. A 5% albumin infusion is recommended using the weight and % TBSA titration depicted on Table 64.1. Typically, this can be added to the crystalloid rate with the goal of decreasing it over the next few hours or adjustments to the crystalloid rate can be made as the albumin infusion is initiated as suggested by the algorithm in Fig. 64.5. Typically, the 5% albumin infusion rate is continued until the 48-hour mark or until the shock state has clinically resolved.

In some centers, plasma is used as the colloid of choice. O'Mara et al. conducted a randomized evaluation of colloid resuscitation with plasma versus crystalloid only and demonstrated a decrease in 24-hour fluid volumes and significantly less intraabdominal hypertension.[28] An alternative approach is to add plasma to 5% albumin infusions in those who are at high risk for resuscitation morbidity. The rate of the combined infusion should be individualized and be geared toward optimizing a compilation of endpoints centered on maintaining urine output. As always, the potential benefit of plasma should be balanced against the known risks of pooled blood product transfusions, which include transfusion-associated lung injury and a variety of infectious complications. Semisynthetic colloids such as hydroxyethyl starch (HES) solutions, succinylated gelatins, urea-linked gelatin-polygeline preparations, and dextrans can also be used.[29] However, use of HES is associated with coagulopathy in high doses, thereby limiting its use. Additionally, HES has been associated with increased prevalence of acute kidney injury (AKI) and death in RCTs, which has affected its wide adoption.[29] Whether these issues apply to all semisynthetic colloids is not well known.



• **Fig. 64.5** Burn fluid resuscitation protocol used at the University of Utah. Physicians order an initial infusion rate of lactated Ringer solution based on Parkland formula calculations and indicate the target maintenance rate. The nursing staff measures hourly urine output and increases or decreases fluids based on this response. If patients develop unexpected changes in vital signs or do not respond appropriately, physicians are contacted. An option for the use of colloid-containing resuscitation is included for patients whose requirements fail to decline. This regimen permits close titration of fluids without requiring hourly physician input. *BP,* Blood pressure; *D5/0.45,* glucose 5.0% and sodium chloride 0.45%; *HR,* heart rate; *KCl,* potassium chloride; *LR,* lactated Ringer solution; *MD,* physician; *NaCl,* sodium chloride.

Vitamin C

Ascorbic acid, or vitamin C, is an inexpensive, readily available essential nutrient that acts as an antioxidant and reactive oxygen species scavenger.[30] Animal studies have demonstrated decreased fluid requirement, edema, and reduction in capillary leak.[30] In one study of sheep, high-dose vitamin C infusion decreased net fluid balance and reduced indices of plasma lipid peroxidation when compared with crystalloids, which suggests an overall decrease of cell damage.[31] Tanaka et al. reported the results of a randomized clinical trial (RCT) demonstrating a decrease in crystalloid fluid volume when high-dose vitamin C at 66 mg/kg per hour was

• BOX 64.4 Resuscitation Morbidity

- Airway edema/facial swelling
- Eschar syndrome (extremities, thorax, abdomen)
- Extremity compartment syndrome
- Abdominal compartment syndrome
- Pulmonary edema
- Orbital compartment syndrome
- Cerebral edema

• BOX 64.5 Resuscitative Adjuncts

- Colloids
  - Albumin
  - Plasma
- High-dose vitamin C
- Hypertonic lactated saline solution
- Therapeutic plasma exchange

TABLE 64.1 5% Albumin Infusion Table

Weight/% TBSA	30–49 %TBSA	50–69 %TBSA	>70 %TBSA
<70 kg	30	70	110
70–90 kg	40	80	140
>90 kg	50	90	160

TBSA, Total body surface area.
Adapted from the U.S. Army Institute of Surgical Research Joint Trauma System Burn Care Clinical Practice Guidelines.[23]

added to the resuscitation.[32] This study also demonstrated improved oxygenation and a decrease in mechanical ventilation duration. Mortality was no different between the groups. A subsequent 3-year retrospective study demonstrated decreased overall resuscitation volumes with high-dose vitamin C without an increased risk of AKI among 17 patients who received the intervention compared with 16 who did not.[33] There is some concern for an osmotic diuresis with this approach with a potential risk of worsening hypovolemia and increasing AKI. Hence, urine output becomes unreliable in the setting of high-dose vitamin C. Additionally, vitamin C has been linked with oxalate nephropathy in nonburn populations and has recently been reported in postmortem examinations of burn patients treated with this adjunct.[34] One other concern is the presence of pseudohyperglycemia seen in these patients as a result of vitamin C interfering with the point of care glucose measurements.[35] Clearly, robust clinical trials are needed to fully characterize its benefits and potential side effects.

Hypertonic Saline Solution

Hypertonic saline solution preparations have been advocated as an adjunct to avoid volume overload since the 1970s. The most widely reported preparation of hypertonic saline solution is hypertonic lactated saline solution. This preparation has 300 mEq/L of sodium, 88 mEq/L of chloride, and 212 mEq/L of lactate. Oda et al. reported a significant decrease in 24-hour fluid volume which correlated with less intraabdominal hypertension in patients resuscitated with hypertonic lactated saline solution compared to lactated Ringer solution.[36] Another hypertonic sodium preparation, lactated Ringer solution plus 160 mEq/L sodium acetate (sodium [Na] = 290 mEq/L), used in burn resuscitation was reported to be associated with increased AKI and death.[37] Regardless, neither of these hypertonic preparations is widely available. On the other hand, hypertonic saline solution in the form of 3% normal saline solution can be used on a limited, intermittent basis. However, it is not recommended at high volumes (>1 L) because of its significant chloride load, which has also been associated with metabolic acidosis, AKI, and death.[38,39] The authors do not recommend the routine use of hypertonic preparations for burn resuscitation.

Therapeutic Plasma Exchange and Other Blood Purification Strategies

Plasma exchange or plasmapheresis has been described as a therapy initiated in anticipation of difficult burn resuscitations or as a rescue therapy during burn shock. Retrospective studies in this population have demonstrated a decrease in the resuscitative fluid requirement, an increase in mean arterial blood pressure, an increase in urine output, and a decrease in lactate levels.[40,41] Except in a few centers, wide adoption of this technique has been limited. During therapy plasma exchange necessitates replacement of the removed plasma volume with either albumin or plasma. One exchange treatment involves at least 5 L of either type of colloid. Repeat treatments, which are often needed, place a significant strain on hospital resources over time. The main therapeutic target for such a therapy involves the indiscriminant removal of proinflammatory and antiinflammatory mediators, which are presumed to be profoundly dysregulated.[42] Hemofiltration is an alternate blood purification approach that could be used in this setting. Evidence suggests a potential clinical benefit of high-volume hemofiltration (doses >70 mL/kg per hour) in the treatment of circulatory shock in other clinical conditions.[43,44] In burns, hemofiltration at a relatively high dose appeared to have a therapeutic effect among those with circulatory shock, mostly from sepsis.[45] A recent RCT failed to detect a significant difference between two doses of hemofiltration (70 mL/kg per hour vs. 35 mL/kg per hour) in the treatment of non-burn ICU patients with septic shock.[46] The Randomized Controlled Evaluation of Hemofiltration in Adult Burn Patients with Septic Shock and Acute Renal Failure (RESCUE) trial (NCT01213914), which recently closed to enrollment, should provide some additional insight with regard to the efficacy of this therapy in burns for the purposes of blood purification. Regardless, it should be noted that this therapy is very difficult to carry out early in burn shock owing to the relative hemoconcentration (i.e., hematocrit >50%) that exists in the immediate postburn period, resulting in clogged filters. Hence, we recommend waiting until sufficient normalization of the hematocrit has occurred in the course of a burn resuscitation (hematocrit 35% to 40%).

Resuscitation Morbidity

As already discussed, a runaway resuscitation is associated with extreme edema in both burned and unburned tissue. Intensivists must understand the clinical implications and the interplay between this degree of edema against burned tissue and relatively nonexpandable regions of the body. In some areas, the clinical consequence may be catastrophic. The various types of resuscitation morbidity

typically occur during the first 48 hours after the burn but can be delayed in presentation in some cases. Hence, intensivists must constantly be on guard and look for evidence of these complications, especially if patients are not following the typical trajectory of hemodynamic and end-organ recovery as burn shock is resolving.

Airway Edema/Facial Swelling

Endotracheal intubation is essential in those with evidence of thermal injury to the oropharynx primarily for airway protection. Edema of the glottis is often maximal at 24 to 48 hours and can persist for a few days. Thus it is very important during this period to assess the need for airway protection separate from the need for the ventilator. This is particularly important in those with isolated facial burns with upper airway injury. A patient may not need ventilator support for gas exchange, but he or she may need airway protection because of the risk of airway obstruction without the endotracheal tube. The decision to extubate must incorporate an assessment of airway edema and patency. This is often done by assessing for the presence of a cuff leak. In general, a review of the literature supports the use of a cuff leak volume of 110 mL as a standard cutoff to determine adequacy of the cuff leak below which postextubation stridor and reintubation rates are likely to be high.[47] Absence of a cuff leak or a cuff leak volume below 100 mL is considered a positive test result. A cuff leak greater than 110 mL is associated with a very low likelihood of extubation failure with a specificity of 99% and negative predictive value of 98%.[47] Serial direct fiberoptic laryngoscopy can be performed to track the resolution of edema in some cases, although measurement of cuff leak is much more objective. Treatment with a short course of steroids may be of benefit but has not been well studied in burns. If the decision is made for a trial of steroids (10 mg of IV dexamethasone), it appears maximal benefit is achieved by giving a dose at least 8 to 12 hours beforehand. For those in whom total body fluid overload is suspected, a trial of diuresis may be helpful. For those at great risk, extubation over an airway exchange catheter has been advocated, although this is technically challenging. Those with postextubation stridor may be managed with an additional dose of steroids (4–6 mg dexamethasone), racemic epinephrine nebulization, and heliox (mixture of helium and oxygen).[47] This should be considered an emergency. Thus providers should not delay the reestablishment of a definitive airway and be ready for an emergent surgical airway if necessary. This is not the time for a trial of noninvasive ventilation, for example. In general, the authors suggest waiting until a sufficient cuff leak (>110 mL) is present before a trial of extubation. If the cuff leak is absent or low, then adjuncts described (steroids and/or diuresis) can be attempted until cuff leak improves.

Facial edema can also be severe enough to make reestablishing an airway extremely challenging. In addition to the presence of a cuff leak, intensivists should incorporate the perceived ease of reintubation into their decision-making process for extubation. Until the patient has a cuff leak and facial edema has decreased to the point where successful reintubation could be achieved, the patient should remain intubated for airway protection. Other maneuvers to expedite resolution of airway and facial edema in burns include head of bed elevation and early mobilization. Early ambulation of intubated patients has been widely advocated in critical care for patients who meet certain criteria.[48] Patients who are awake, spontaneously breathing, and intubated primarily for airway protection often meet these criteria and can be ambulated safely.

• **Fig. 64.6** Example of thoracic, abdominal, and lower extremity escharotomies.

Eschar Syndrome (Extremities, Thorax, Abdomen)

Eschar is the leathery noncompliant skin that results from deep burns to the epidermis and dermis.[23] Circumferential eschar creates unique problems in different areas of the body. For example, eschar surrounding the thorax will decrease overall pulmonary compliance, making adequate ventilation of patients challenging. Abdominal eschar can also restrict lung compliance, particularly when abdominal wall and bowel edema has reached a critical threshold. Circumferential eschar to the extremities will eventually lead to compromise of arterial blood flow during the course of burn resuscitation as tissue edema ensues underneath. In all of these scenarios, empiric surgical release of regions of eschar is indicated in the form of escharotomies (Fig. 64.6). It is important to note that the need for escharotomies is seldom a true "emergency." Rather, the procedure is urgent and often done empirically or even prophylactically. There is time to optimize conditions to perform the procedure in the ICU or operating room setting. Thus these procedures should not be done in the emergency department unless a prolonged transport time (>6 hours) is anticipated. Surgical incisions should only be necessary through true eschar. Ideally, electrocautery should be used to minimize bleeding. The depth of the incision should be to the level of the subcutaneous fat, whereas the length should extend through the entire extent of the circumferential portion of the eschar. Although full-thickness burns are insensate, patients often require IV analgesics. For thoracic and abdominal escharotomies, lung compliance should be assessed before and after the procedures. Extremity escharotomies require the assessment of perfusion by detection of distal arterial pulses, usually by palpation or via Doppler signal. Upon completion of escharotomies, wounds should be covered with nonrestrictive dressings. Extremities should then be elevated as much as possible to minimize swelling.

Extremity Compartment Syndrome

Severe burn injury can also result in compartment syndrome of any muscle compartment in the body and is not always adjacent to burned tissue. Those with electrical injury are particularly at risk for compartment syndromes and should be closely monitored. Intensivists should always look for the classic findings of pain, pallor, paralysis, paresthesia, and pulselessness, although these are often obscured when patients are heavily sedated and intubated.[49] Intractable pain can be among the first clues of the possibility of compartment syndrome. Additionally, it is important to serially

monitor pulses throughout burn resuscitation. Also, serial assessment for laboratory evidence of myonecrosis, such as elevation of serum myoglobin, creatine phosphokinase, and aspartate aminotransferase, is clinically helpful in detecting occult compartment syndromes. Finally, intensivists should not underestimate the value of a serial manual palpation of major compartments. Those compartments thought to be at risk should be investigated by measuring compartment pressures. This can be performed at the bedside using an 18-gauge needle attached to a transducer. If available, compartment pressure measuring device such as an intracompartmental pressure monitor (Stryker, Kalamazoo, MI) can be used. An absolute pressure that exceeds 30 cm of H_2O generally indicates a compartment at risk and is an indication for decompression. Others have advocated the use of "ΔP" (diastolic blood pressure-intramuscular pressure), with a value less than 30 being the cutoff for compartmental ischemia.[49] As in escharotomies, perfusion should be serially assessed even after fasciotomies are performed owing to the potential need for extension as fluid resuscitation continues. Generally, prophylactic fasciotomies are discouraged because of the increased risk of infection.[23]

Abdominal Compartment Syndrome

Abdominal compartment syndrome resulting in a decompressive laparotomy is a significant resuscitation-related morbidity associated with a mortality near 90% in those with large burns.[50,51] Hence, measures should be taken to prevent abdominal compartment syndrome with resuscitation adjuncts as previously described, while optimizing nonsurgical management when it is encountered. For those at risk, measurement of bladder pressures is recommended to estimate intraabdominal pressure (IAP). There is no consensus regarding the appropriate volume used to measure IAP. We recommend a volume of between 25 and 50 mL, maintaining consistency in whatever volume is used, for serial measurements using a transducer located at the level of the symphysis pubis.[23] Diagnosis of abdominal compartment syndrome should be suspected in patients with abdominal distention, decreased lung compliance with a progressive drop in minute ventilation, hypotension, acidosis, and oliguria. A persistent IAP of 20 mm Hg or higher with organ failure is indicative of abdominal compartment syndrome and should be managed urgently.[52] Various medical treatment options include improving abdominal wall compliance by optimally relaxing the patient, optimally evacuating the gastrointestinal (GI) tract, drainage of any peritoneal fluid, and minimizing volume. Box 64.6 lists the various medical treatment options.

Of the various medical therapies, early albumin and improved burn resuscitation documentation decreases abdominal compartment syndrome–associated outcome.[53] Other resuscitative adjuncts such as vitamin C can be used as a rescue maneuver in this situation.[30] Latenser et al. demonstrated that percutaneous decompression of peritoneal fluid was effective at decreasing intraabdominal hypertension and preventing abdominal compartment syndrome.[54] We recommend temporary placement of a pigtail drainage catheter through an incision similar to that required for a diagnostic peritoneal lavage. Aside from a full decompressive laparotomy, other less invasive surgical approaches include escharotomy (if not already done) and component separation. Oda and colleagues demonstrated that escharotomy improved cardiopulmonary function and gut perfusion in patients with ACS.[55] O'Mara et al. described a modified separation of parts technique that effectively released intraabdominal hypertension with a reversal of physiologic derangements associated with abdominal compartment syndrome in a swine model.[56] This involves sequentially releasing the muscular fascia to allow the abdominal wall to relax; this technique is often used as a method of releasing tension to allow closure of an abdominal wall defect. Based on the recent experience of the burn community, decompressive laparotomy, the only definitive acute therapy, should be performed as a last resort.

• BOX 64.6 Medical Treatment Options to Reduce Intraabdominal Pressure in Burns

1. Improve abdominal wall compliance
   a. Sedation/analgesia
   b. Neuromuscular blockade
   c. Body positioning (laying patient flat in a reverse Trendelenburg position)
2. Evacuate intraluminal contents
   a. Gastric decompression via orogastric or nasogastric tube.
   b. Rectal decompression or enema
3. Evacuate abdominal fluid collections
   a. Percutaneous drainage of fluid[54]
4. Minimize positive fluid balance
   a. Colloid rescue (albumin/plasma)
   b. Renal replacement therapy/ultrafiltration

Adapted from Cheatham ML, Malbrain MLNG, A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. Intensive Care Med. *2007;33:951–962.*

Orbital Compartment Syndrome

High resuscitation volumes in burns are associated with elevated intraocular pressures (IOPs).[57,58] Increased IOP can result in optic nerve ischemia and result permanent vision loss. Hence, an ophthalmology consultation should be obtained for all patients with large burns for whom a large resuscitation is anticipated to assist with serial IOP measurements. An IOP above 30 mm Hg is indicative of orbital compartment syndrome and is a surgical emergency.[59] Rapid decompression with lateral canthotomy and inferior cantholysis remain the mainstays of management. In some cases, where facial burns are present along with a large burn, this procedure can be done empirically.

Cerebral Edema

Cerebral edema is among the most underrecognized and underreported resuscitation-related morbidities. In one pediatric burn autopsy study, cerebral edema leading to brain herniation was seen in more than half of their brain-related deaths.[60] It is unclear if these episodes were correlated to fluid volume. Clearly, those who have anoxic injury or traumatic brain injury are at high risk for developing brain edema during resuscitation. However, the association between crystalloid volume and brain edema is well described in the literature in both injured and uninjured brain.[61,62] In the experience of the authors, cerebral edema resulting in ischemia and herniation can occur with massive resuscitation in burns. However, there are no studies in the literature that have characterized the prevalence and impact of this problem in the burn population. Thus this represents a tremendous gap in knowledge in the burn literature.

Optimizing Burn Wound Coverage (Phase III)

Surgical Management

This phase of care likely has the most impact on burn survival. Early surgical excision of the burn wounds and definitive coverage with autograft has been the standard of care since the early 1970s

and has been widely recognized as among the greatest advancements in burn care.[63–65] Before wide adoption of this technique, burn eschar would often be left in place and allowed to separate over time as large quantities of fibroproteolytic proteins were released by neutrophils and bacteria present at the wound bed. This resulted in the separation of leathery eschar from granulation tissue below that eventually healed into a mass scar. Most patients died of overwhelming sepsis while waiting for this to happen. The advent and wide adoption of topical antimicrobials significantly improved outcomes.[66] However, it was not until widespread adoption of early surgical excision that significant gains could be made in terms of length of stay and survival. This technique dramatically shortened the severe hypermetabolic state and period of infectious risk while decreasing pain, allowing for earlier mobilization, relatively preserving muscle mass, and ultimately improving functional recovery among survivors.

Intensivists should be aware that the most expert critical care will have little impact on ultimate outcome if definitive coverage of the burn wound does not occur. Definitive coverage can be defined as the replacement of devitalized skin with autologous skin and should be viewed in the same light as achieving source control in sepsis. Autologous split-thickness skin is harvested from all available areas of nonburned skin and managed as a superficial partial-thickness wound. Definitive coverage can be achieved in one operation for burns less than 30% to 40% TBSA, as enough areas of normal skin exist available for harvest. Autograft is often meshed to expand the area of coverage. The goal after surgery is to maintain optimal wound healing conditions to achieve 100% engraftment with minimal graft loss. Graft loss can occur if wound excision has been inadequate or if wound infection sets in. In patients with larger burns, definitive coverage must occur in stages as autologous skin is not sufficiently available. Hence, excised burn wound must be covered temporarily with skin substitutes (i.e., cadaver skin [allograft] or pig skin [homograft]), providing temporary coverage for up to 14 days. This allows previous donor sites to heal sufficiently to allow for a reharvest of autograft. Depending on the relative skin thickness, donor sites may be harvested multiple times.

In addition to allograft and homograft, artificial skin substitutes that can be used to provide temporary coverage are listed on Table 64.2.[67] These artificial skin substitutes have characteristics and indications for use that are specific to each product with local expertise based on experience with the product. For superficial partial-thickness burns, some of these temporary products can be used while the skin heals underneath and hence they act as definitive coverage. For those with larger percent TBSA burns, cultured epithelial autograft (CEA) can be used. Epicel (Genzyme, Cambridge, MA) is cultured skin that is derived by an autologous skin biopsy that is harvested to provide keratinocytes. This is then expanded over 2 to 3 weeks into sheets of epidermal autograft. CEA can be used to cover large areas but it is very fragile owing to its monolayer characteristic. Hence, significant expertise is required for optimal graft take. A recent review suggests CEA should be used in conjunction with acellular dermal matrices for optimal outcomes.[68]

Critical Care (Phase III Continued)

Regardless of the surgical strategy used for timely definitive coverage, intensivists should keep in mind that every aspect of critical care should be geared toward optimizing conditions for wound healing. Optimizing critical care management complements surgical intervention of burn wounds to optimize overall outcomes. A comprehensive organ system approach is most practical when managing critically ill burn patients.

Neurologic

During the course of acute burn care, intensivists can anticipate a variety of neurologic issues that can affect outcome and alter long-term function. The most common manifestation of neurologic dysfunction in the ICU is delirium. The etiology is often multifactorial and is typically associated with an underlying organic problem such as sepsis or shock. It is important to use an assessment tool such as the Confusion Assessment Method for the ICU (CAM-ICU) score to screen for this on a regular basis as prevalence can be as high as 80% among mechanically ventilated burn patients.[69] Mainstays of therapy include minimizing polypharmacy, frequent reorientation, management of the sleep-wake cycle, sleep hygiene, minimization of benzodiazepine use, and judicial use of atypical antipsychotics. Evidence guiding the management of established delirium in burns is scant. In general, atypical antipsychotics, such

TABLE 64.2 Commercially Available Artificial Skin Substitutes

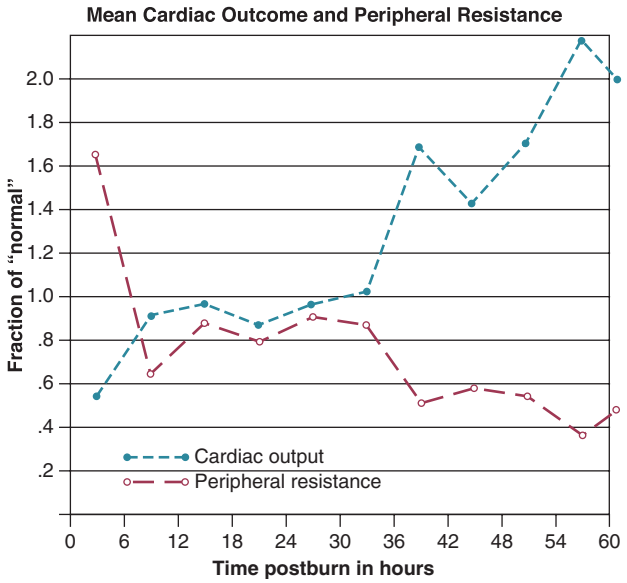
Product Name	Classification	Characteristics	Manufacturer
Alloderm	Acellular	Dermal matrix	LifeCell/Allergan Bridgewater, NJ
Graftjacket	Acellular	Tissue scaffold	KCI San Antonio, TX
Integra	Acellular	Bovine/shark origin bilayer matrix	Integra Plainsboro, NJ
Biobrane	Acellular	Biocomposite dressing, nylon fibers in silicone with collagen	Smith & Nephew London, UK
Dermagraft	Cellular	Bioabsorbable polyglactin mesh scaffold with human fibroblasts (neonatal origin)	Organogenesis Canton, MA

Adapted from Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. *Crit Care.* 2015;19:243.

as risperidone, olanzapine, or quetiapine, are preferred over haloperidol because of the potential for extrapyramidal side effects. Use of dexmedetomidine appears to have some promise in delirium management.[70] Finally, melatonin may have a role in restoring sleep regulation and decreasing delirium.[71]

Sedation and Analgesia

Perhaps the most challenging aspect of burn care may be the day-to-day management of sedation and analgesia. Patients with severe burn experience tremendous discomfort. Although areas of full-thickness burns with complete damage to nerve ending are considered to be insensate, many areas have incomplete damage that readily trigger pain. The added inflammatory host response augments pain sensitivity at the site of the nerve endings and induces hyperalgesia. Thus any mechanical manipulation, such as wound care, showers, and rehabilitation, typically amplifies pain and anxiety. Patients experience background pain, breakthrough pain, and procedural pain that may require different approaches to therapy. Additionally, the approach may differ based on whether the patient is supported by a ventilator or not. Pain control with adequate doses of opioids without causing respiratory depression is the mainstay of therapy. Acutely, IV fentanyl or morphine infusions can be used for background pain. All opioids, with the exception of methadone, downregulate the mu receptor and have potential downstream consequences, such as tolerance, hyperalgesia, and a high propensity for chronic pain syndromes. Hence, patients should be transitioned to methadone as the preferred opioid for background pain once they are able to tolerate oral medications. Often a well-coordinated sedation strategy can augment effective analgesia, making the patient's pain more bearable. Negative consequences of deep sedation include hemodynamic instability and inability to participate in rehabilitative activity. Guidelines for sedation and analgesia published by Society of Critical Care Medicine can be applied in burns effectively.[72] An assessment tool such as the Richmond Agitation-Sedation Scale score should be applied to avoid oversedation.[72] Also, avoidance of benzodiazepines and leading with dexmedetomidine or propofol as primary agents is reasonable in patients with burns. Often ketamine may be needed because of its favorable hemodynamic profile, its opioid-sparing effects, and its potential to decrease long-term neurocognitive dysfunction.[73] In nonintubated patients, dexmedetomidine is often used as an adjunct to opioids to relieve anxiety with minimal impact on respiratory drive. The addition of ketamine to dexmedetomidine has been advocated in this setting as well.[74,75] Combining ketamine and dexmedetomidine was associated with less respiratory depression when compared to ketamine and propofol while providing the same level of sedation and analgesia in burned children.[76] The principles of multimodal therapy for the treatment of pain may be applied in burns while avoiding the pitfalls of polypharmacy. Acetaminophen can be used as an adjunct but should be limited when liver dysfunction is present. IV acetaminophen has been particularly helpful in those with gut motility issues. Nonsteroidal antiinflammatory drugs should be avoided acutely in critically ill burn patients owing to the likelihood of frequent volume shifts. They may be considered in those who are in stable condition to transfer out of the ICU. Studies to address neuropathic pain, particularly after electrical injury, phantom limb pain after amputation, or long-term management of postburn allodynia, have been mixed. Although gabapentin has been shown to be ineffective,[77] pregabalin appears helpful in burns as demonstrated in a RCT.[78] Finally, regional anesthesia may be considered in select patients with regional procedural or postprocedural pain.[72]



• **Fig. 64.7** This classic graph shows characteristic postburn changes in cardiac output and peripheral vascular resistance in a group of seven patients (mean burn size 64.5% total body surface area [TBSA]) resuscitated with the Brooke formula (lactated Ringer solution 1.5 mL/kg per % TBSA; albumin 0.5 mL/kg per % TBSA; plus 2000 mL dextrose/water in the first 24 hours). Cardiac output falls acutely before blood volume has changed appreciably and then rebounds gradually, with return to normal by 24 to 36 hours and thereafter remaining above normal. Peripheral vascular resistance shows an opposite effect. (From Pruitt BA Jr, Mason AD Jr, Moncrief JA. Hemodynamic changes in the early postburn patient: the influence of fluid administration and of a vasodilator (hydralazine). *J Trauma*. 1971;11:36–46.)

Cardiovascular

Hemodynamic changes acutely after severe burn have been well characterized[79] (Fig. 64.7). An initial decrease in cardiac output and high peripheral vascular resistance is replaced by a high cardiac output and low peripheral vascular resistance state with a relative normalization at 36 hours or so. It has been demonstrated that cardiac index and heart rate remain elevated in burns, up to 160% of predicted, through discharge from the hospital.[80] This is due to a general hypercatabolism64-7 and a sustained hypercatecholamine state. Stress hormones such as serum and urine cortisol also remain elevated throughout the hospital course.[80] Intensivists need to consider these burn-specific characteristics hemodynamically managing patients through various insults that occur during the course of a typical hospitalization to include surgery and episodes of sepsis and respiratory failure. For example, when the sustained sympathetic tone is suddenly removed in the form of induction of general anesthesia or rapid sequence intubation for respiratory failure, the potential for sudden hypotension is high. This sudden drop in blood pressure was found to be related more to burn size than the agent used for induction.[81]

Hemodynamic Support

When choosing among the various strategies and vasoactive agents to treat hemodynamic instability, intensivists must keep in mind that the conditions for wound healing must simultaneously be optimized. This begins with ensuring optimization of intravascular volume and ends with ensuring adequate end-organ perfusion. Various endpoints exist to assess intravascular volume and cardiac

output, such as central venous pressure, pulmonary capillary wedge pressure, variations in pulse pressure, and variations in stroke volume.[82] It is our opinion that a compilation of endpoints should be used in conjunction with an experienced clinician applying the principles and art of the fluid challenge.[83] This age-old technique involves identifying the fluid, the rate, the critical endpoint, and safety limits to ensure the rapid correction of the hypovolemic state while minimizing risks.[83] Over the course of a burn hospitalization, the choice of fluid should be driven by the need to minimize wound edema and total volume. Hence, blood products should be used preferentially as a first-line treatment for volume expansion if the patient is anemic or coagulopathic. As a second-line treatment, colloid in the form of albumin is preferred over crystalloid as a volume expander.

Once intravascular volume is optimized, vasopressors should be added to maintain vascular tone and ensure end-organ perfusion. During this time, continuous assessment of intravascular volume should be combined with an assessment of end-organ perfusion with global (i.e., lactate, base deficit, and central/mixed venous saturation) or regional markers if available.[84] Currently, norepinephrine, vasopressin, and epinephrine are advocated as first-, second-, and third-line agents in the management of septic shock.[85] However, the choice of vasoactive medication should be individualized and driven by the need to optimize end-organ perfusion while keeping the vulnerable wound bed in mind. Burn patients have been documented as having a robust sympathetic tone with elevations in endogenous catecholamines that is sustained throughout the course of the hospitalization.[86] As such, addition of more catecholamines has potential detrimental effects to microcirculation and the wound bed.[87] On the other hand, vasopressin is known to rapidly decline to inappropriately low levels during critical illness.[88] Hence, vasopressin is ideal given this affinity as a direct vasoconstrictor and its potentiation of circulating catecholamines.[89] It can be used as a first-line agent in some cases and as a second-line agent to decrease the norepinephrine dose. In select patients who are euvolemic and without risk of myocardial ischemia, dobutamine can be added to increase stroke volume and improve forward flow without affecting microcirculation.[90] Use of dopamine should be avoided because of the increased prevalence of tachyarrythmias,[91] whereas use of phenylephrine should be minimized because of its detrimental impact on peripheral microcirculation.[92] In those with relative catecholamine resistant shock, relative adrenal insufficiency must be considered. This is especially relevant in patients who may have received etomidate for their induction for intubation.[93] Other reasons for catecholamine-resistant shock include severe acidosis, hypophosphatemia, and hypocalcemia.[94] In addition to optimizing intravascular volume and addressing any reversible causes of shock, alternative strategies to treat catecholamine-resistant shock in burns include plasmapheresis,[40] high-volume hemofiltration,[45] and methylene blue.[95,96] Angiotensin II appears to have some promise as a catecholamine-sparing agent in resistant shock but is not yet widely available.[97] Overall, optimizing the conditions for wound healing from a cardiovascular standpoint requires an aggressive approach to minimize and reverse circulatory shock when it is encountered.

Pulmonary

Intensivists encounter a variety of challenging pulmonary problems while caring for burn patients in the ICU. Dealing with the diagnosis and manifestations of smoke inhalation is perhaps the most unique to this population. The prevalence of smoke inhalation injury, generally limited to lower airway involvement, is approximately 10% to 20% among patients admitted to burn centers.[10] Proposed diagnostic criteria are limited to the severity of bronchoscopic findings only and do not take parenchymal involvement into consideration[98] (Table 64.3). Although chest radiography alone on admission was rarely helpful in determining the presence or severity of inhalation injury,[99] detecting the presence of parenchymal involvement via a chest computer tomography scan was shown to correlate with a higher likelihood of downstream pulmonary complications.[100] However, conducting a chest computed tomography scan on admission for all patients admitted with a suspicion of smoke inhalation may not be practical. Combining chest radiography findings with fiberoptic bronchoscopy may be helpful but has not been studied.

TABLE 64.3 Abbreviated Injury Score Grading Scale for Inhalation Injury on Bronchoscopy

Grade	Class	Description
0	No injury	Absence of carbonaceous deposits, erythema, edema, bronchorrhea, or obstruction
1	Mild injury	Minor or patchy areas of erythema, carbonaceous deposits, bronchorrhea, or bronchial obstruction
2	Moderate injury	Moderate degree of erythema, carbonaceous deposits, bronchorrhea, or bronchial obstruction
3	Severe injury	Severe inflammation with friability, copious carbonaceous deposits, bronchorrhea, or obstruction
4	Massive injury	Evidence of mucosal sloughing, necrosis, endoluminal obstruction

Adapted from Albright JM, Davis CS, Bird MD, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. *Crit Care Med.* 2012;40:1113–1121.

Once a diagnosis has been made, pulmonary challenges owing to lower airway injury result in a variety of anatomically clinical problems that require active management. As discussed, lower airway injury is typically a chemical injury that results in damage to the normal tracheobronchial mucosa with involvement that can extend all the way down to the level of the alveoli. The most immediate problem encountered in the intubated patient with smoke inhalation is the collection of carbonaceous debris mixed with desiccated proximal tracheobronchial mucosa and bloody thick mucus that can result in life-threatening airway obstruction. The mainstay of management is maintenance of a well-humidified circuit and frequent bronchoscopy to ensure a patent tracheobronchial tree. Nebulized heparin has been shown to be beneficial in decreasing fibrinaceous clots without increasing the risk of bleeding.[10] Adding N-acetylcysteine to heparin appears to have some additive benefit. Farther down the tracheobronchial tree, reactive airways can result in significant problems with ventilation characterized by air trapping and hypercapnia. Inhaled bronchodilators may be helpful in this case.[101] In select cases, inhaled glucocorticoids may be helpful, especially if patients have a history of underlying

• BOX 64.7 Adjunctive Therapies for the Manifestations of Smoke Inhalation Injury

- Proximal airway obstruction
  - Nebulized heparin 5000 units every 4–6 h
  - Add N-acetylcysteine to heparin nebulization
- Reactive lower airway disease
  - Bronchodilators (β_2-agonist, muscarinic receptor antagonist)
  - Inhaled corticosteroids

asthma or chronic obstructive pulmonary disease.[101] As with any treatment strategy, the regimen should be individualized as assessed by the bedside intensivist (Box 64.7)

Ventilator Management in Burns

Even in the absence of inhalation injury, burns alone introduce unique challenges owing to a variety of issues including those derived from massive fluid resuscitation combined with an often noncompliant chest wall as well as a baseline hypermetabolic state that increases minute ventilation requirements. The addition of inhalation injury adds a variety of other variables that make ventilator management far from routine. Thus it is difficult to extrapolate standard mechanical ventilator practice guidelines to this population. A recent survey of mechanical ventilator practices in North America demonstrated wide practice variation with no one predominant ventilator mode preferred.[102] A striking finding was that less than half the respondents regularly were prescribed a low–tidal volume strategy as widely advocated for the general critical care population.[102] Quite frankly, strict adherence to a low–tidal volume strategy in a patient with a high metabolic demand and pulmonary mechanics impeded by decrease chest wall compliance and intraabdominal hypertension is ineffective. This was demonstrated in a recent RCT in which one of three burn patients failed to meet oxygenation and ventilation goals when randomly assigned to a strict low–tidal volume strategy as prescribed by the ARDS Network.[103] Among those with smoke inhalation injury, two-thirds required an alternative mode because of inadequate gas exchange with low–tidal volume ventilation. Alternatively, high-frequency percussive ventilation (HFPV), a pressure-limited, time-cycled mode of ventilation that delivers high-frequency bursts of subtidal volumes, was found to be just as "lung protective" with a similar inflammatory signature and fewer ventilator-induced events.[103] Additionally, HFPV has been shown to decrease the incidence of ventilator-associated pneumonia in patients with inhalation injury while improving gas exchange at lower peak and mean airway pressures.[104,105] Thus HFPV is the preferred mode in many burn centers, particularly in the setting of smoke inhalation injury.[106] We advocate an individualized approach to ventilator management with the adherence to the basic principles of lung protection regardless of ventilator mode.[107]

Acute Respiratory Distress Syndrome in Burns

Among burn patients who require mechanical ventilation, acute respiratory distress syndrome (ARDS) has been reported to occur in 34% to 54% depending on the definition of ARDS.[108–110] It is clear that categorizing ARDS via the Berlin definition into mild, moderate, and severe disease is useful in burns.[111] There is a clear stepwise and significant increase in mortality from mild (17%), moderate (44%), and severe ARDS (60%).[110] Once ARDS is diagnosed, intensivists should adhere as much as possible to the principles of lung protection by minimizing volutrauma, barotrauma, and atelectrauma while meeting gas exchange goals. The potential value of HFPV in this population has already been discussed. Other alternative modes of ventilation such a pressure-regulated volume control, airway pressure release ventilation, and high-frequency oscillatory ventilation are regularly used by the burn community with varying success.[102] High-frequency oscillatory ventilation has been well described in the setting of severe ARDS, reducing barotrauma and facilitating early burn surgery.[112] Various nonventilator adjuncts can be leveraged on an individualized case-by-case basis. These include fluid restriction and aggressive diuresis in conjunction with albumin infusion,[113] neuromuscular blockade with cisatracurium,[114] prone ventilation,[115] and even corticosteroid infusions.[116,117] Despite concerns for graft loss, prone ventilation applied in burn patients with severe ARDS did not significantly affect wound healing while demonstrating improvement in oxygenation.[118] Many centers have recently incorporated extracorporeal membrane oxygenation for severe ARDS in patients with burns with some success.[119]

Tracheostomy in Burns

The decision to perform a tracheostomy in burn patients is multifactorial and should take into consideration clinical stability, preexisting and concurrent comorbidities, and anatomic barriers such as deep burns to the neck. However, despite the inherent challenges, the majority of burn centers agree on tracheostomies being generally indicated when the expected time of mechanical ventilation exceeds 2 weeks.[102] In one survey, the majority of burn surgeons prefer performing an open procedure in the operating room rather than a percutaneous tracheostomy at the bedside. This is likely due to the fact that percutaneous tracheostomy may be challenging owing to anatomic considerations. One study, however, demonstrated that percutaneous tracheostomy was associated with a lower complication rate and could be safely performed at the bedside in burn patients, most of whom had neck burns.[120]

Gastrointestinal

The GI tract represents a complex end-organ that is highly susceptible to decreased perfusion in early stages of shock. Intensivists must be highly attentive to the various presentations of end-organ dysfunction of the GI tract. GI dysfunction can manifest in a variety of ways. Decreased motility of the proximal gut is the most likely and clinically apparent presentation characterized by nausea, emesis, tube feeding intolerance, or small bowel ileus. The presence of gastric emptying abnormalities should be considered when deciding the appropriate route of medications. In severe cases, proximal GI dysfunction can present as gastritis or an erosive ulcer heralded by an upper GI bleed as the result of persistent mucosal hypoperfusion. The development of a gastric ulcer has been historically linked with burns and is classically known as a Curling ulcer.[121] The combination of early enteral feedings and acid suppression has resulted in the reported decrease of this complication.[122] Distal GI dysfunction can manifest as constipation, diarrhea, or colonic pseudo-obstruction.[123] Distinguishing hypoperfusion-related GI dysfunction from other metabolic (electrolytes) or iatrogenic causes (opioids) can be quite challenging. Constipation can often be treated by providing laxatives such as polyethylene glycol or lactulose on a regular basis. Methylnaltrexone 12 to 24 mg subcutaneously daily appears to be effective in antagonizing the opioid-related slowing of

the entire gut and relieves some of these symptoms.[124] In patients in whom all reversible causes of colonic pseudo-obstruction have been identified and treated, neostigmine may be useful.[125] Perhaps the most catastrophic presentation of GI dysfunction is intestinal ischemia with full-thickness necrosis presenting with or without abdominal compartment syndrome.[51] The heterogeneous nature of the GI tract makes it extremely difficult to characterize this end-organ as a single entity. A standard consolidated definition of GI dysfunction for critically ill patients with four stages of severity coined "acute gastrointestinal injury" (AGI) has been proposed.[126] This standardized definition has not yet been adopted widely in the critical care or the burn community. It does represent, however, an opportunity for further research to determine if these staging criteria can reliably characterize this end-organ dysfunction in the burn population. Biomarkers of such as citrulline may also be helpful in detecting GI dysfunction at the cellular level.[127] Currently close monitoring of upper GI symptoms, gastric residuals, stool output, and evidence of ischemia remain the mainstays of detecting GI dysfunction.

Other Abdominal Complications in Burns

Intensivists must be aware of other intraabdominal issues that may be specific to the burn population. Perhaps the most ubiquitous abnormality among patients with large burns are hepatic enzyme elevations.[128] Abnormal hepatic enzymes reflect the profound hypermetabolic and hypercatabolic stress response characterized by an accentuated cycle of glucose, lipid and protein synthesis, and degradation.[129] The liver, because of its complex metabolic, inflammatory, immune, and acute-phase functions, plays a central role in recovery from burns. Nearly all patients with large burns develop fatty infiltration (steatosis) of the liver over time. Other variables such as gasoline involvement, which occurs in up to a quarter of all burn admissions,[130] can contribute to the severity of liver injury owing to effects from hydrocarbon toxicity.[131] Thus it is not surprising that those with baseline liver dysfunction at the time of burn injury have a significantly higher mortality than those without.[132,133] Shock liver is the most severe ischemic end-organ manifestation and presents with profoundly elevated liver enzymes, hyperbilirubinemia, and coagulopathy. A relatively uncommon but clinically significant complication is acute acalculous cholecystitis. In one large series over a 21-year period, the prevalence was 0.18% (20 cases among 10,762 patients).[134] Diagnosis of cholecystitis in burn patients is extremely challenging as physical symptoms can often be obscured owing to burns (pain, fever, and so on). Thus intensivists must maintain a high index of suspicion when encountering sepsis with a source that is not readily obvious. Finally, acute pancreatitis is associated with increased mortality in burns.[135] In one series, 40% patients with large burns developed pancreatic enzyme elevations with an associated increase in risk of mortality.[136] Likely cholecystitis, symptoms of pancreatitis are often obscured by the nature of burn injury and subsequent care. Thus increased vigilance on the part of the treatment team is necessary.

Nutrition and Metabolism

The hypermetabolic and hypercatabolic state in burns is multifold greater in both magnitude and duration when compared with other critically ill populations.[137,138] Optimizing nutritional requirements during ICU care is critical in promoting wound healing while mitigating against the metabolic derangements that result in loss of lean muscle mass, increase in fat mass, and immune compromise over time.[139,140] Intensivists face a fine balance between meeting the high energy needs of the hypercatabolic burn patient while avoiding the negative consequences of nutrient overconsumption. Nutrition support after a burn injury is highly complex owing to several physiology-, injury-, and treatment-related variables that come into play in determining energy expenditure. Many of these variables, such as age, premorbid nutritional status, need for mechanical ventilation, sedation, and activity level, are no different than other ICU populations. Burn care–specific variables that intensivists must incorporate into energy expenditure estimates include initial burn size, pain control, need for frequent surgical procedures, degree of wound closure, and the impact of environmental temperature regulation. It is important to recognize that like other ICU populations, energy expenditure changes throughout the course of the hospitalization must be reassessed for burn patients on a regular individualized basis. Daily contributions of a dedicated registered dietician with burn experience integrated as part the multidisciplinary burn team are invaluable in optimizing care. Energy requirements can be estimated using a variety of predictive equations. Among all variety of predictive equations, the Carlson and Milner equations appeared to correlate best with actual energy expenditure as measured by indirect calorimetry[141–143] (Box 64.8).

• BOX 64.8 Predictive Equations That Best Estimate Energy Expenditure in Burns

- Carlson (1992)[141]
  BMR × [0.89142 + (0.01335 × TBSA)] x BSA x 24 x AF
- Milner (1994)[142]
  [BMR × (0.274 + 0.0079 × TBSA − 0.004 × PBD) + BMR] × 24 × BSA × AF
- BMR (kcal/m^2 per hour)
  Men: 54.337821 − (1.19961 × Age) + (0.02548 × Age^2) − (0.00018 × Age^2)
  Women: 54.73942 − (1.54884 × Age) + (0.03580 × Age^2) − (0.00026 × Age^2)
- BSA (m^2)
  Square root of (Height in cm × Weight in kg)/3600

AF, Activity factor (typically 1.2–1.4)[143]; BMR, basal metabolic rate (in kcal/m^2/h) in healthy population; BSA, body surface area; TBSA, total body surface area burns.

Once energy expenditure and the estimated caloric requirement have been determined, intensivists must ensure the right amount of nutrition is delivered. Although underfeeding can predictably affect wound healing and muscle mass, overfeeding can also be problematic. In one series of 250 burn patients, overfeeding significantly above the resting energy expenditure as measured by indirect calorimetry increased only fat mass with little impact on lean muscle mass.[144] Excess calories from carbohydrates leads to hyperglycemia that can exacerbate systemic inflammation and promote further decrease in muscle mass.[145] As such, no more than 5 mg/kg per minute of glucose should be infused.

Perhaps the most important macronutrient in burns is protein. Provision of dietary protein and/or amino acids is essential for minimizing net protein catabolism and muscle protein breakdown. It appears that higher than normal intake of protein may appear worthwhile, but intake of 1.5 g/kg per day does not appear to provide much advantage while it increases concentrations of urea and ammonia.[146] Although up to 3 g/kg of protein has been recommended in children, 1.5 to 2 g/kg is generally advocated in adults

per recent guidelines.[147–149] It is clear, however, that net protein catabolism and eventual loss of muscle mass persist in burns regardless of the amount of protein intake. Anabolic agents, such as oxandrolone, have been shown to increase lean body mass recovery, decrease length of stay, and improve overall outcomes, including wound healing.[150,151] β-Blockade with propranolol has also been shown to reverse muscle protein catabolism thought to be mediated by endogenous catecholamines in burned children.[152] This intervention is currently being evaluated in a RCT in adults (ClinicalTrials.gov Identifier NCT01902810). Insulin appears to be a another promising anabolic agent that has been shown to reduce protein catabolism and increase skeletal muscle protein synthesis.[153,154] However, use of insulin as a primary anabolic agent in the absence of hyperglycemia in burns lacks definitive trials and has not been widely adopted. Specific amino acids, such as glutamine, which plays a role in maintaining gut barrier function, have been associated with decreased infections, decreased length of stay, and reduced mortality via either the enteral or IV routes.[155] Although a small amount of fat is necessary to prevent deficiency of essential fatty acids, excess fat may exacerbate the immunosuppressed state and lead to increased infection and sepsis.[156,157] Finally, essential vitamins such as vitamins A, C, and D as well as trace elements such as iron, copper, selenium, and zinc are all recommended to optimize wound healing and skeletal, neuromuscular, and immune function.[147–149]

Overall, early enteral nutritional support has been correlated with shorter hospital stays, accelerated wound healing, and decreased risk of infection.[158] Hence, enteral feedings should be initiated as soon as possible after the burn injury if the patient is hemodynamically stable, being weaned from vasopressors, with minimal gastric output.[149] Some clinical judgment is required as to what constitutes the right time to initiate enteral feedings. In those with larger burns, postpyloric enteral feedings may offer an advantage to minimize interruptions in nutrition delivery over gastric feedings, which many institutions hold before surgery. In patients unable to tolerate enteral feedings, early parenteral nutrition has been advocated as early as 24 hours after burn injury.[147]

Environmental Temperature Control

Increasing ambient temperature to mitigate the loss of thermoregulation and decrease the impact of hypermetabolism has been a long-standing practice among many burn centers around the world. As such, rooms are commonly heated to as high as 100°F. A recent review demonstrated limited data demonstrating the physiologic benefits of this routine practice in the ICU.[159] Although avoiding hypothermia is certainly considered important in maintaining hemostasis intraoperatively, clinical studies in nonburn patients have not demonstrated an associated increased blood loss.[159] Excessive ambient temperatures also have the potential to cause detriment to both the patient and ICU staff. Elevated temperatures may be an occupational hazard to the staff with an additional downside of affecting cognitive performance. The effect of a warm ICU on the growth of nosocomial bacteria and fungi is of some concern, as is increased perspiration of staff with the possibility of wound contamination during dressing changes and other procedures. Alternative measures to maintain core temperature in burn patients are much needed. Additionally, further studies to elucidate the physiologic impact of increased environmental temperature on burn hypermetabolism will be helpful. In the meantime, the current practice of reflexively increasing room temperature when caring for burn patients requires careful consideration. Again, an individualized approach in this regard may prove to be optimal as evidence of this practice is extremely weak at best.

Renal

Historically, the prevalence of AKI among burn patients has been difficult to pinpoint owing to the lack of a standard definition. What has been well documented is its association with an exceedingly high mortality of 80% to 100%.[160–162] Over the past decade, standard definitions of AKI have been applied to the burn population. A recent comprehensive review determined that AKI occurred in 25% of patients among burn patients and was associated with a median mortality of 35% when defined by the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) consensus classification.[163] Among those requiring renal replacement therapy (RRT), mortality was reported as 80%.[163] The Acute Kidney Injury Network (AKIN) criteria were later applied and found to be more sensitive in the detection of AKI.[164] The Kidney Disease Improving Global Outcomes (KDIGO) consensus panel has further refined these criteria but they have yet to be applied to burns.[165] Although these definitions have been helpful in better characterizing this end-organ and linking AKI severity to a stepwise increase in mortality, they still do not provide a comprehensive picture. Further clarity on the role of various injury biomarkers in burns, such as cell cycle arrest markers and urinary neutrophil gelatinase-associated lipocalin, will help complement these function-specific diagnostic criteria.[166,167] Once the diagnosis is made, the mainstay of therapy for AKI includes the maintenance of adequate organ perfusion and the prevention of secondary insults such as nephrotoxins. In select patients, the use of fenoldopam, a selective dopamine-1 agonist, at a dose of 0.03 to 0.09 mg/kg per minute, may be considered as it may be helpful in preserving renal function and increases urine output without inducing hypotension.[168] Vasoactive medications such as fenoldopam or atrial natriuretic peptide were not recommended for routine treatment of AKI in the general ICU population.[165]

Renal Replacement Therapy in Burn Patients

In the management of burn patients with severe AKI, a traditional approach of waiting for classic triggers for initiation of RRT (such as acidosis, severe electrolyte abnormalities, intractable fluid overload, and uremic complications) may result in an unacceptably high mortality. An aggressive approach of initiating RRT with early AKI combined with metabolic derangements led to an absolute reduction in mortality by 30% when compared with historical control subjects, most of whom never met classic criteria for renal replacement and thus were not offered RRT.[44] A recent RCT demonstrated a survival benefit with a similarly aggressive approach in a nonburn ICU population.[169] Such a study would be helpful in the burn population. However, the likelihood of an adequately powered randomized controlled study is unlikely to be feasible in the near future in this unique population. The Randomized Controlled Evaluation of Hemofiltration in Adult Burn Patients with Septic Shock and Acute Renal Failure (RESCUE) trial recently closed to enrollment after 6 years because of difficult and slow recruitment (ClinicalTrials.gov Identifier: NCT01213914). Findings from this study and a concurrent observational study among RESCUE trial participating burn centers will help provide some future guidance for burn providers. However, findings are unlikely to be definitive. Again, an individualized approach, with extrapolation of findings and interventions from similar populations, is most likely to result in optimal outcomes.

Hematologic Considerations

Acutely, the most common burn-specific hematologic abnormality that intensivists encounter is hemoconcentration. In large burns, hematocrit levels often exceed 60%. Practically speaking, this degree of hemoconcentration results in significant sludging that may affect blood flow, especially to the distal extremities. Thus this important variable must be considered when assessing distal pulses early after a burn injury. Often allowing a few more hours of fluid resuscitation allows for normal flow. Additionally, a savvy clinician can take advantage of this expected abnormality to uncover subtle clinical defects. For example, a "normal" hematocrit despite a large burn could signal the presence of a chronic anemia. Hemoconcentration that fails to normalize over the course of a fluid resuscitation can be indicative of underresuscitation. Normalization of the hematocrit level is expected within 24 to 36 hours and may even fall below normal as the blood becomes hemodiluted. Other acute direct burn-related cellular changes can occur to the blood, including intravascular hemolysis, spherocytosis, fragmentation, and vesiculation.[170] Pseudothrombocytosis as the result of red cell microvesicles being incorrectly counted as platelets has also been reported.[171]

Burns can uniquely affect other cell lines. A reactive leukocytosis is common after immediately after burns, reflective of a generalized stress response. In up to 46% of patients, this is followed by a relative leukopenia down to an average nadir of 5/μL of blood around 3 days after the burn.[172] On the other hand, thrombocytopenia as defined by less than 150,000/μL of blood has been reported to occur in up to 60% of burns.[172] Generally thereafter a reactive leukocytosis and thrombocytosis is thought to be a normal physiologic response to the stress of burns and a variety of subsequent physiologic insults during the course of burn care. One study demonstrated the poor congruence between BSI and white blood cell count owing to its lack of specificity in burns.[173] Severe thrombocytopenia as defined by less than 20,000/μL of blood has been associated with increased mortality.[172]

Anemia in Burns

Over the course of a hospitalization, nearly all patients with significant burns experience anemia. This anemia is due to a combination of blood loss from surgery as well as multifactorial issues related to critical illness.[174] Estimating perioperative blood loss during burn surgery has been a significant challenge and hence the focus of clinical researchers over the past few decades. Providers must carefully predict blood transfusion requirements to avoid waste of cross-matched blood. In one study, more than half of the red blood cell units typed and cross-matched were not transfused during surgery.[175] For planning purposes, it appears that burn patients require approximately 2 units of packed red blood cells (pRBCs) per 1000 cm^2 of burn wound excised.[176] Clearly, this estimate should be individualized as variables such as age, presence of a coagulopathy, and delays in burn excision affect intraoperative transfusion needs. During the course of a burn hospitalization, total transfusions are, not surprisingly, tied to TBSA. For example, one study demonstrated that an average of 4, 8, 12, and 20 units of pRBCs were transfused for patients with less than 10%, 11% to 19%, 20% to 40%, and greater than 41% TBSA burns, respectively, over the course of a hospitalization.[175] Another study found an average of 14 and 30 units of pRBCs were transfused for patients with more than 20% and more than 50% TBSA burns, respectively.[177] Various techniques to minimize transfusion requirements have been described.[174] Intraoperative techniques minimizing intraoperative blood loss, such as epinephrine tumescence and tourniquet application, appear to be quite effective and have been widely adopted.[174] Extrapolating the accumulating evidence in the critical care literature regarding restrictive transfusion practices to burns may also be helpful in decreasing total in-hospital transfusions.[174] Preliminary evidence suggests that mild to moderate anemia has little impact on wound healing in the setting of adequate perfusion.[178] A recent multicenter RCT confirmed that a restrictive strategy in burns resulted in a decrease of blood transfusions by half without a noticeable impact on various outcomes.[178a] Finally, the role of erythropoietin in addressing the blunted endogenous erythropoietin response in critically ill burns is unclear. Two trials in burns demonstrated that exogenous erythropoietin administration had no impact on transfusions.[179,180] The lack of impact of erythropoietin on transfusion requirement was corroborated in a large RCT in trauma. However, an alternative protective benefit may be plausible as erythropoietin seemed to convey a survival advantage despite an increase in thrombotic complications.[181] More studies are clearly needed.

Venous Thromboembolism

The prevalence of venous thromboembolism reported in the literature varies widely, from as low as 0.25% to as high as 23%.[182–187] A major reason for this wide variation is likely due, in part, to the detection of occult deep vein thromboses (DVT) during active surveillance. Clearly the higher rates were detected and reported in prospective studies in which routine surveillance was conducted.[184,186] It is unclear if treatment of previously occult DVT affects outcome in a positive way. In burn patients the initiation of anticoagulation is not without complication. As such, it should not be surprising that only 75% of burn centers surveyed routinely prescribed prophylaxis.[188] The most recent study identified various risk factors associated with a predisposition for DVTs to include male sex, age, smoking, alcoholism, the percent TBSA, use of a central line, and increased number of surgeries and blood transfusions.[187] Those with these risk factors should probably undergo routine prophylaxis while keeping in mind that optimizing chemoprophylaxis may be challenging in this population.[189] Clearly more clinical trials are needed to provide more definitive guidance with regard to identification and quantification risk, understanding the role of routine surveillance, and optimization of chemoprophylaxis.

Infectious Complications

As many as 61% of all deaths in burns occur as a result of infection.[190] This should not be surprising as severe burns are characterized by the loss of the cutaneous protective barrier to infection, immune-inflammatory dysregulation, and a frequent use of invasive devices. Perhaps among the most significant challenges intensivists face while caring for burn patients includes early detection of sepsis. The typical manifestations of systemic inflammation, which include fever, tachycardia, and leukocytosis, are regularly seen in burn patients even in the absence of infection. Thus prior sepsis definitions that relied on these variables to detect systemic inflammatory response syndrome were too sensitive in the burn population. As a result, the burn community proposed more burn-specific indicators.[191] These include temperature (>39°C or <36°C); a higher threshold for tachypnea (>25 breaths/min without ventilation or >12 L/min with ventilation); a higher threshold for tachycardia (>110 beats/min); thrombocytopenia (<100,000/μL of blood); hyperglycemia (untreated glucose >200 mg/dL, >7 units/h insulin infusion, or >25% increase in insulin dosing over 24 hours); and enteral feeding intolerance (abdominal distention, residuals over

twice the feeding rate, or diarrhea >2500 mL/24 hr).[191] The presence of three or more of these findings increases the likelihood of systemic infection and is a reasonable prompt for clinicians to initiate further workup, and if indicated, initiation of broad-spectrum antibiotics. The quick Sepsis-Related Organ Failure Assessment (qSOFA) was advocated by the most recent sepsis consensus conference.[192] Two of three qSOFA elements (altered mental status, respiratory rate ≥22 breaths/min, and systolic blood pressure ≤100 mm Hg) were determined to best identify patients at risk for clinical deterioration in a large metadata-driven model.[192] Although not yet validated in burns, it is reasonable incorporate qSOFA along with the burn-specific indicators to identify burn patients who may have sepsis. Once a determination is made, broad-spectrum antibiotic coverage should be initiated promptly.

Wound Infections

In addition to early surgical excision, wide adoption of topical antimicrobial agents for burn wounds has virtually eliminated death from invasive, gram-negative burn wound infection.[193] Table 64.4 lists the most common topical antimicrobial agents.[194] The diagnosis of invasive wound infection should still be entertained if there has been a delay in surgical excision or if there are areas of poor wound healing from either temporary or definitive coverage. Signs include obvious discoloration of the wound bed, exudate, and a spreading margin of erythema around the wound edges and is confirmed by full-thickness biopsy and histopathology. Later in the ICU course, the possibility of invasive fungal wound infection should be entertained as it is a major cause of morbidity and mortality.[195,196] Invasive wound infection typically requires broad-spectrum antimicrobials to include antifungals if fungus is suspected and rapid surgical excision.

Other Infections

Pneumonia is a frequent cause of infection in the burn ICU with a prevalence of 25% to 38%.[197] Inhalation injury increases the risk of pneumonia as a result of damage to the ciliary layer of the tracheobronchial mucosa, sloughing leading to distal airway obstruction, and immune dysfunction. Preventive measures include all the bundle elements found to be important in the general ICU population.[198] Application of HFPV may be considered a preventive strategy based on its mechanism of allowing for improved pulmonary secretion mobilization and data suggesting a decreased prevalence of pneumonia.[104,105]

BSI was diagnosed in 33% of 11,793 patients entered into the national burn repository.[199] *Staphylococcus aureus* was the most frequent isolate associated with BSI followed by *Pseudomonas aeruginosa.* A large bacteriology study also revealed *S. aureus* as the most common pathogen among burn patients in the United States.[200] Interestingly this study demonstrated a change in recovered pathogen over time. Although *S. aureus* was most commonly recovered during the first 15 days, *P. aeruginosa* and *Klebsiella pneumoniae* were most commonly recovered after 15 days. Bacteriology recovery patterns differed in military service members burned and transferred from the Middle East with *Acinetobacter baumanii* most predominant organism found early.[200] In addition to geographic and longitudinal differences in bacteriology, a well-known challenge in the care of infections among burns is the high prevalence of multidrug-resistant organisms. Burn clinicians must take these factors into consideration when choosing empiric antibiotic coverage. Efforts to decrease the rate of BSI in burns include frequent catheter exchanges (either over a wire or to a new access site) and routine use of antimicrobial-coated catheters.[201–203]

Other pertinent burn population infectious complications deserve specific mention. Although relatively rare, with a reported prevalence of 0.3%, a diagnosis of established endocarditis among burn patients is associated with a mortality of 100%.[204] Any burn patient with persistent or recurrent bacteremia should have a workup for infectious organisms. *Clostridium difficile* infection is a clinically important infection in burn patients and should be suspected in those with unexplained diarrhea with septic physiology.[205] Viral infections such as herpes simplex virus and cytomegalovirus have been reported to play a role in contributing to burn morbidity.[206] There is no consensus, however, regarding a specific prophylactic or treatment strategy with these infections. Diagnosis of a true

TABLE 64.4 Topical Antimicrobial Agents

Product	Application	Penetration	Side Effects
Mafenide acetate cream	Apply 1/16-inch layer twice daily[a]	Penetrates eschar	Painful on application, metabolic acidosis
Silver sulfadiazine cream	Apply 1/16-inch layer twice daily[a]	Poor eschar penetration	Transient leucopenia
Mafenide acetate solution	Dress wounds with multiple layers of coarse gauze and apply solution to keep gauze continually moist	Partially penetrates eschar	Electrolyte disorders
Silver nitrate solution	Dress wounds with multiple layers of coarse gauze and apply solution to keep gauze continually moist	Poor eschar penetration	Painful on application
Silver-impregnated dressings (Acticoat, Silverlon, Silverseal)[b]	Moisten dressing with sterile water, cut to size, secure to wound with secondary dressing, change in 3–5 days	Poor eschar penetration	

[a]Consider alternating mafenide in the morning with silver sulfadiazine in the evening.
[b]Application information obtained from package insert.
Adapted from D'Avignon LC, Chung KK, Saffle JR, et al. Prevention of infection associated with combat-related burn injuries. *J Trauma.* 2011;71(2 suppl 2):S282–S289.

invasive viral infection is exceedingly difficult as it requires histologic evidence. A balance of risk-benefit must be weighed when deciding to treat patients empirically with antiviral drugs. Finally, pharmacokinetics and pharmacodynamics are extremely complex in burns with significant patient-to-patient variability and fluctuations over time.[207] As such, the importance of incorporating a dedicated clinical pharmacist with burn experience into the daily workflow of a burn ICU cannot be understated.

Rehabilitation (Phase IV)

Despite the focus during the acute phase of patients with severe burns appropriately placed on survival from the original injury and subsequent ICU complications, a concurrent emphasis should also be placed on overall function when the patient leaves the hospital. As a result, functional survival should be the ultimate goal of ICU care. Optimal care to achieve functional survival begins immediately upon admission. A true multidisciplinary burn team must incorporate both physical and occupational therapists early during care. Even patients who are heavily sedated using mechanical ventilation can have certain rehabilitative principles incorporated into their care plan. Some of these measures range from elevation of limbs to decrease edema during the resuscitative phase to application of splints to prevent contractures after burn surgery, to incremental weight-bearing to engage core muscles, to early ambulation when appropriate.[208,209] Unfortunately, evidence demonstrating benefit of specific and early rehabilitative interventions in burn care is lacking. A recently completed multicenter observational study in burns should be helpful in further linking specific rehabilitative interventions with patient outcomes (ClinicalTrials.gov Identifier: NCT01161810). Finally, the psychosocial challenges for both the patient and the family members after immediately after burn injury must not be ignored.[210] Social workers, vocational counselors, and psychologists should all contribute to the care of severely burned patients as part of the multidisciplinary burn team.

Key Points

- All ICU therapeutic interventions should be individualized to the patient: one size does not fit all.
- Optimal fluid resuscitation is guided by basic critical care principles of optimizing perfusion centered on adequate urine output at the least physiologic cost.
- Early excision of all full-thickness and deep partial-thickness burns and timely definitive coverage are the keys to survival.
- Every effort should be made to optimizing the conditions for wound healing by limiting vasopressors, minimizing edema, and providing adequate nutrition.
- The hypermetabolic and catabolic response to severe burns is multifold greater than for the general trauma population.
- Clinicians must be aggressive in identifying and treating infectious complications early.
- A multidisciplinary team approach to care is vital for optimal burn care.
- Functional survival is the ultimate goal.

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Review Questions

1. In patients with critically ill burns of total body surface area (TBSA) greater than or equal to 40%, which of the following is the most common early and acute hematologic abnormality?

a. Thrombocytopenia
b. Leukopenia
c. Anemia
d. Hemoconcentration

Answer: d. Acutely, the most common burn-specific hematologic abnormality that intensivists encounter is hemoconcentration. In large burns, hematocrit levels often exceed 60%. Hemoconcentration that fails to normalize over the course of a fluid resuscitation can be indicative of underresuscitation. A reactive leukocytosis is common immediately after burns, reflective of a generalized stress response. In up to 46% of patients, this is followed by a relative leukopenia. Thrombocytopenia (defined by <150,000/μL of blood) has been reported to occur in up to 60% of burns. Generally thereafter, a reactive leukocytosis and thrombocytosis is considered a normal physiologic response to the stress of burns and a variety of subsequent physiologic insults during the course of burn care.

2. Acute kidney injury (AKI) occurs in large TBSA burns (>40%) in critically ill patients approximately which percentage of the time?

a. 2%
b. 25%
c. 10%
d. 50%

Answer: b. Historically, the prevalence of AKI among burn patients has been difficult to pinpoint because of the lack of a standard definition. What has been well documented is its association with an exceedingly high mortality. Over the past decade, standard definitions of AKI have been applied to the burn population. A recent comprehensive review determined that AKI occurred in 25% of patients among burn patients and was associated with a median mortality of 35% when defined by the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) consensus classification. Among those requiring renal replacement therapy (RRT), mortality was reported as 80%.

65 Poisonings

JANICE L. ZIMMERMAN

CHAPTER OUTLINE

Resuscitation and Stabilization

Diagnosis
- History
- Physical Examination
- Toxidromes
- Laboratory Tests

Gastrointestinal Decontamination

Enhanced Elimination

Specific Poisonings
- Alcohols
- Analgesics
- Carbon Monoxide
- Cardiovascular Drugs
- Cyanide
- Dietary and Nutritional Agents
- Methemoglobin Inducers
- Organophosphate and Carbamate Agents
- Psychotropic Drugs
- Sedatives
- Stimulants
- Valproic Acid

Poisonings may result from intentional or unintentional ingestion, inhalation, injection, or skin contact. Toxic complications can also result from therapeutic use of medications. Although the mortality rate from toxin exposures is low, patients requiring hospitalization are often cared for in the intensive care unit (ICU). Limited evidence-based information on management of poisonings is available because the variety of drugs and doses that patients are exposed to limit the ability to conduct clinical trials of specific interventions. In addition, animal and human volunteer studies fail to fully replicate the clinical situations that are commonly encountered. Therapeutic recommendations are based on extrapolation of data from animal models, human volunteer studies, case reports, pharmacokinetic information, known pathophysiology, consensus opinion, and a limited number of clinical trials. Toxicologists and local poison control centers are valuable sources of additional information for the clinician.

The approach to the poisoned patient requires an organized evaluation and management plan that often requires the input of emergency physicians, primary care physicians, intensive care clinicians, and clinical pharmacists. The basic steps include initial resuscitation and stabilization, diagnosis, gastrointestinal (GI) decontamination and toxin elimination, institution of specific antidotes or interventions, and supportive care. This chapter addresses these components of management with regard to poisonings and toxicities most likely to be encountered in ICU patients. Although discussed separately, these steps are usually initiated concurrently in a severely ill patient.

Resuscitation and Stabilization

The initial management of seriously ill poisoned patients requires assessment of airway patency, breathing difficulties, circulatory problems, and the level of consciousness. These issues, along with immediate resuscitation interventions, are usually addressed in the emergency department but may be continued in the ICU (Box 65.1).

Diagnosis

History

A complete history should be obtained regarding the involved substance or substances, including the route of exposure, quantity used, time of exposure, form of medication (regular or sustained-release), and chronicity of use to determine the significance of the presenting symptoms. Specifically, the clinician should inquire about the patient's baseline mental and health status and the medical, occupational, and social history. A detailed medication history should include information about over-the-counter, prescription, illicit, and nutritional or herbal medications. Intentional ingestions often involve multiple coingestants or alcohol, or both. Additional or corroborating information should be obtained from family, friends, paramedics, or witnesses, if available. All available containers found at the site should be brought in for examination.

Physical Examination

The initial physical examination should focus on vital signs and neurologic findings that may provide physiologic clues to the toxicologic cause. Many toxic substances affect the autonomic nervous system, which is responsible for changes in vital signs mediated by the sympathetic and parasympathetic pathways. Attention to these initial and subsequent clinical signs is of paramount importance in identifying patterns or changes suggesting a particular drug or category of drugs (Table 65.1). Changes in the clinical examination after a therapeutic intervention or the administration of an antidote should be noted. Continued

• BOX 65.1 Approach to Resuscitation and Stabilization of the Poisoned Patient

Assess airway and breathing:
- Supplemental oxygen for patients with low oxyhemoglobin saturation; FIO_2 1.0 for carbon monoxide or cyanide exposure
- Intubation and mechanical ventilation for airway protection, airway obstruction, hypoventilation, or hypoxemia

Assess hemodynamic status:
- Isotonic fluids initially for hypotension; vasopressor if condition is refractory to fluids
- Treat significant arrhythmias

Assess mental status

Consider the following for altered mental status[1]:
- 50% glucose (25–50 g IV)
- Thiamine (100 mg IV)
- Naloxone (0.4–2 mg IV or IM initially)
- Flumazenil (not routinely recommended)[a]

[a]*See section on benzodiazepines for further information.*

monitoring and reevaluation are necessary because drug effects may not be present on initial evaluation.

Altered mental status is common in a toxicologic emergency. A detailed assessment of neurologic status should be made to determine if there is any alteration in level (stupor/coma or agitation) or content of consciousness (confusion/delirium). The evaluation should include an assessment of pupillary reactivity, ocular movements, and motor responses. Ruling out structural versus toxic or metabolic reasons for the altered state is important. Drug-induced seizures are often difficult to treat and may respond only to specific antidotal therapy. In general, benzodiazepines are more effective in terminating drug-induced seizures than other agents.

Pupils should be assessed for size and reactivity, and ocular movements should be evaluated for the presence of sustained nystagmus. Agents associated with miosis include organophosphates/carbamates (mydriasis also seen), other cholinergic agents, opioids, acetone, clonidine, phencyclidine, phenothiazines, and nicotine. Both anticholinergics and sympathomimetics may cause mydriasis; the pupils are reactive to light with cocaine but unreactive in diphenhydramine overdose. Opioid withdrawal may also result in dilated pupils. The pupillary assessment may be difficult in the setting of multiple coingestants, whereby the response may be blocked or partially manifested. Horizontal nystagmus is commonly seen with alcohols, lithium, carbamazepine, solvents, and primidone. Phenytoin, sedative-hypnotics, and phencyclidine may cause a combination of vertical, horizontal, or rotatory nystagmus.

The clinical examination should also include evaluation of bowel sounds (decreased/hyperactive), skin (moist/dry), and mucosa (secretions).

TABLE 65.1 Drug Effects on Vital Signs

Increased	Decreased
Blood Pressure	
Amphetamines	Antihypertensive agents
Anticholinergics	Cyanide
Bath salts	Cyclic antidepressants
Cocaine	Ethanol, other alcohols
Ephedrine	Iron
Phencyclidine	Opioids
Sympathomimetic agents	Organophosphates/carbamates
Synthetic cannabinoids	Sedative-hypnotics
Heart Rate	
Amphetamines	β-Blockers
Anticholinergics	Calcium channel blockers
Antihistamines	Clonidine
Bath salts	Digitalis glycosides
Caffeine	Gamma-hydroxybutyrate
Carbon monoxide	Lithium
Cocaine	Opioids
Cyanide	Organophosphates/carbamates
Cyclic antidepressants	Physostigmine
Ephedrine	Sedative-hypnotics
Ethanol	
Phencyclidine	
Synthetic cannabinoids	
Theophylline	
Respiratory Rate	
Alcohols	Ethanol, other alcohols
Amphetamines	Gamma-hydroxybutyrate
Anticholinergics	Opioids
Carbon monoxide	Organophosphates
Hydrocarbons	Sedative-hypnotics
Salicylates	
Theophylline	
Temperature	
Amphetamines	β-Blockers
Anticholinergics	Carbon monoxide
Bath salts	Ethanol
Cocaine	Gamma-hydroxybutyrate
Cyclic antidepressants	Hypoglycemic agents
Lithium	Opioids
Phencyclidine	Sedative-hypnotics
Salicylates	
Theophylline	

Toxidromes

A complex of signs and symptoms may be identified by physical examination and grouped into a toxic syndrome, or "toxidrome." In many cases, recognition of this toxic pattern is more important than identifying a specific offending agent. Identifying a toxidrome enables the clinician to initiate the assessment, derive a differential diagnosis, and formulate a treatment plan. The most common toxidromes are listed in Table 65.2.[2] Importantly, the clinician should note that patients may not present with a classic toxidrome owing to variable manifestations of toxins and overlapping features that exist between toxidromes.

Laboratory Tests

A laboratory test for a patient exposed to toxic agents should be helpful in diagnosis or monitoring.[3] Select laboratory examinations may be used when appropriate to determine the three gaps of toxicology—the anion gap, the osmolar gap, and the oxygen saturation gap. An arterial blood gas analysis will identify hypoxemia or hypoventilation, as well as acid-base abnormalities. Agents associated with a gap in oxygen saturation (>5% difference between measured and calculated saturation) include carbon monoxide (CO) and

TABLE 65.2 Toxidromes

Drug Group	VITAL SIGNS BP	HR	RR	T	ADDITIONAL MANIFESTATIONS Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
Sympathomimetic (adrenergic) agents	±	↑	↑	↑	Altered, agitation	↑	↑	↑	Flushing, potential for seizures
Anticholinergic agents	±	↑	±	↑	Altered, hallucinations	↑	↓	↓	Dry mucous membranes, thirst, flushing, urinary retention
Cholinergic (muscarinic, nicotinic) agents	±	±	—	—	Altered	±	↑	↑	Salivation, lacrimation, urination, emesis, bronchorrhea, fasciculations
Opioids	↓	↓	↓	↓	Altered, sedation	↓	↓	↓	Hyporeflexia
Sedative-hypnotics or ethanol	↓	↓	↓	↓	Altered, sedation	±	↓	↓	Hyporeflexia

BP, Blood pressure; *HR*, heart rate; *RR*, respiratory rate; *T*, temperature; ↑, increase; ↓, decrease; ±, variable; —, change unlikely.
Adapted from Nelson NS, Lewin NA, Howland MA, et al. Initial evaluation of the patient: vital signs and toxic syndromes. In: Nelson NS, Lewin NA, Howland MA, et al., eds. *Goldfrank's Toxicologic Emergencies.* 9th ed. New York: McGraw-Hill Medical; 2011:33.

• BOX 65.2 Selected Agents Associated With Anion Gap Acidosis

Acetaminophen
Carbon monoxide
Cyanide
Ethylene glycol
Iron
Isoniazid
Metformin
Methanol
Propofol
Propylene glycol
Salicylates
Toluene
Valproic acid

methemoglobin inducers. In these exposures, a pulse oximeter inaccurately reflects the oxygen saturation of tissues and co-oximetry is necessary to identify abnormal hemoglobins. Determination of electrolytes with blood urea nitrogen and creatinine will detect renal abnormalities and allow calculation of the anion gap. Some common drugs associated with an anion gap acidosis are listed in Box 65.2. Hypoperfusion must also be considered as a cause of metabolic acidosis. An osmolar gap (>10 mOsm/L) may be caused by any small particle (toxin) that increases the measured osmolarity as measured by freezing point depression. Such agents include ethanol, ethylene glycol, glycerol, isopropyl alcohol, mannitol, methanol, propylene glycol, and sorbitol. An electrocardiogram (ECG) should be obtained when potential cardiac toxicity exists.

A qualitative urine drug screen is a combination of tests that serves to identify common drugs encountered in overdoses. However, a "tox screen" is usually unnecessary because the results rarely alter management, many toxins are not detectable, and positive results do not assess the severity of exposure. Quantitative determination of drug/toxin concentrations in blood is indicated by history and clinical examination to diagnose the intensity of toxicity, monitor the treatment or course of a patient, or define indications for specific interventions. Serum concentration measurements may be required as criteria for therapy or to assess the effectiveness of therapy. Because of the ubiquity of acetaminophen in over-the-counter and prescription preparations and the potential for significant morbidity and even death, a level should be obtained in any suspected polydrug ingestion.

Gastrointestinal Decontamination

GI decontamination techniques in the poisoned patient with an oral ingestion have included gastric emptying procedures (ipecac-induced emesis, gastric lavage), adsorption of drugs (activated charcoal), and increasing transit through the GI tract (cathartics, whole bowel irrigation [WBI]). Use of these interventions has decreased owing to uncertain evidence of benefit and recognition of adverse effects of the techniques. The consideration of a GI decontamination technique depends on the toxicity of the substance ingested, potential for deterioration in respiratory and mental status, severity of symptoms, dose, time since ingestion, presence of spontaneous emesis, and contraindications of the procedure.

Ipecac, which contains emetic alkaloids, stimulates gastric mucosal sensory receptors and the chemoreceptor trigger zone in the brain to produce vomiting. The amount of ingested drug removed by ipecac-induced emesis is highly variable, and no benefit of ipecac has been confirmed even when administered less than 60 minutes after ingestion. Currently, ipecac is not used in the management of poisoning victims.[4] Complications associated with ipecac administration include aspiration pneumonitis, esophageal rupture, Mallory-Weiss tear, pneumomediastinum, and protracted vomiting that can delay administration of activated charcoal.

Gastric lavage with a large-bore (36F–40F) orogastric tube is a technique used to empty the stomach of orally ingested substances that can be associated with significant complications. After insertion of the tube, lavage is accomplished with sequential 250 mL aliquots of normal saline solution or water until no pill fragments are retrieved. Intubation for airway protection is required before the procedure in patients with a depressed level of consciousness or potential for sedation. Gastric lavage should not be used routinely in the management of poisoned patients, if at all.[5] The clinician must

consider contraindications and the potential risks if gastric lavage is considered. Serious complications include aspiration pneumonitis, esophageal perforation, and cardiovascular instability. Gastric lavage is contraindicated with ingestions of substances such as acid, alkali, or hydrocarbons when the risk of aspiration is increased. Patients with a risk of GI perforation or severe bleeding diathesis or who are combative should also not be subjected to gastric lavage.

Single-dose activated charcoal potentially adsorbs the toxin in the GI tract and minimizes systemic absorption. The optimum dose of activated charcoal has not been established, but the usual dose for adults is 25 to 100 g (1 g/kg). Activated charcoal is not effective in adsorbing iron, lithium, cyanide, strong acids and bases, alcohols, and some hydrocarbons. Use of activated charcoal may be considered when a potentially toxic amount of a substance adsorbed by charcoal has been ingested within 1 hour.[6,7] Later administration may be appropriate if clinical factors suggest the ingested substance has not yet been completely absorbed. Activated charcoal is contraindicated in patients with a depressed level of consciousness unless intubated, when administration increases the risk of aspiration, or the patient is known or suspected to have a GI perforation. Few complications are associated with the appropriate use of single-dose activated charcoal. Emesis has been reported but may be related to sorbitol administered with charcoal or the ingested toxin.

Cathartics have been administered in poisoning ingestions based on the hypothesis that absorption and overall bioavailability of the agent are decreased by reducing contact time in the GI tract. Sorbitol (70% solution with activated charcoal) is the most commonly used cathartic, but magnesium citrate and magnesium sulfate have also been used. No clinical studies have demonstrated beneficial effects of cathartics in poisoned patients. A cathartic alone has no role in the management of poisonings, and even the routine use of a cathartic in combination with activated charcoal cannot be recommended.[8] A cathartic should not be administered in patients with ileus, GI obstruction or perforation, recent GI surgery, or hemodynamic instability. Complications of cathartics include nausea, vomiting, and abdominal cramping. Multiple doses of magnesium-containing cathartics may result in significant dehydration and electrolyte abnormalities.

WBI has been proposed as a technique to prevent absorption of ingested poisons by rapidly expelling the bowel contents. WBI involves the enteral administration (usually by nasogastric tube) of large volumes (1–2 L/h in adults) of polyethylene glycol electrolyte lavage solution; this is continued until the rectal effluent is clear or elimination of the toxin has been confirmed. During the procedure, the head of the bed should be elevated to 45 degrees to decrease the likelihood of vomiting and aspiration. No data exist to suggest improved patient outcomes with WBI. Currently, there are no established indications for WBI, but it may be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, iron, lithium, and illicit drug packets.[9] WBI is contraindicated in the presence of ileus, GI obstruction or perforation, GI bleeding, hemodynamic instability, or intractable vomiting. In the patient with decreased level of consciousness or respiratory depression, the airway must be protected before instituting WBI.

Enhanced Elimination

Multiple-dose activated charcoal (MDAC) therapy involves the repeat oral administration of activated charcoal to prevent absorption of drugs that persists in the GI tract and to enhance elimination of drugs already absorbed into the body by functioning as an adsorbent "sink" at several sites in the gut.[10] First, it can interrupt enterohepatic circulation of drugs or metabolites that are actively secreted into bile. Second, it can adsorb drugs or metabolites that enter the gut by active secretion or passive diffusion and prevent reabsorption. Finally, it may prevent desorption of drugs, particularly acidic substances that bind two to three times less avidly to activated charcoal in the alkalotic milieu of the intestinal lumen than in the acidic environment of the stomach. Drugs with a prolonged elimination half-life after overdose and a small volume of distribution are more likely to have elimination enhanced significantly by MDAC.

One suggested regimen for administering MDAC is to follow the initial dose of activated charcoal with 0.5 to 1 g/kg every 4 hours. Alternatively, it is possible to administer charcoal as an aqueous solution by continuous infusion via a nasogastric tube at a rate of 0.25 to 0.5 g/kg per hour (not <12.5 g/h). Additionally, the smaller doses (and volumes) administered more frequently may reduce the likelihood of vomiting. It may still be necessary to give an antiemetic intravenously to ensure effective administration. The dosing schedule will be dictated by clinical parameters, such as patient cooperation, level of consciousness, the presence of ileus and vomiting, laboratory parameters, plasma concentrations of drug, and clinical improvement. Patients receiving MDAC should be monitored carefully for the development of constipation or obstruction and for the prevention of aspiration.

There is no convincing evidence that MDAC reduces morbidity and mortality rates in poisoned patients.[11] However, MDAC may be considered if the patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline and may obviate the need for invasive extracorporeal techniques. Insufficient evidence exists to support routine use of MDAC in ingestions of other substances.

Forced diuresis involves the intravenous (IV) administration of large volumes of isotonic fluids and diuretics to enhance renal excretion of drug or metabolite. This method is of limited clinical benefit and should not be used because of the potential for fluid overload and acid-base disturbances.

Urinary alkalinization is beneficial in increasing renal clearance of weak acids such as salicylates and phenobarbital. These weak acids are ionized at alkaline urine pH, trapped in the renal tubules, and not reabsorbed. Alkalinization can be initiated by adding 75 to 150 mEq sodium bicarbonate to 1 L of 5% dextrose in water. Urine pH should be tested every hour, and the rate of the bicarbonate infusion should be titrated to achieve a urine pH of 7.5 to 8.5. Alkalinization may be difficult to achieve if metabolic acidosis is present. Hypokalemia is a common complication and requires correction to facilitate urinary alkalinization. Increasing the urine pH with carbonic anhydrase inhibitors such as acetazolamide is not recommended because metabolic acidosis will worsen. Urine alkalinization can be considered in patients with significant salicylate ingestions who do not require hemodialysis. Phenobarbital poisonings are more effectively treated with MDAC.[12]

Hemodialysis is useful to increase the clearance of certain drugs and metabolites, as well as to correct metabolic acidosis induced by some substances. The concentration gradient of the unbound toxin provides the driving force for clearance. The following criteria should be applied to a drug to determine the potential for enhanced elimination by hemodialysis: low volume of distribution (<1 L/kg), single-compartment kinetics, low endogenous clearance (<4 mL/min per kilogram), molecular weight less than 500 Da, water solubility, and low plasma protein binding. Drugs for which hemodialysis should be considered in the presence of a significant

intoxication include methanol, ethylene glycol, salicylates, lithium, valproic acid, boric acid, and thallium.

Hemoperfusion is a form of extracorporeal toxin removal, whereby whole blood is passed through an adsorbent-containing (charcoal) cartridge. In general, if a compound is well adsorbed by activated charcoal, then charcoal hemoperfusion clearance may exceed that of hemodialysis. In contrast to hemodialysis, substances with a high degree of plasma protein binding can be removed. However, advancements in hemodialysis and the limited availability of hemoperfusion cartridges have resulted in decreased use of hemoperfusion. The risks of hemoperfusion are similar to those of hemodialysis. Additionally, hypoglycemia, hypocalcemia, and hypothermia may occur.

Continuous renal replacement therapies have been used less frequently for drug removal in the treatment of poisoning.[13] Clearance rates achieved with these techniques are considerably lower than those achieved with hemodialysis. Such therapy may be instituted after hemodialysis or hemoperfusion to further remove the drug after it slowly redistributes from tissue to blood. This is a potential option for agents such as lithium or procainamide. Continuous renal replacement techniques may also be advantageous in hemodynamically unstable patients who cannot tolerate conventional hemodialysis or hemoperfusion. Despite many case reports demonstrating significant drug clearance, there are no data demonstrating that these techniques affect outcome.

Specific Poisonings

Alcohols

Ethylene Glycol and Methanol

Methanol and ethylene glycol are toxic alcohols that have similar properties in overdose. Toxicity can occur through ingestion, inhalation, or dermal absorption. Cardiopulmonary and central nervous system (CNS) symptoms are common, and both agents can produce an anion gap metabolic acidosis and an osmolar gap. However, absence of an osmolar gap or anion gap does not exclude a toxic ingestion. The osmolar gap may be normal if all alcohol is metabolized to acid metabolites, and an anion gap may be normal if metabolism of alcohol has not yet produced acid metabolites (e.g., concomitant ethanol ingestion or early presentation). If toxic alcohol ingestion is suspected, regardless of whether the patient is symptomatic, blood should be immediately sent for serum methanol, ethylene glycol, and ethanol levels, and definitive treatment initiated based on the clinical history and acid-base status. Significant toxicity is associated with methanol and ethylene glycol levels greater than 50 mg/dL. The severity of acid-base disturbances appears to be directly correlated with the likelihood of survival.

Ethylene glycol is found in antifreeze and deicing solutions. Ethylene glycol causes acidemia as a result of metabolism by alcohol dehydrogenase to glycolic and oxalic acids. Oxalate crystals in the urine may be detected on microscopic examination, but they may not be present in the majority of exposed patients. Three classic phases of ethylene glycol toxicity have been described: neurologic, cardiopulmonary, and renal. During the first 0.5 to 12 hours after ingestion, ethylene glycol produces transient inebriation without the usual odor of ethanol, along with GI symptoms (nausea, vomiting). After toxic metabolites form (4–12 hours after ingestion), a metabolic acidosis develops along with CNS depression. The CNS symptoms may progress to coma associated with hypotonia, hyporeflexia, and occasionally seizures, meningismus, and cerebral edema. In the second stage (12–24 hours after ingestion), tachycardia and hypertension often occur along with progression of metabolic acidosis. Hypoxia may result from aspiration, heart failure, or acute respiratory distress syndrome. Death is most common in this stage. In the third stage (24–72 hours after ingestion), oliguria, flank pain, acute tubular necrosis, and renal failure develop.

Methanol is found in windshield washer fluid, solvents, and bootleg whiskey. It is metabolized by alcohol dehydrogenase to formaldehyde, which is then metabolized by aldehyde dehydrogenase to formic acid. Uncoupling of the mitochondrial oxidative metabolism produces lactic acid. The metabolic derangements are caused by lactic and formic acid; the latter is responsible for ocular disturbances. When methanol is ingested, peak levels occur within 30 to 60 minutes but there is often a latent period of about 24 hours (range 1–72 hours) before the development of toxic symptoms or metabolic acidosis. GI (abdominal pain, nausea, vomiting), CNS (dizziness, headache, seizures, coma), and ocular toxicities (blurred vision, photophobia, retinal edema, disc hyperemia, blindness) are seen.

Practice guidelines are available for the treatment of ethylene glycol and methanol intoxication.[14,15] If the patient has symptoms and is significantly acidemic, sodium bicarbonate may be administered as a temporizing measure to enhance formate and oxalate elimination by ion trapping. Fluid overload and hyperosmolarity may result from bicarbonate administration. Hydration is helpful because ethylene glycol is well excreted by the kidney as long as renal function is maintained. The definitive treatment of intoxication with methanol or ethylene glycol is inhibition of the alcohol's metabolism and hemodialysis to remove the alcohol and toxic metabolites and to correct metabolic abnormalities. Hemodialysis should be considered for the following conditions: deteriorating vital signs despite intensive supportive care, significant metabolic acidosis (pH < 7.25–7.3), blood level of methanol or ethylene glycol higher than 25 mg/dL, or any evidence of renal failure or electrolyte imbalances unresponsive to conventional therapy.[14,15]

Antidotal treatment of significant poisoning involves inhibition of alcohol dehydrogenase to prevent metabolism of the alcohols to toxic metabolites with ethanol or fomepizole. Ethanol (IV or oral) allows preferential metabolism of ethanol over methanol and ethylene glycol. Ethanol should be administered to maintain a blood level of 100 to 150 mg/dL. A loading dose should be followed by a maintenance infusion according to the established dosing requirements for nondrinkers, drinkers, and during hemodialysis.[14,15] Problems encountered during ethanol administration include CNS depression, hypoglycemia, dehydration, and fluctuating serum concentrations. A second IV line using 0.9% sodium chloride may be necessary to avoid development of hyponatremia because of the large free water content and significant hypertonicity (1713 mOsm/L) of 10% ethanol solution. If IV ethanol is not available, oral ethanol can be used.

Fomepizole, a competitive inhibitor of alcohol dehydrogenase, is approved for use in ethylene glycol and methanol overdose.[16] It is easier to administer than ethanol, does not cause sedation, and is associated with fewer severe and serious adverse events.[17] Fomepizole administration should be considered instead of ethanol if the patient develops altered consciousness, seizures, or a significant metabolic acidosis. Administration of ethanol or fomepizole should continue after dialysis until the serum ethylene glycol or methanol concentration is undetectable or less than 20 mg/dL or acidosis is resolved and the patient is asymptomatic. In the absence of renal dysfunction and a significant metabolic acidosis, the use of fomepizole potentially could obviate the need for hemodialysis, even though the serum ethylene glycol or methanol concentration

exceeds 50 mg/dL.[18] If patients with high serum concentrations of ethylene glycol are not treated with hemodialysis, then their acid-base balance should be monitored closely and hemodialysis instituted if a metabolic acidosis develops.

Additional therapeutic measures for ethylene glycol ingestions may include thiamine 100 mg IV and pyridoxine 50 mg every 6 hours until the ethylene glycol level is zero and no acidosis persists. If the patient becomes hypocalcemic as a result of precipitation of calcium oxalate crystals, calcium should be replaced. In methanol overdose, it may be reasonable to also administer IV folate (folinic or folic acids) at 50 to 75 mg IV every 4 hours for at least 24 hours to provide the cofactor for enhancing formic acid elimination.

Isopropyl Alcohol

Isopropyl alcohol may also be ingested, particularly by individuals with chronic alcoholism with no access to ethanol. It is found in rubbing alcohol and some hand sanitizers in high concentrations. Oral absorption occurs rapidly (within 0.5 hour), and it undergoes metabolism to acetone, carbon dioxide, and water. Symptoms may include severe abdominal pain, GI bleeding, nausea, and vomiting. Isopropyl alcohol is two to three times more potent than ethanol as a CNS depressant, and acetone is comparable with ethanol. Patients frequently present with headache, lethargy, ataxia, or coma. Respiratory depression occurs secondary to the CNS depression. Laboratory findings include an osmolar gap without a metabolic acidosis.[19] Patients may, however, have a fruity odor on their breath from acetone, and ketonemia and ketonuria may also be present. Treatment is supportive with fluid administration for significant dehydration. Hemodialysis should be considered when isopropyl alcohol levels exceed 400 to 500 mg/dL, evidence of hypoperfusion exists, coma is present, or a failure to respond to supportive therapy is noted.

Propylene Glycol

Propylene glycol is another alcohol that can cause toxicity in critically ill patients receiving high doses of IV medications containing the alcohol as a solvent. Medications that contain propylene glycol include lorazepam, diazepam, phenobarbital, pentobarbital, nitroglycerin, phenytoin, esmolol, etomidate, and sulfamethoxazole/trimethoprim. Propylene glycol toxicity is more commonly observed with lorazepam because of the use of high doses in some patients and the high concentration of propylene glycol—approximately 830 mg/mL.[20] Common manifestations of propylene glycol accumulation are anion gap metabolic acidosis and increased osmolar gap.[21] Additional toxicities include renal dysfunction, hemolysis, cardiac arrhythmias, seizures, and CNS depression or agitation. Clinical studies suggest that an elevated osmolar gap correlates with propylene glycol accumulation. Accumulation can occur when doses of lorazepam exceed 0.1 mg/kg per hour and when renal or hepatic insufficiency is present. Although toxicity is more common after long periods of lorazepam infusion (>3 days), toxicity has occurred with short-term, high-dose use. The treatment of choice is to stop the lorazepam infusion and sedate with an agent that does not contain propylene glycol. Hemodialysis removes propylene glycol but is usually not required unless severe renal dysfunction develops.

Analgesics

Acetaminophen

Acetaminophen (N-acetyl-p-aminophenol [APAP]) is present in many prescription and over-the-counter medications and is frequently a coingestant with other drugs. In addition, unintentional overdoses result from patients unknowingly ingesting multiple products containing APAP (particularly APAP-narcotic combinations). Because APAP overdose may result in significant hepatotoxicity and even death that is preventable, it is important to recognize and initiate appropriate therapy. With higher doses of APAP, a greater proportion is hepatically metabolized by the cytochrome P450 (CYP) system of mixed function oxidases (CYP 450) to the toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which can result in cell injury and death. Hepatic glutathione facilitates detoxification and elimination of NAPQI with therapeutic doses of APAP, but glutathione supply is overwhelmed in APAP overdoses. The clinical course of APAP toxicity has been divided into stages on the basis of the development of hepatotoxicity (Table 65.3).[22]

If possible, an estimate of the quantity and dosage form of APAP ingested and the time of ingestion should be obtained. In adults, hepatic toxicity can occur after ingestion of more than 7.5 to 10 g during 8 hours or less but has been reported with exposures of 4 g. The maximum daily dose of acetaminophen has been reduced to 3 g because of concerns for toxicity. The risk of toxicity may be increased in patients with low glutathione stores (malnutrition, fasting state, chronic alcoholism) or induction of CYP 450 enzymes (chronic alcoholism, phenytoin or carbamazepine use). For patients with a recent single, acute ingestion, an APAP level should be obtained at least 4 hours after ingestion. Liver enzyme levels need to be evaluated only if the APAP level indicates potential toxicity or the clinical examination suggests hepatic injury. If the time of ingestion is unknown, an APAP level should be obtained on admission. An APAP level and liver function tests should be determined in patients presenting late (>24 hours after ingestion), patients with multiple ingestions over time, or chronic ingesters of APAP.

Activated charcoal does adsorb acetaminophen, and it is reasonable to administer charcoal up to 2 hours after ingestion. Acetaminophen is absorbed rapidly from the GI tract, so later use of charcoal is not warranted unless gastric emptying is likely to be delayed. Administration of activated charcoal will not interfere with subsequent administration of oral N-acetylcysteine (NAC) therapy.

TABLE 65.3 Stages of Acetaminophen Toxicity

Stage	Time Course (After Ingestion)	Characteristics
I	0–24 h	Asymptomatic or nausea, vomiting; normal LFT results
II	24–72 h (latent stage)	Right upper quadrant pain; abnormal LFT results and PT; renal dysfunction possible
III	72–96h (hepatic stage)	Encephalopathy, jaundice, bleeding, renal dysfunction; maximal hepatic injury, synthetic dysfunction
IV	4 days–2 weeks (recovery stage)	Recovery of liver function

LFT, Liver function test; *PT*, prothrombin time.

NAC is the antidote for APAP poisoning, but the optimal route and duration of treatment are still debated. NAC limits toxicity by combining with NAPQI and by serving as a precursor of glutathione, which inactivates NAPQI. For patients with a single, acute ingestion of APAP, the serum acetaminophen level assessed at least 4 hours after ingestion is compared with the Rumack-Matthew nomogram. Treatment with NAC is initiated in the United States if the value falls above the lower possible hepatotoxicity line. Only the initial APAP level is used in making the decision to initiate or continue NAC treatment. Subsequent levels are unnecessary unless extended-release preparations are ingested (see later text). The Rumack-Matthew nomogram is not useful for patients with multiple ingestions of APAP over time, chronic ingesters, or those ingesting extended-release forms (see later discussion). If APAP levels are not available, NAC treatment should be initiated if more than 150 mg/kg or 10 g acetaminophen is ingested. For extended-release APAP, a second level 4 hours after an initial nontoxic level should be evaluated to assess for delayed absorption. If the second value is above the lower line on the Rumack-Matthew nomogram, NAC treatment is initiated.

NAC is most effective in preventing toxicity if administered within 8 hours of ingestion. NAC therapy can be initiated pending results of the APAP level if the patient is presenting late or APAP level results will be delayed. The oral regimen for NAC includes a loading dose of 140 mg/kg followed by 17 oral maintenance doses of 70 mg/kg administered 4 hours apart (72-hour regimen). Because of the odor of the oral form, a nasogastric tube for administration and antiemetic therapy may be necessary to control vomiting, which occurs in up to 50% of patients. If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, the dose should be repeated. IV NAC is administered as a loading dose of 150 mg/kg over 60 minutes followed by 50 mg/kg infused over 4 hours and then 100 mg/kg infused over 16 hours (21-hour regimen). Anaphylactoid reactions may occur in 14% to 18% of patients with IV NAC. Oral and IV regimens of administering NAC are similar in efficacy.[23] However, either the oral regimen or prolonged IV NAC administration, both of which deliver a higher dose of NAC, may be more appropriate in patients who present later after ingestion (>18 hours) and when large amounts of APAP are ingested.[24,25] If the patient has a serum APAP level in the potentially toxic range, the aspartate aminotransferase or alanine aminotransferase level should be evaluated daily. If results are abnormal, additional tests, such as bilirubin, prothrombin time, creatinine, blood urea nitrogen, blood glucose, and electrolytes, should also be obtained. In patients with elevated liver enzymes, NAC may be continued beyond the full course of therapy until transaminases are decreasing.

Chronic ingesters of APAP or patients with multiple ingestions over time are problematic when determining the need to administer NAC. There are no established guidelines for administration of NAC in these circumstances and when patients present beyond 24 hours after ingestion. A marker of toxicity that may be useful is the evaluation of aspartate aminotransferase and alanine aminotransferase. If enzymes are elevated at the time of presentation (>50 IU/L) or the APAP level is greater than 10 µg/mL (>10 µmol/L), a course of NAC should be strongly considered. A course of NAC should also be administered to patients with hepatic failure caused by APAP.

Patients with evidence of toxicity from APAP should be monitored for signs and symptoms of hepatic failure. This includes evaluating mental status and frequently assessing blood glucose levels. If fulminant hepatic failure develops, appropriate consultation with a hepatologist should be obtained. Transplantation may be an option in severe cases.

Opioids

An epidemic of illicit and prescription opioid use has led to marked increases in associated morbidity and mortality. The rates of death from prescription opioid overdose quadrupled between 2000 and 2014 in the United States.[26] In addition, the rate of death from heroin use has increased sharply since 2010.[26] Prescription opioids can be abused through ingestion, nasal insufflation, inhalation, and IV use. Fentanyl (sometimes extracted from analgesic patches) and related drugs, such as acetyl fentanyl, butyryl fentanyl, and carfentanil (used in large animal sedation), are often abused intravenously but nasal insufflation has also been described. Heroin is rapidly absorbed by all routes of administration, including IV, intranasal, intramuscular, subcutaneous, and inhalation, but most fatal overdoses occur with IV administration. Toxicity depends on the potency of the agent, dose ingested, tolerance of the individual, and concomitant use of other drugs.

All opioids can result in a toxidrome characterized by depressed level of consciousness, respiratory depression, and miosis. However, manifestations may be variable depending on the drug used and the presence of other drugs or alcohol. Miosis is not seen with meperidine, propoxyphene, and tramadol toxicity. Although tramadol and tapentadol typically result in depressed level of consciousness and respiratory depression, presentations with agitation have also been described. Additional clinical findings may include hypotension, pulmonary edema, bronchospasm (heroin), ileus, nausea, vomiting, and pruritus. Seizures may be a manifestation of toxicity with meperidine, propoxyphene, and tramadol. Methadone use is associated with QT-interval prolongation and ventricular arrhythmias.

Diagnosis of an opioid overdose is made by characteristic clinical findings, exposure history, qualitative urine toxicology assay, and response to naloxone. Qualitative urine assays may not detect all opioid derivatives (e.g., fentanyl). Tramadol use may result in a false-positive urine toxicology assay for phencyclidine.[27]

The immediate priorities in a patient with opioid toxicity are support of ventilation, correction of hypotension, and reversal of the toxic effects with an opioid antagonist. If reversal of respiratory depression cannot be accomplished quickly, intubation may be necessary. Isotonic fluids should be administered for hypotension. Naloxone, a potent competitive opioid antagonist, is the antidote for opioid toxicity, including toxicity from tramadol and tapentadol. It can be administered intravenously, intramuscularly, subcutaneously, intranasally, by sublingual injection, by nebulization, or through an endotracheal tube. The initial dose of naloxone in a suspected opioid overdose is 0.04 to 2 mg; the lower dose should be considered in patients with chronic addiction to avoid precipitating acute withdrawal symptoms. Doses of 2 mg have been used with nebulization and intranasal administration. The goal of therapy is to restore adequate spontaneous respirations rather than complete arousal. Doses of naloxone up to 10 to 20 mg may be required to reverse the effects of synthetic opioids, such as pentazocine, methadone, and fentanyl.

The effects of naloxone last approximately 60 to 90 minutes, necessitating continued observation of the patient for possible resedation. Patients may require continuous infusion of naloxone to maintain adequate respirations, particularly with long-acting opioids. The dose for infusion is typically one-half to two-thirds of the initial amount of naloxone that reversed the respiratory depression administered on an hourly basis. Adjustments of the

dose should be made to achieve clinical endpoints and avoid withdrawal symptoms. Nalmefene, a long-acting opioid antagonist, has also been used to treat opioid overdoses, but prolonged withdrawal symptoms may be a concern.[28] Potential APAP toxicity should be considered in patients ingesting opioids formulated with APAP. Patients should also be observed for potential complications of opioid overdose, including aspiration pneumonitis and noncardiogenic pulmonary edema. Noncardiogenic pulmonary edema is usually self-limited (24–36 hours) and managed with supportive care that may include intubation and mechanical ventilation.[29] Other complications that may be related to injection drug use include wound botulism, endocarditis, rhabdomyolysis, and compartment syndrome.

Salicylates

Salicylates should be considered as a potential toxin if a metabolic acidosis with an anion gap of unknown cause is present. The uncoupling of mitochondrial oxidative phosphorylation by salicylates results in metabolic acidosis and hyperthermia, and the stimulation of medullary respiratory centers results in tachypnea and respiratory alkalosis. Initial symptoms of toxicity include tinnitus and nausea or vomiting. Systemic acidosis promotes penetration of salicylate into the CNS, resulting in a depressed level of consciousness, coma, and seizures. Coagulopathy, transient hepatotoxicity, and hypoglycemia may also develop. Noncardiogenic pulmonary edema occurs more frequently in chronic salicylate toxicity than in acute overdose. The organ dysfunction and acid-base findings of salicylate intoxication can mimic sepsis and mislead clinicians.

Activated charcoal can be used for GI decontamination. Salicylates in large ingestions or enteric-coated forms can result in gastric concretions providing a depot for continued absorption; multiple doses of activated charcoal can be considered in this situation or when levels continue to rise despite other therapy.[11,30] A salicylate ingestion is considered toxic if symptoms are present, if more than 150 mg/kg has been ingested, or if levels are higher than 35 mg/dL at 6 hours after ingestion. The Done nomogram was developed in pediatric ingestions and does not provide good clinical correlation with toxicity in adults. Acute intoxication with salicylate levels in excess of 35 mg/dL at 6 hours after ingestion should be treated with sodium bicarbonate to alkalinize the urine to a pH 7 to 8, which increases the renal clearance of salicylate metabolites through ion trapping.[12] Alkalemia shifts the gradient of movement of salicylate from brain and tissues to blood.

Fluid status must be closely monitored, along with coagulation parameters, complete blood cell count, acid-base status, electrolytes, and urine pH. Hemodialysis may be required for levels greater than 100 mg/dL in an acute ingestion, seizures, persistent alteration in mental status, refractory acidosis, persistent electrolyte abnormalities despite adequate therapy, or fluid overload resulting from sodium bicarbonate therapy. Additional indications for hemodialysis may include congestive heart failure (relative), noncardiogenic pulmonary edema, hepatotoxicity with coagulopathy, or renal insufficiency

Carbon Monoxide

CO poisoning may be accidental or intentional and continues to be a significant cause of morbidity in the United States. Sources of CO include motor vehicle exhaust fumes, gasoline-powered generators, poorly functioning heating systems, and inhaled smoke. CO binds to hemoglobin with an affinity 200 to 250 times greater than oxygen. Toxicities result from impaired release of oxygen at the tissue level, causing cellular hypoxia and possibly direct CO-mediated damage at the cellular level. The clinical manifestations of CO poisoning are nonspecific and may suggest other illnesses unless exposure is known or suspected. Headache, nausea, and vomiting are common. Cellular hypoxia may also result in confusion, angina, arrhythmias, syncope, and seizures. Tachycardia and tachypnea are frequently present as compensatory mechanisms for hypoxia. Classic findings of cherry red lips, cyanosis, and retinal hemorrhages occur rarely. Symptoms can range from mild to severe, and carboxyhemoglobin levels do not necessarily correlate with symptom severity. After recovery from acute CO exposure, delayed neuropsychiatric sequelae may occur.

Diagnosis requires a high level of suspicion. Carboxyhemoglobin levels can be measured in venous or arterial blood and must be interpreted carefully. Carboxyhemoglobin levels may be as high as 10% in smokers and are higher in urban compared with rural areas. An elevated level of carboxyhemoglobin may often be diagnostic, but a normal level does not rule out the diagnosis. The carboxyhemoglobin level may have decreased because of removal of the patient from the exposure and intervention with oxygen before hospital arrival.

Management of CO poisoning includes a detailed evaluation of neurologic and cardiorespiratory status. Acid-base status should be determined and an ECG examined for evidence of ischemia or arrhythmia. Oxygen is the antidote and shortens the half-life of carboxyhemoglobin by competing for binding with hemoglobin. High-concentration oxygen should be instituted as soon as possible and continued until the carboxyhemoglobin level has decreased to normal. Pulse oximetry overestimates arterial oxygenation because carboxyhemoglobin is misinterpreted as oxyhemoglobin. Analysis of arterial blood by co-oximetry is required for an accurate assessment of oxygen content. Intubation may be necessary in patients exposed to CO from fire. Hyperbaric oxygen therapy shortens the half-life of carboxyhemoglobin to 15 to 30 minutes compared with 40 to 80 minutes when patients breathe 100% oxygen. However, controversy exists over the specific indications for instituting hyperbaric oxygen therapy in CO poisoning.[31–33] Coma has been used as an indication for hyperbaric oxygen therapy; other suggested indications include a period of unconsciousness, neurologic findings other than headache, carboxyhemoglobin level greater than 40%, pregnancy with carboxyhemoglobin level greater than 15%, cardiac ischemia or arrhythmia, history of ischemic heart disease with carboxyhemoglobin level greater than 20%, and symptoms that do not resolve with normobaric oxygen after 4 to 6 hours. Hyperbaric oxygen treatment may decrease postexposure cognitive deficits.[34]

Cardiovascular Drugs

Cardiovascular drugs are increasingly involved in adult overdose exposures and fatalities. Although a large number of cardiovascular drugs are available, the most clinically relevant agents are β-blockers, calcium channel blockers, and digoxin. Note that the clinical manifestations and management of β-blocker and calcium channel blocker toxicity share similarities.[35]

β-Blockers

β-Adrenergic blockers differ in their lipid solubility, oral availability, first-pass effect, protein binding, metabolism, β_1 selectivity, membrane stabilization, and intrinsic sympathomimetic activity. Clinical findings with β-blocker toxicity include bradycardia, atrioventricular (AV) conduction abnormalities (QRS prolongation,

first-degree AV block), and hypotension. The hypotension is primarily due to the negative inotropic effects of these agents. With the exception of sotalol, ventricular fibrillation and other arrhythmias are not usually seen. The more lipophilic β-adrenergic antagonists, such as propranolol, metoprolol, acebutolol, and timolol, can cause delirium, coma, and seizures. Hypoglycemia is rare in adults. Toxicity generally occurs within 6 hours of ingestion of immediate-release preparations. Ingestion of sotalol or extended-release preparations may result in delayed toxicity, and these patients should be observed for 24 hours or longer if absorption is delayed. Propranolol is associated with the highest mortality rate, which may reflect its greater toxicity attributable to membrane-stabilizing effects.[36] Bradyarrhythmias and asystole usually precede death.

GI decontamination techniques may be considered based on the specific drug and quantity involved, time of ingestion, and clinical condition of the patient. Extracorporeal removal is ineffective for lipid-soluble β-blockers because of the large volume of distribution. Hemodialysis may be rarely considered for atenolol, a water-soluble β-blocker.

The initial focus of treatment is to reverse hypotension rather than to increase heart rate. Increases in heart rate do not always result in improvements in blood pressure. Although atropine is frequently administered for bradycardia, it is usually ineffective. Isotonic fluids can be administered for hypotension, but caution is warranted owing to the negative inotropic effects of β-blockers on myocardial function. Pharmacologic interventions that have been used in β-blocker overdoses include glucagon, calcium, high-dose insulin therapy, catecholamines, IV lipid emulsion, and phosphodiesterase inhibitors.[35] Many patients with significant toxicity require treatment with multiple agents. Glucagon is administered as 2 to 5 mg IV followed by a dose of 10 mg if necessary. If there is a positive clinical response, a continuous infusion (usually 2–10 mg/h) is necessary owing to the short duration of action of glucagon. Glucagon is a chronotropic and inotropic agent that stimulates cyclic adenosine monophosphate by bypassing adrenergic receptors. Evidence for efficacy is limited to animal studies and use as a first-line agent is debated.[37] Adverse effects of glucagon include nausea, vomiting, hyperglycemia, and hypocalcemia.

Calcium salts may be considered as another intervention for reversing hypotension if digoxin ingestion has been excluded.[35,38] Although calcium is more likely to be effective in calcium channel blocker toxicity, efficacy has been reported in some cases of β-blocker toxicity. Calcium chloride 10% (1 g by slow IV push, preferably through a central venous catheter) may be administered initially, and up to 3 g is recommended. If access is limited, 10% calcium gluconate can be administered but an increased dose is required.

High-dose regular insulin infusions and glucose administration to maintain euglycemia have been shown to be effective in β-blocker and calcium channel blocker toxicity and are now often recommended as first-line therapy.[38,39] The beneficial effect may be caused in part by the metabolic effects of decreasing cardiac uptake of free fatty acids and increasing carbohydrate use. Reported insulin doses have been variable, but a bolus dose of regular insulin 1 unit/kg is recommended followed by an infusion of 1 unit/h.[39] Doses of insulin up to 10 units/h may be considered if the patient is unresponsive to interventions. A glucose infusion should be initiated at the same time to maintain euglycemia and a glucose bolus may also be needed. Careful monitoring of glucose and potassium is required.

Catecholamine infusions are frequently administered in β-blocker toxicity concomitantly with other interventions. No agent is known to be more effective than others, and response to various agents is often inconsistent in these clinical situations. Very large doses may be required owing to the β-adrenergic receptor antagonism; as a result, tachyarrhythmias can occur. The combination of dobutamine and norepinephrine may allow for titration of desired effects against cardiac output and blood pressure. Alternatively, phenylephrine may be used in conjunction with dobutamine. Epinephrine has been shown to be more effective than isoproterenol.[40] Infusion of any vasoactive agent should be started at usual doses and rapidly escalated to achieve a clinical response, but it should be stopped if there is a further fall in blood pressure or no beneficial effect.

Case reports suggest that bolus administration of 20% lipid emulsion (1.5 mL/kg lean body mass) may be beneficial in refractory hemodynamic collapse owing to β-blocker and calcium channel blockers. A repeat bolus can be given for persistent instability. An infusion of 0.25 mL/kg per minute is usually continued for at least 10 minutes after hemodynamic stabilization. The exact mechanism of effect is unknown, but it has been proposed that lipids serve as a "sink" for the toxin that reduces free drug levels and limits distribution to tissues. Another possibility is that the fatty acids of lipids improve inotropy by providing an energy source for myocytes.[41] Adverse effects of lipid emulsion include interference with laboratory analyses owing to lipemia, pancreatitis, acute respiratory distress syndrome, and potentially asystole.[41,42]

Phosphodiesterase inhibitors such as milrinone and enoximone have been reported to be effective in some cases of human ingestions.[35,38] These agents may be considered in patients in whom other pharmacologic interventions fail, although experience is limited and they may cause further hypotension through peripheral vasodilation. Invasive hemodynamic monitoring may be needed in some patients.

Ventricular pacing (transthoracic or transvenous) may be considered, but electrical capture is often unsuccessful. Even when pacing increases the heart rate, blood pressure often fails to improve. Intraaortic balloon pump, extracorporeal membrane oxygenation, and cardiopulmonary bypass are potential options to maintain circulation until drug is metabolized in the unstable patient unresponsive to other interventions.

Calcium Channel Blockers

Calcium channel blockers have varying degrees of negative inotropic effect (verapamil), vasodilatory effect (nifedipine, diltiazem), depression of rate of discharge of the sinus node (verapamil, diltiazem), and slowed conduction through the AV node (verapamil, diltiazem). Verapamil and diltiazem are most commonly associated with severe toxicity. All are well absorbed with clinically significant protein binding (80%) and a large volume of distribution. All undergo extensive hepatic metabolism, many through the cytochrome P450 system, and have varying degrees of active metabolites.

Signs and symptoms of toxicity occur within 6 hours for immediate-release formulations but are delayed for sustained-release preparations. Gastric concretions can form, acting as a further reservoir for sustained absorption. Nausea, vomiting, and hypotension are usually accompanied by bradycardia with verapamil and diltiazem or reflex tachycardia with nifedipine. Conduction abnormalities associated with verapamil and diltiazem may include first-degree block, Wenckebach block, junctional rhythm, third-degree AV block, and AV dissociation. Hypoperfusion secondary to decreased cardiac output may lead to tissue ischemia, metabolic acidosis, and CNS symptoms such as lethargy, confusion, and

coma. Hyperglycemia can result from a decrease in insulin secretion and insulin resistance and may be a marker of severe exposure.

Activated charcoal is the preferred method of GI decontamination in recent ingestions. As with β-blockers, initial treatment of symptomatic calcium channel blocker overdose should be aimed at treating hypotension and significant conduction defects. Calcium salts should be administered as first-line therapy in toxicity owing to calcium channel blockers.[43] The recommended dose is 1 to 2 g of 10% calcium chloride every 10 to 20 minutes. If blood pressure improves with calcium chloride, an infusion can be considered at doses of 0.2 to 0.4 mL/kg per hour. Ionized calcium concentrations can be monitored, but high serum concentrations may be necessary for beneficial effects. High-dose insulin therapy (dosed as for treatment of β-blocker toxicity) should be initiated if calcium is ineffective in reversing toxicity.[39,43] As with β-blocker overdose, large doses of catecholamines may be required. Norepinephrine can be used to increase blood pressure, and epinephrine may be effective in improving contractility and heart rate.[43] Use of vasopressin alone is not recommended. Atropine can be administered for bradycardia but is often ineffective and any effects are transient.

Second-line therapies should be considered when toxicity does not respond to initial interventions. Higher doses of insulin and lipid emulsion administration are options.[41,43] Glucagon and transvenous pacing can also be considered as second-line interventions.[37] Venoarterial extracorporeal membrane oxygenation or cardiopulmonary bypass may be helpful for refractory hypotension.

Digoxin

Digoxin toxicity results from the complex influence of the drug on the electrophysiologic properties of the heart, as well as the cumulative result of the direct, vagotonic, and antiadrenergic actions of digoxin. The alterations in cardiac rate and rhythm occurring in digoxin toxicity can produce almost every type of arrhythmia. Toxicity should be suspected if there is evidence of increased automaticity (ectopic rhythms) or depressed conduction (prolonged PR interval, AV node blockade, decreased QT interval). Early in acute intoxication, depression of sinoatrial or AV node function may be reversed by atropine, but atropine subsequently does not reverse the direct and vagomimetic actions of the drug. Noncardiac manifestations of acute digitalis intoxication include anorexia, confusion, visual disturbances, nausea or vomiting, and increased potassium ion concentrations.

GI decontamination in digoxin overdose consists of activated charcoal, if the timing is appropriate. Late administration of activated charcoal or MDAC may be considered owing to enterohepatic metabolism of the drug.[16] Forced diuresis, hemoperfusion, and hemodialysis are not effective in hastening the elimination of digoxin because of the large volume of distribution (4–10 L/kg). Only 1% of total body stores of digoxin is present in the serum; of that, 25% is protein bound.

The treatment for life-threatening digitalis toxicity is administration of digoxin-specific antibody fragments.[44,45] Administration of digoxin-specific antibody fragments results in a sharp decrease in free digoxin levels, an increase in total serum digoxin, an increase in renal excretion of digoxin bound to Fab (fragment, antigen binding), and a decrease of serum potassium toward normal. The time to response is approximately 30 minutes (range 20–90 minutes). Indications for administration of digoxin-specific antibody fragments include life-threatening tachy-bradyarrhythmias, potassium concentration greater than 5 mEq/L in the setting of suspected digoxin toxicity, rapidly progressive cardiac or GI symptoms, an increasing potassium concentration, serum digoxin concentration greater than 15 ng/mL at any time or more than 10 ng/mL at steady state, ingestion of more than 10 mg of digoxin in a previously healthy adult, and to establish the diagnosis. In the event that digoxin-specific fragments are not immediately available, other interventions may be considered. Atropine may work for severe supraventricular bradyarrhythmias or varying degrees of AV block if administered early. β-Blockers may be used for supraventricular and ventricular tachycardias. Magnesium sulfate may be an effective temporizing measure for the treatment of ventricular arrhythmias in the absence of digoxin-specific antibodies, even in the presence of hypermagnesemia. Limited evidence suggests phenytoin or lidocaine may be considered. All class Ia antiarrhythmic drugs are contraindicated. Isoproterenol should be avoided because there is an increased risk of ventricular ectopy in the presence of toxic digoxin levels. Transthoracic or transvenous pacing has limited value in this setting.[45]

Hypokalemia, hyperkalemia, and hypomagnesemia can exacerbate digoxin cardiotoxicity and should be aggressively corrected. When hyperkalemia exists with toxic digoxin levels and ECG evidence of potassium toxicity, the serum potassium should be treated with conventional interventions if digoxin-specific Fab fragments are not immediately available. Calcium administration in the presence of digoxin toxicity is not usually recommended for hyperkalemia because it may worsen digoxin-induced intracellular hypercalcemia. Intractable ventricular fibrillation or tachycardia may result.

After digoxin-specific antibodies have been administered, serum digoxin levels are no longer reliable because they represent free and bound digoxin. The digoxin-specific antibodies are effective even in anephric patients. In renal insufficiency, the Fab half-life is prolonged 10-fold with no change in volume of distribution. Fab concentrations remain detectable for 2 to 3 weeks. Although there is no dissociation of the complex in renal insufficiency, free digoxin levels rebound (redistribution from tissue sites) and Fab fragments leave the vascular space over 7 to 14 days.[46] During this time symptoms may recur and a second dose may be necessary.

Cyanide

Inhalation or ingestion of cyanide is rare but can produce severe poisoning rapidly leading to death. A history of potential cyanide exposure is extremely important in suggesting the diagnosis because rapid cyanide assays are not available and clinical manifestations are nonspecific. Cyanide exposure may occur from incomplete combustion of products containing carbon and nitrogen in fires and from industrial processes such as electroplating, metal refining, photography, fumigation, and gold or silver extraction. Cyanogenic substances are also found in a variety of plants, although severe toxicity is rare. Iatrogenic cyanide intoxication may occur during nitroprusside administration with high doses or in the presence of hepatic dysfunction.

Cyanide is a nonspecific inhibitor of enzymes; inhibition of mitochondrial cytochrome oxidase results in anaerobic metabolism with decreased adenosine triphosphate production, lactic acidosis, and decreased oxygen utilization. Clinical characteristics of acute cyanide poisoning are rapid deterioration, loss of consciousness, anion gap metabolic acidosis, and cardiopulmonary failure. CNS signs and symptoms include headache, anxiety, agitation, confusion, seizures, and coma. Cardiovascular responses manifest as initial bradycardia and hypertension, followed by hypotension with reflex tachycardia that can progress to terminal bradycardia and hypotension. Ventricular arrhythmias and myocardial ischemia also occur.

Pulmonary findings include cardiogenic and noncardiogenic pulmonary edema. GI symptoms of abdominal pain, nausea, and vomiting are less common. A bitter almond odor from vomitus or gastric contents is described in cyanide poisonings but may not be present and is often not detectable by health care personnel.

Early diagnosis, rapid administration of antidote, and aggressive supportive care are necessary to stabilize patients with severe cyanide poisoning. A cyanide level may be requested for confirmation, but results will not be available to guide immediate care. Intubation and mechanical ventilation are usually required. Fluids, inotropes, and vasopressors may be indicated for hypotension. If the poison was ingested, gastric lavage may be considered but should not delay the administration of antidote.

As soon as cyanide poisoning is suspected, hydroxocobalamin or a cyanide antidote kit should be administered.[47] Hydroxocobalamin, a vitamin B_{12} precursor administered at an initial dose of 5 g, is a commonly used antidote for acute cyanide poisoning.[48] It displaces cyanide from the cytochrome oxidase and forms cyanocobalamin, which is then excreted in the urine or metabolized by hepatic rhodanese. A second dose of 5 g can be administered for severe poisoning or lack of clinical response. Thiosulfate has been administered with hydroxocobalamin but efficacy is unclear.

The cyanide antidote kit contains amyl nitrite ampules, 3% sodium nitrite, and 25% sodium thiosulfate. Amyl nitrite is used initially when lack of IV access delays the administration of sodium nitrite. It is an immediate source of nitrite that oxidizes hemoglobin to methemoglobin, which has a higher affinity for cyanide than cytochrome oxidase. Cyanmethemoglobin is formed, which eventually dissociates, but at such a rate that cyanide can be metabolized by hepatic rhodanese. The ampules are crushed in a gauze sponge and initially intermittently inhaled. This is followed by IV administration of 300 mg of sodium nitrite (10 mL 3% solution) as soon as possible. The optimum methemoglobin level that should be achieved is unknown, but clinical responses have occurred with levels of 3.6% to 9.2%. The second component of the antidote package is 25% sodium thiosulfate (12.5 g for adults), which provides sulfur for conversion of cyanide to thiocyanate by hepatic rhodanese. Thiocyanate is then excreted by the kidneys. Hyperbaric oxygen has also been proposed for treating cyanide toxicity, but data supporting efficacy are not available.

Dietary and Nutritional Agents

Dietary and nutritional products are categorized as supplements and can be marketed without testing for safety or efficacy. Although some herbs and supplements may have inherent toxicity, poisoning may result from product misuse, contamination of the product, or through interaction with other medications.[49–51] Patients and their families should always be questioned regarding use of nutritional supplements, herbal preparations, weight loss or performance-enhancing products, energy drinks, or natural remedies when considering possible toxin exposure as a cause of clinical abnormalities. Adverse effects resulting from these products should be reported to the appropriate authorities such as U.S. Food and Drug Administration.

Herbal teas may contain aconitine or digoxin-like substances.[52] Management is usually supportive. A digoxin level should be obtained in any patient demonstrating symptoms consistent with digoxin toxicity. The level may not correlate with clinical findings because numerous cardiac glycosides will not cross-react in the digoxin immunoassay. With significant toxicity, digoxin-specific antibody fragments should be administered.

Products containing ephedrine and ephedrine-free products are often used for weight loss. These products can result in manifestations similar to a sympathomimetic syndrome with cardiovascular and cerebrovascular complications.[53–55] Similarly, caffeinated energy drinks can precipitate atrial and ventricular arrhythmias.[56]

Hepatoxicity may occur with numerous single herbal and nutritional agents such as kava and black cohosh but also occurs with marketed weight loss and performance-enhancing products with multiple, often ill-defined ingredients.[57]

Toxicity from ingestion of herbal preparations and nutritional supplements may result from product contaminants. Products may contain heavy metals, unlisted drugs, or other ingredients.[58] The California Department of Health Services, Food and Drug Branch, screened 260 Asian patent medicine products and found 32% contained undeclared pharmaceuticals or heavy metals.[59] Unusual symptoms or toxidromes in patients ingesting such products may require the assistance of the local health department or toxicologist to identify a possible toxin.

Methemoglobin Inducers

Methemoglobin results from the oxidation of ferrous iron in hemoglobin to ferric iron. Methemoglobin is not able to bind oxygen and high concentrations lead to a functional anemia that results in cellular hypoxia by limiting oxygen delivery. The most common inducers of methemoglobin in the health care setting are topical spray anesthetics (benzocaine, tetracaine, butyl aminobenzoate) and dapsone. Procedures using topical anesthetics that are associated with the development of methemoglobinemia are transesophageal echocardiography, GI endoscopy, intubation, and bronchoscopy.[60] Predisposing factors include sepsis, anemia, and hospitalization. Dapsone may cause prolonged methemoglobinemia in patients with AIDS because of its long half-life.

Clinical manifestations are related to the impaired oxygen delivery, and the severity varies with the concentration. Cyanosis is apparent when methemoglobin concentrations are 10% or greater owing to the deep color of methemoglobin. Concentrations of 20% to 50% may cause headache, dyspnea, dizziness, and fatigue, and concentrations greater than 50% can result in metabolic acidosis, arrhythmias, tachypnea, seizures, lethargy, and depressed level of consciousness. Diagnosis requires measurement of methemoglobin concentrations in arterial or venous blood gas assays by co-oximetry. Pulse oximetry is not usually accurate for determining the presence or concentration of methemoglobin depending on the specific characteristics of the monitor. A helpful clue is the observance of a saturation gap between the measured oxyhemoglobin saturation by pulse oximeter and the calculated oxyhemoglobin saturation provided by arterial blood gas assay. In the presence of methemoglobin, the calculated concentration will be higher than the measured saturation by pulse oximeter. Co-oximetry is required to identify the abnormal hemoglobin.

Methylene blue is the antidote for methemoglobinemia and should be administered when there are significant symptoms indicating impaired oxygen delivery.[61] In addition, individuals with lower methemoglobin concentrations may also warrant treatment if further oxidant stress may increase the concentrations. High-flow oxygen should be administered. The usual dose of methylene blue is 1 to 2 mg/kg IV over 5 minutes. Clinical improvement in symptoms and cyanosis is usually evident within a few minutes. A second dose can be administered if cyanosis does not resolve within 1 hour. Although there is concern for methylene blue causing hemolysis in patients with glucose-6-phosphate

dehydrogenase (G6PD) deficiency, this information will not usually be known at the time of treatment and methylene blue should not be withheld in symptomatic patients.

Organophosphate and Carbamate Agents

Organophosphates and carbamates are cholinesterase inhibitors that are usually a component of insecticides. However, nerve agents used in chemical warfare such as sarin and VX are also organophosphate compounds. Cholinesterase inhibitors exert toxicity by blocking the activity of acetylcholinesterase, resulting in acetylcholine accumulation at cholinergic receptors. When organophosphates or carbamates bind to acetylcholinesterase, they form a conjugate that is infinitely more stable than the acetylcholine-acetylcholinesterase conjugate. The carbamate-acetylcholinesterase bond spontaneously hydrolyzes in minutes to hours so that acetylcholinesterase is eventually regenerated (reversible binding). Most carbamate poisonings spontaneously resolve within 24 to 48 hours and do not have significant morbidity or mortality risk. Phosphorylated or phosphonylated enzymes resulting from organophosphate exposure, however, degrade over days to weeks, making acetylcholinesterase essentially inactive (irreversible binding). For the physiologic enzyme activity to return, new enzyme must be generated or antidote given. After the acetylcholinesterase is phosphorylated over 24 to 48 hours, "aging" occurs, and the enzyme can no longer spontaneously hydrolyze and is permanently inactivated.[62]

Organophosphates may be absorbed by virtually any route, including transdermal, transconjunctival, inhalation, across the GI or genitourinary mucosa, and through direct injection. Onset of systemic symptoms may occur in 5 minutes with inhalation, and most patients develop symptoms within 12 hours of ingestion, unless exposure to fat-soluble organophosphates (e.g., fenthion, clorfenthion) has occurred or if significant metabolic activation must occur (e.g., parathion, malathion). Cholinesterase poisoning manifests as a cholinergic toxidrome and signs and symptoms are listed in Table 65.4. Pulmonary toxicity from bronchorrhea, bronchospasm, and respiratory depression is the primary concern.[63]

Diagnosis of poisoning with these agents is usually based on a history of exposure and clinical manifestations. Early intubation is usually indicated with significant toxicity, and use of succinylcholine should be avoided because of prolonged paralysis. Initially, atropine 2 to 4 mg is given intravenously and repeated every 5 minutes with increasing doses, if needed, to reverse muscarinic toxicity. If there are no CNS symptoms, glycopyrrolate may be substituted. The endpoint of atropinization is clearing of secretions. Tachycardia is not a contraindication to atropine use because it may represent hypoxia and autonomic stimulation. The tachycardia may resolve with improved oxygenation. In massive exposures, hundreds of milligrams of atropine may be required over days or weeks. A continuous infusion of atropine should be initiated at 0.05 mg/kg per hour and titrated to effect. After the patient's condition is adequately stabilized, atropine must be carefully and slowly withdrawn because secretions will likely return if the drug is still bound to acetylcholinesterase or leaches from fat stores. Inhaled ipratropium can be considered if bronchoconstriction is present.[62]

Atropine does not reverse nicotinic effects, and patients with significant respiratory muscle weakness are usually treated with an oxime. Oximes regenerate acetylcholinesterase at muscarinic, nicotinic, and CNS sites. Treatment with oximes may be most effective when started early. Oximes are usually continued as long as atropine is continued. The evidence for benefit of any oxime in pesticide poisoning is limited.[64] Pralidoxime (2-PAM) is available in the United States and is usually administered as a loading dose (1 to 2 g in normal saline solution 500 mL administered over 30 minutes) and then as a continuous infusion at 200 to 500 mg/h to maintain serum levels higher than 4 μg/L.[65] Higher dosing regimens have also been proposed.[63] Pralidoxime may also be protective against the development of the intermediate syndrome and other long-term neurologic sequelae. Pralidoxime therapy is usually not needed if the toxin is known to be a carbamate.

In addition to acute toxicity, organophosphates may cause persistent effects, which may manifest while the patient is in the ICU and last several weeks to months. These effects include organophosphate-induced delayed neurotoxicity and delayed polyneuropathy that occur 1 to 3 weeks after exposure.[62] Recovery may occur gradually or not at all. Another complication is intermediate syndrome.[66] The syndrome develops 24 to 96 hours after resolution of an acute, severe cholinergic crisis, and patients develop acute respiratory paralysis, weakness in the bulbar musculature, nuchal weakness, proximal limb weakness, and depressed reflexes. Electromyography studies show decremental conduction with repetitive nerve stimulation and suggest both presynaptic and postsynaptic nerve impairment. Recovery takes 2 to 4 times longer than the development.

TABLE 65.4 Signs and Symptoms of Cholinesterase Poisoning

Muscarinic Effects	Nicotinic Effects	CNS Effects
Salivation	Muscle fasciculations, cramping, weakness	Restlessness
Lacrimation	Diaphragmatic fatigue	Headache
Urination	Respiratory failure	Tremor
Diarrhea	Areflexia	Drowsiness
Nausea, vomiting	Paralysis	Confusion, delirium
Bronchorrhea	Hypertension	Slurred speech
Bronchoconstriction	Mydriasis	Ataxia
Miosis	Tachycardia	Seizures
Bradycardia		Psychosis
		Respiratory depression

CNS, Central nervous system.

Psychotropic Drugs

Cyclic Antidepressants

Deaths caused by overdose with cyclic antidepressants have declined significantly because of the increasing use of alternative antidepressants. The principal toxicities of cyclic antidepressants result from central and peripheral anticholinergic activity, α-adrenergic antagonism, and inhibition of norepinephrine reuptake. They also exert a membrane-depressant local anesthetic effect on the myocardium by blocking rapid sodium influx during phase 0 of the action potential. Clinical toxicities include a depressed level of consciousness, wide-complex arrhythmias, seizures, and hypotension. Acidosis, hypoxia, and seizures may increase the risk of wide-complex arrhythmias. Anticholinergic effects include mydriasis, fever, dry skin, delirium, agitation, tachycardia, ileus, and urinary retention. Life-threatening events usually occur within 6 hours of ingestion,

most often in the first 2 hours.[67] Several electrocardiographic criteria have been proposed to predict complications: QRS duration greater than 0.1 second correlates with risk of seizures, QRS duration greater than 0.16 second correlates with increased risk of arrhythmias, and the presence of an R wave in lead aVR greater than 3 mm predicts seizures and arrhythmias.[68,69] However, the performance of these criteria in predicting complications including death is relatively poor.[70]

If poisoning with a cyclic antidepressant is suspected, electrocardiographic monitoring should be instituted and IV access obtained. Intubation may be needed in patients with CNS depression who are unable to protect their airway. If wide-complex arrhythmias (or ECG changes described previously), hypotension, or seizures are present, stabilization requires immediate alkalinization of the blood and sodium loading with sodium bicarbonate.[71] Sodium bicarbonate should be administered in 50 to 100 mEq (1–2 mEq/kg) boluses to alkalinize the blood pH to 7.5 to 7.55. Clinical endpoints are normalization (narrowing) of the QRS complex, reestablishment of an adequate blood pressure, and termination of seizure activity. Alkalinization appears to decrease the free drug by increasing protein binding and shifting the concentration gradient away from tissues. Sodium loading may have a greater benefit by overcoming the blockade of the myocardial sodium channels. The bolus doses of sodium bicarbonate should be immediately followed with a continuous infusion, which can be prepared by adding 150 mEq (sodium bicarbonate) to 1 L of 5% dextrose in water. This should be titrated to the desired blood pH, QRS interval, and blood pressure. The infusion may be discontinued after 4 to 6 hours if the width of the QRS complex remains less than 100 msec without the administration of sodium bicarbonate. Hyperventilation to achieve blood alkalinization may be less effective but useful in patients who cannot tolerate the sodium and volume load or in those in whom pulmonary edema develops from treatment with sodium bicarbonate.[71,72] Hyperventilation without the administration of sodium bicarbonate may also be considered for patients with cerebral edema, head trauma, or poorly controlled congestive heart failure. Hypertonic saline solution has been effective in treating cardiac toxicity refractory to initial blood alkalinization.[73,74]

If torsades de pointes is associated with QT prolongation, magnesium sulfate 1 to 2 g IV over 2 to 5 minutes should be administered.[71] Hypotension refractory to volume expansion is best treated with a direct-acting catecholamine such as norepinephrine or phenylephrine in the setting of depleted norepinephrine stores.[75] If hypotension remains refractory to fluids and vasopressors, the use of an intraaortic balloon pump may be considered as a temporizing measure. IV lipid emulsion has also been reported to successfully treat refractory hemodynamic instability associated with cyclic antidepressant toxicity.[41]

After the patient with a known or suspected cyclic antidepressant overdose has been stabilized and the airway protected, activated charcoal is indicated. Gastric lavage should be performed only if the patient is seriously ill and the ingestion occurred within 1 hour of presentation. A second dose of activated charcoal may be given in several hours if it seems plausible that the drug still remains in the GI tract in the case of a massive ingestion or hypotension. MDAC to enhance elimination is not warranted given the extremely large volume of distribution (10–50 L/kg) and the low-protein binding of cyclic antidepressants.[16] Forced diuresis, hemodialysis, and hemoperfusion are ineffective. Physostigmine should also be avoided because of the potential anticholinergic toxicity of seizures and asystole.

If the patient has had altered mental status, seizures, or cardiac arrhythmia, the patient should remain in the ICU for 12 hours after all supportive therapeutic interventions have been discontinued. If the patient remains asymptomatic with a normal ECG during this phase of observation, the patient may then be transferred for additional care.

Lithium

Although lithium is used to treat bipolar affective disorder and other psychiatric disorders, its narrow therapeutic index predisposes to toxicity.[76] After oral ingestion, lithium is absorbed within 1 to 2 hours, reaching peak blood levels in 2 to 4 hours with regular preparations or in 4 to 12 hours with sustained-release preparations. Lithium does not bind to plasma proteins and is excreted almost entirely by the kidneys. Toxicity may occur with acute, acute on chronic, or chronic ingestions. Drugs that increase lithium reabsorption (angiotensin-converting enzyme inhibitors, thiazides, spironolactone, nonsteroidal antiinflammatory drugs), sodium restriction, volume depletion, and intrinsic renal dysfunction increase the risk of toxicity. Lithium levels do not necessarily correlate with toxic symptoms. With an acute ingestion, the patient may be asymptomatic with a lithium level of 6 to 8 mmol/L. In chronic lithium ingestion, a high total-body lithium burden results in more toxicity at lower serum levels.

The clinical presentation of patients with lithium toxicity varies with the type of ingestion. In an acute ingestion, nausea, vomiting, and diarrhea occur early with CNS symptoms developing later because of a delay in tissue distribution. In chronic ingestions, neurologic abnormalities are usually the major presenting manifestations. Patients with acute on chronic ingestions may manifest GI and neurologic symptoms. Neurologic abnormalities include tremor, hyperreflexia, agitation, fasciculations, clonus, and altered mental status. Confusion may be followed by lethargy, coma, and seizures. The tremor, hyperreflexia, and clonus usually precede altered mental status. Lithium can impair urine-concentrating ability in acute ingestions and cause nephrogenic diabetes insipidus and renal dysfunction in chronic ingestions that result in volume depletion. Although myocardial dysfunction and rhythm abnormalities have been reported in lithium toxicity, they occur infrequently. Lithium toxicity may produce flattened or inverted T waves and U waves on ECG.

Lithium toxicity is confirmed by assessment of the serum lithium level. A lithium level should be assessed immediately and 2 hours later to evaluate for increasing levels. Levels higher than 2.5 mmol/L in a chronic ingestion or higher than 4 mmol/L in an acute ingestion are potentially life-threatening. Renal function and volume status should also be assessed.

Management decisions in treating lithium toxicity may depend on the type of ingestion (acute versus chronic) and the product ingested (regular versus sustained-release). Lithium is not adsorbed by activated charcoal, but charcoal may be administered if other drugs are ingested or suspected. A forced diuresis is not effective in enhancing lithium excretion, but isotonic fluids should be administered to replete and maintain intravascular volume and promote adequate urine output.[76,77] Diuretics can worsen lithium toxicity and should be avoided. WBI has been proposed for GI decontamination with acute or acute on chronic ingestions, ingestion of sustained-release products, or when serial lithium levels are rising. Despite the lack of proven clinical benefit, this approach may be considered with appropriate precautions. Hemodialysis is effective in removing lithium, but indications for treatment and duration of therapy have varied.[78] Proposed indications that have

not been validated include renal dysfunction, severe neurologic dysfunction, inability to tolerate fluid replacement, lithium level higher than 4 or 5 mmol/L in an acute overdose, and lithium level higher than 2.5 mmol/L in chronic toxicity. The lithium level, duration of exposure, and severity of clinical symptoms should be balanced against the risks of the procedure before initiating hemodialysis. Hemodialysis clears lithium only from the plasma, and a rebound increase can develop from drug redistribution. A lithium level should be assessed immediately after hemodialysis and 6 to 8 hours later. Repeat dialysis can be considered if the lithium level increases or neurologic toxicity persists at that time. Although a lithium level of 1 mmol/L is recommended as the endpoint for hemodialysis, no systematic investigations have established the ideal endpoint for optimal outcome. Because of redistribution of lithium, improvement of neurologic toxicity lags behind the decrease in plasma level. Prolonged monitoring of lithium levels may be necessary, especially when sustained-release preparations are ingested. Continuous renal replacement therapy has also been used to remove lithium and may be associated with less rebound.[78] This technique results in a slower lithium clearance compared with hemodialysis and is not recommended if hemodialysis is available and can be tolerated. Sodium polystyrene sulfonate resin has been proposed to bind and remove lithium, but it is not currently recommended and may result in hypokalemia, hypernatremia, and fluid overload.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) and related antidepressants have decreased lethality and fewer adverse cardiovascular effects compared with cyclic antidepressants. Manifestations of an acute SSRI overdose may include nausea, vomiting, dizziness, blurred vision, and rarely CNS depression. Seizures and a wide QRS complex occur rarely but may be more likely with citalopram and bupropion, a unicyclic antidepressant. A syndrome characteristic of SSRIs is the serotonin syndrome, which may occur after a single dose, therapeutic doses, overdose, or when combined with other serotonergic agents, such as monoamine oxidase inhibitors, cyclic antidepressants, lithium, opioids (meperidine, tramadol, dextromethorphan, and pentazocine), amphetamine, serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), trazodone, and drugs that inhibit hepatic cytochrome P450.[79,80] The pathophysiology is related to excessive stimulation of central and peripheral serotonergic receptors. Clinical manifestations include altered mental status ranging from agitation to coma; autonomic dysfunction including diaphoresis, tachycardia, hyperthermia, unstable blood pressure, and diarrhea; and neuromuscular abnormalities that may range from tremors to myoclonus and rigidity.[80] Severe cases may be complicated by rhabdomyolysis, renal failure, disseminated intravascular coagulation, or acute respiratory distress syndrome.

Management of an acute overdose of SSRIs is largely supportive. Gastric lavage is not warranted because of the low toxicity of these compounds, but use of activated charcoal may be considered. An ECG should be obtained to assess for a wide QRS complex or other electrocardiographic abnormality. Although clinical experience is limited, there are reports of sodium bicarbonate administration resulting in narrowing of the QRS complex. The treatment of serotonin syndrome is primarily supportive therapy after discontinuing the precipitating agents. Intubation and mechanical ventilation may be necessary for patients with significant alteration of mental status. Benzodiazepines are useful for control of agitation and external cooling for sustained hyperthermia. Rarely, neuromuscular blockers may be necessary for control of muscle rigidity or tremor. The syndrome usually resolves in 24 to 72 hours. Treatment of patients with serotonin antagonists has been proposed, but experience is limited to case reports. Cyproheptadine in varying dose regimens (12–32 mg/24 h) has been most commonly recommended as a treatment option. Currently there is no role for the use of bromocriptine or dantrolene.[80]

Sedatives

Benzodiazepines

Although ingestions are relatively common, fatalities from benzodiazepines alone are uncommon. Benzodiazepine overdose results in a typical sedative-hypnotic toxidrome characterized by depressed level of consciousness, respiratory depression, hyporeflexia, and potentially hypotension and bradycardia. The clinical manifestations may be exacerbated by concomitant ingestion of other agents with sedating properties, such as ethanol, opioids, or antidepressants. Alprazolam is commonly seen in overdoses owing to wide availability and may result in greater toxicity than other benzodiazepines.[81] Flunitrazepam is a benzodiazepine not approved for use in the United States that has been associated with sexual assault. Diagnosis of benzodiazepine ingestion is primarily based on the history and clinical manifestations. Many benzodiazepines are detected in qualitative urine toxicology assays, but a negative test result does not rule out exposure. If warranted, gas chromatography/mass spectrometry can be requested for definitive detection.

Managing benzodiazepine ingestions should be guided by the clinical presentation of the patient. The airway is assessed and stabilized if necessary. Activated charcoal is the primary method of GI decontamination for recent ingestions. Supportive care with intubation and mechanical ventilation may be necessary for patients with significant toxicity. Hypotension usually responds to volume infusion.

Flumazenil is a competitive benzodiazepine receptor antagonist that will reverse the sedative effects of benzodiazepines. It may be a helpful diagnostic tool in evaluating a patient with overdose but should not be routinely used as a substitute for adequate airway protection.[82] A dose greater than 1 mg is seldom necessary in overdose victims. The short half-life of flumazenil (0.7–1.3 hours) makes resedation likely because of the longer half-life of benzodiazepines. Continuous monitoring must be instituted if flumazenil is used to arouse the patient. Flumazenil use has been associated with seizures in patients with chronic benzodiazepine use and when cyclic antidepressants are present.[82,83] It is best to avoid flumazenil in those situations and in patients with a seizure disorder or when a drug capable of causing seizures has been ingested. Slow titration of flumazenil (0.1 mg/min) and limiting the total dose to 1 mg may minimize the risk of seizures. If seizures occur with flumazenil, benzodiazepines (often in higher doses) may be effective.

Gamma-Hydroxybutyrate

Gamma-hydroxybutyrate (GHB), a naturally occurring substance found in the brain and peripheral tissues, is banned in many countries except for the treatment for narcolepsy. It is one of several agents characterized as a "date rape" drug and has been promoted to build muscle, improve performance, produce euphoria, induce fat loss, and enhance sleep. Deaths resulting from respiratory failure have been attributed to GHB and related agents.[84] The drug is usually available as a colorless, odorless liquid with a mild, salty taste that is easy to mask in drinks. GHB is rapidly absorbed from the stomach (usually within 10–15 minutes) and readily crosses the blood-brain barrier. It is metabolized to carbon dioxide and

water without active metabolites. Stimulatory effects occur from resulting increased dopamine levels in the brain and sedative effects by potentiation of endogenous opioids. The manifestations of GHB toxicity are dose related and include agitation, coma, seizures, respiratory depression, and vomiting.[84,85] Other effects include amnesia, tremors, myoclonus, hypotonia, hypothermia, decreased cardiac output, and bradycardia. Coma and respiratory depression may be potentiated by the concomitant use of ethanol. GHB is not detected by urine toxicology assays but can be detected in plasma or urine by gas chromatographic and mass spectrophotometric techniques. Diagnosis is usually determined by the clinical course and history of exposure elicited after the patient recovers. Gamma-butyrolactone, also known as 2(3H)-furanone dihydro, and 1,4-butanediol, also called tetramethylene glycol, have been abused with the same adverse effects as GHB including death. Both agents are metabolized in the body to GHB.[84]

The primary management for ingestion of these drugs is supportive care with particular attention to airway protection and ventilation. In some cases, intubation and mechanical ventilation are required. Gastric lavage and activated charcoal are not indicated because of the small amounts involved and the rapid absorption. Naloxone and flumazenil are of no benefit. Patients with mild intoxication may be observed in the emergency department and released after symptoms resolve. A rapid recovery of consciousness from an obtunded condition is frequently observed. In patients requiring intubation and mechanical ventilation, symptoms can be expected to resolve within 2 to 96 hours unless complications such as aspiration or anoxic injury have occurred. The concomitant use of alcohol may prolong the CNS depression. Although physostigmine has been used to awaken patients with GHB intoxication, its use is not recommended.[86]

A withdrawal syndrome has been described in patients who frequently ingest high doses of GHB (every 1–3 hours).[84,85] Mild symptoms such as anxiety, insomnia, nausea, vomiting, and tremors begin within 6 hours of the last dose and may progress to severe delirium with autonomic instability (usually mild) requiring hospitalization and sedation. The duration of symptoms requiring treatment may be as long as 2 weeks. Benzodiazepines are the initial choice for management, and high doses may be required. Propofol and barbiturates have also been used successfully.

Propofol

Propofol is a sedative-hypnotic used for general anesthesia, procedural sedation, prolonged sedation in critically ill patients, and treatment of status epilepticus. It has also been implicated in abuse, accidental overdose, suicide, and even murder.[87] A potentially fatal toxicity associated with more prolonged infusions of propofol is known as propofol-related infusion syndrome (PRIS).[88] The syndrome is usually associated with doses of propofol greater than 4 mg/kg per hour for longer than 48 hours' duration. However, metabolic acidosis has been reported within 1 to 4 hours after the initiation of propofol infusion. Predisposing factors that have been associated with PRIS include young age, CNS or respiratory illness, vasopressor use, glucocorticoid use, greater severity of illness, sepsis, and impaired oxygen delivery. Clinical features of the syndrome can include refractory bradycardia progressing to asystole, other arrhythmias, myocardial failure, lactic acidosis, rhabdomyolysis, renal failure, and hypertriglyceridemia.[88,89] The pathophysiology is hypothesized to be related to mitochondrial utilization of free fatty acids and genetic predisposition.

Propofol infusions should be limited to less than 4 mg/kg per hour and no longer than 48 hours of infusion when possible. Prompt recognition of early signs of PRIS (elevated serum lactate, elevated creatine kinase, hypertriglyceridemia) is essential for successful intervention. Another clinical clue to possible PRIS is the unexplained need for increasing doses of pressor or inotropic agents. Management includes discontinuation of propofol and the use of alternative sedative agents. The most effective treatment for severe PRIS is cardiorespiratory support and hemodialysis or hemofiltration to decrease blood levels of metabolic acids and lipids.[89]

Stimulants

Amphetamines/Methamphetamines

Amphetamines, methamphetamines, and related agents cause central and peripheral release of catecholamines, which result in a sympathomimetic toxidrome (see Table 65.2). Hallucinations (visual and tactile) and acute psychoses are frequently observed. The clinical manifestations associated with abuse of these agents may last up to 24 hours owing to the longer duration of pharmacologic effects. The acute adverse consequences are similar to those seen with cocaine abuse (see later text) and include myocardial ischemia and arrhythmias, pulmonary hypertension, seizures, intracranial hemorrhage, stroke, hepatotoxicity, rhabdomyolysis, necrotizing vasculitis, and death.[90] Chronic use of these drugs may result in dilated cardiomyopathy.[91] Poor oral hygiene and severe dental caries ("meth mouth") can be clues to chronic methamphetamine use.[92]

Methamphetamine hydrochloride in a crystalline form called "ice," "crank," or "crystal" is one of the more popular drugs in this class. It has high purity and can be orally ingested, smoked, insufflated nasally, or injected intravenously. An amphetamine-like drug (3-4-methylenedioxymethamphetamine) is a designer drug commonly known as ecstasy, XTC, or MDMA that acts as a stimulant and hallucinogen.[93] It results in serotonin release in the brain with inhibition of serotonin reuptake and has been reported to produce serotonin syndrome. Complications are usually a result of the drug effects and excessive physical activity. Complications include hyperthermia, hyponatremia (excessive water intake or syndrome of inappropriate antidiuretic hormone secretion), rhabdomyolysis, renal failure, cardiac collapse, cerebral infarction/hemorrhage, and multiple-organ failure. MDMA and other amphetamines will usually be detected on qualitative toxicology assays of urine but false-positive and false-negative results occur.

Management of amphetamine intoxication is primarily supportive. Gastric lavage is not recommended because absorption after oral ingestion is usually complete when patients present. Activated charcoal may be considered if a recent oral ingestion is known to have occurred. Further interventions are dependent on patient complaints and clinical findings. A careful assessment for complications should be made, including measurement of core temperature, obtaining an ECG, and evaluating laboratory data for evidence of renal dysfunction and rhabdomyolysis. IV hydration for possible rhabdomyolysis is warranted in individuals with known exertional activities pending creatine phosphokinase results. Benzodiazepines, often in high doses, are used to control agitation and recent reports suggest dexmedetomidine may be effective.[94] Antipsychotic medications, such as haloperidol, risperidone, and quetiapine, have also been used for agitation and psychosis.[94] Seizures are best treated with benzodiazepines.

Cocaine

Cocaine abuse is declining but still results in significant medical complications.[95] Cocaine hydrochloride is water soluble and can be injected intravenously, ingested, or snorted intranasally. Crack

or rock cocaine is the alkaloid form primarily abused by inhalation. The onset, peak, and duration of physiologic effects of cocaine vary with the route of use, form of cocaine used, and concomitant use of other drugs.[95] Both forms of cocaine are absorbed from all mucosal surfaces and undergo hydrolysis by plasma and liver cholinesterases. The major metabolites, benzoylecgonine and ecgonine methyl ester, are excreted in the urine and can be detected by qualitative urine assays. The metabolites of cocaine may be detectable in urine for 24 to 36 hours after use, but prolonged detection can occur in frequent users of high doses.

Cocaine inhibits the presynaptic reuptake of biogenic amines, such as norepinephrine, dopamine, and serotonin, throughout the body including the CNS. Characteristic clinical findings of a sympathomimetic syndrome include tachycardia, mydriasis, hypertension, hyperthermia, diaphoresis, euphoria, and agitation. The sympathetic stimulation also results in multiple potential complications (Box 65.3). Complications such as myocardial ischemia or cerebral infarction may occur several days after the last use of cocaine. Complications of transporting cocaine in body cavities may include rupture of packets with drug absorption and bowel obstruction.

No specific antidote exists for cocaine. Treatment is primarily aimed at detecting complications, intervening as indicated, and preventing further injury. Benzodiazepines should be used liberally for control of agitation. Haloperidol is reserved for overt psychosis because of its potential for lowering the seizure threshold.

No large clinical trials have evaluated therapeutic strategies for myocardial ischemia resulting from cocaine use. Aspirin should be administered if the risk of intracranial hemorrhage is low because a significant number of patients have thrombotic occlusion as the cause of ischemia. Benzodiazepines and nitroglycerin are first-line agents for relief of chest pain, but small clinical studies have yielded conflicting results on the benefit of combining the agents.[96] α-Adrenergic blockers such as phentolamine and calcium channel blockers have been recommended as second-line treatment for unrelieved pain but are rarely necessary.[96] β-Blockers were often considered to be contraindicated in the management of potential ischemia related to cocaine because of the potential for unopposed α-adrenergic–mediated vasoconstriction leading to elevated blood pressures. However, β-blocker use was not found to be detrimental in two retrospective studies of patients with recent cocaine use and may be beneficial in some patients.[97,98] It may be appropriate to avoid administration of β-blockers in patients manifesting acute sympathomimetic findings. In addition, routine use of IV β-blockers is no longer recommended for acute coronary syndromes. Reperfusion interventions, primarily percutaneous coronary interventions, should be considered for patients with myocardial infarction.[96] Ventricular arrhythmias are not common and may be related to cocaine blockade of myocardial sodium channels leading to QRS and QT-interval prolongation. Wide-complex arrhythmias may respond to treatment with sodium bicarbonate.[99] Class IA antiarrhythmic drugs such as procainamide should be avoided. Treatment of life-threatening arrhythmias should otherwise follow advanced life support guidelines.

Cerebral complications should be managed by standard interventions specific for the injury. Seizures are best managed with benzodiazepines. The reported incidence of underlying vascular malformations in intracranial hemorrhage has been variable, but if present these problems may require specific intervention. Severe hyperthermia is managed the same as heat stroke with either conductive or evaporative cooling.[100] When there is suspicion of rhabdomyolysis, IV hydration should be instituted immediately pending assessment of renal function and creatine phosphokinase levels. Asymptomatic transporters of cocaine packets should be managed conservatively with activated charcoal, possible WBI, and supportive care. Surgery is reserved for patients exhibiting manifestations of cocaine poisoning or GI perforation or obstruction.[101] Contamination of cocaine with other drugs or fillers can result in toxicities that are not directly related to the effects of cocaine. Levamisole, an anthelminthic agent used in veterinary medicine, has been found in cocaine supplies and linked to the development of reversible agranulocytosis.[102] Retiform purpura and skin necrosis secondary to thrombotic vasculopathy have also been linked to cocaine contaminated with levamisole.[103,104] The potential for suicidal intent should be recognized in cocaine abusers, and psychiatric consultation may be appropriate after stabilization.

• BOX 65.3 Complications Associated With Cocaine Use

Cardiovascular
Myocardial ischemia, infarction
Arrhythmias
Aortic dissection, rupture
Hypertension
Atherosclerosis
Cardiomyopathy
Vasculitis

Central Nervous System
Seizures
Cerebral infarction
Transient ischemic attack
Intracranial hemorrhage (intraparenchymal, intraventricular, subarachnoid)
Cerebral vasculitis
Cognitive dysfunction

Pulmonary
Bronchospasm
Barotrauma
Noncardiogenic edema
Pulmonary hypertension

Renal
Renal infarction
Renal failure
Scleroderma renal crisis

Gastrointestinal
Mesenteric ischemia, infarction
Gastrointestinal tract perforations

Metabolic
Hyperthermia
Rhabdomyolysis
Weight loss
Multiple organ failure

Other
Deep venous thrombosis
Skin ischemia
Dystonic reactions

Mephedrone/Methylenedioxypyrovalerone (Bath Salts)

Mephedrone and 3,4-methylenedioxypyrovalerone (MDPV) are synthetic stimulants marketed in products sold as bath salts to

avoid regulation. MDPV inhibits reuptake of dopamine and norepinephrine, and mephedrone may act as a monoamine reuptake inhibitor.[105] The products have been ingested, snorted, smoked, and injected and are often used in combination with alcohol or other drugs. These agents are not detected by qualitative toxicology screens.

Clinical manifestations are similar to those of other stimulant drugs and include agitation, tachycardia, hyperthermia, hypertension, mydriasis, chest pain, palpitations, seizures, hallucinations, delusions, and paranoia.[105,106] Symptoms may be prolonged for more than 24 hours after use of mephedrone despite a short expected half-life.[106] Management includes IV benzodiazepines for significant agitation and psychotic symptoms. Symptoms may recur as sedation wears off, requiring repeat dosing. A thorough clinical evaluation is required to identify other complications, such as rhabdomyolysis, myocardial ischemia, and organ dysfunction. Seizures are best treated with IV benzodiazepines.

Synthetic Cannabinoids

Synthetic cannabinoids include a heterogeneous group of drugs that are full agonists of cannabinoid receptors in the brain and spinal cord and have a greater risk for toxicity compared with marijuana. These substances are often sprayed on herbal potpourri products marketed as incense that can be inhaled or ingested. Liquid forms may be used in e-cigarettes.[107,108] Synthetic cannabinoids are not detected in routine urine toxicology assays. Clinical manifestations related to use of these products vary from mild to severe. Serious adverse effects of synthetic cannabinoids may include agitation, psychosis or delirium, tachycardia, arrhythmias, myocardial ischemia, respiratory depression, hyperemesis, hyperthermia, renal failure, rhabdomyolysis, stroke, seizures, and death.[107,108] Management of toxicity from synthetic cannabinoids is mainly supportive and includes the use of benzodiazepines for agitation.

Valproic Acid

Use of valproic acid (VPA) for seizure disorders, psychiatric disorders, migraine prophylaxis, neuropathic pain, and cancer therapy has resulted in increased toxicity reported with therapeutic doses and overdoses. The most common manifestation of toxicity in overdoses is CNS depression with higher drug levels associated with an increased incidence of coma and respiratory depression requiring intubation.[109] Cerebral edema may occur 48 to 72 hours after overdoses and may be related to hyperammonemia that usually occurs in the absence of hepatotoxicity. The increase in ammonia may be related to carnitine deficiency, renal abnormalities, or defects in the urea cycle.[109] Large VPA ingestions can result in refractory hypotension. Pancreatitis has been associated with chronic ingestion and acute overdose. Metabolic abnormalities of VPA toxicity include hypernatremia, hyperammonemia, anion gap metabolic acidosis, hypocalcemia, and acute renal failure. Hepatotoxicity is rare with VPA overdoses, but mild, asymptomatic abnormalities may occur with chronic use.

Initial and serial VPA levels should be obtained because of delayed peak serum levels in overdose. Patients may be comatose with normal serum VPA concentrations caused by unmeasured metabolites. An ammonia level should be obtained in patients with altered level of consciousness. Activated charcoal should be administered if the patient presents early after ingestion. MDAC may be beneficial because of a potential enterohepatic recirculation of drug, but routine use is not currently recommended. Although VPA is highly protein bound, protein binding is saturated at high serum concentrations, resulting in more free drug being available for removal by extracorporeal techniques. Hemoperfusion, combined hemodialysis-hemoperfusion, or high-flux hemodialysis may be considered in patients with severe or persistent hemodynamic instability, coma, or metabolic acidosis.[110] No antidote exists for VPA toxicity, but L-carnitine administration has been proposed for patients with VPA toxicity and hyperammonemia. Chronic VPA therapy has been associated with carnitine deficiency and case reports suggest that L-carnitine administration is safe.[111] However, there is no evidence that L-carnitine alters clinical outcome and more rigorous study is needed. Dosing of L-carnitine in reports has been variable but a suggested regimen is 100 mg/kg IV bolus or infusion over 15 to 30 minutes, followed by 50 mg/kg (maximum 3 g/dose) every 8 hours until the ammonia level is decreasing and the patient clinically improves.[111]

Key Points

- Evaluating and managing the poisoned patient involves resuscitation and stabilization, diagnosis, GI decontamination and toxin elimination, institution of specific antidotes or interventions, and supportive care.
- In the poisoned patient with altered mental status, hypertonic dextrose, thiamine, and naloxone should be considered for administration.
- Patterns of signs and symptoms identified by physical examination may often suggest a toxidrome that is associated with classes of toxins.
- Single-dose activated charcoal is most effective when administered within 1 hour of toxin ingestion; later administration may be appropriate if clinical factors suggest the toxin has not yet been completely absorbed.
- Recognition of potential acetaminophen toxicity is essential for appropriate treatment and prevention of morbidity.
- Findings of bradycardia and hypotension should suggest possible ingestion of a β-blocker or calcium channel blocker.
- Dietary and nutritional supplements can result in significant cardiac, hepatic, and cerebrovascular toxicities.
- Cyclic antidepressant toxicity with increased QRS duration or wide-complex tachyarrhythmia requires immediate alkalinization of the blood with sodium bicarbonate or hyperventilation.
- The initial treatment for patients presenting with a clinical syndrome suggesting a stimulant toxin (cocaine, amphetamines, bath salts, synthetic cannabinoids) is IV benzodiazepines for control of agitation.
- Be aware of potential toxicities that can develop in ICU patients exposed to propylene glycol–containing medications, topical anesthetics, and propofol.

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Review Questions

1. A 28-year-old patient was found unconscious in a park. In the emergency department, his vital signs were heart rate 62 beats/min, blood pressure 88/40 mm Hg, respiratory rate 10 breaths/min, and temperature 36.6°C. He was noted to have small pupils that were minimally reactive and he did not withdraw to pain in any extremity. The emergency department physician administered 0.2 mg of naloxone without effect. The intensivist was called for admission and consultation. Which of the following is the most appropriate intervention at this time?
   a. Administer norepinephrine
   b. Intubate the patient
   c. Administer a higher dose of naloxone
   d. Administer flumazenil

   Answer: c. The patient's presentation is classic for an opioid toxidrome with depressed level of consciousness, respiratory depression, and miosis. The next step in the care of the patient is to administer higher doses of naloxone to assess for response given that many synthetic opioids such as methadone, oxycodone, and fentanyl require higher doses for reversal of effects. Although intubation may be considered, it is usually not needed if adequate arousal is achieved with naloxone. Hypotension often responds to fluids and naloxone and vasopressors should be reserved for refractory cases. Flumazenil should not be administered because of the potential for seizures, and the clinical presentation is more consistent with an opioid overdose.
2. A 40-year-old man is admitted to the ICU after ingesting a total of 60 tablets of acetaminophen 500 mg and 50 tablets of hydrocodone/acetaminophen (5 mg/325 mg) on multiple occasions over the past 48 hours. He is lethargic but arousable. Vital signs are blood pressure 118/70 mm Hg, heart rate 96 beats/min, RR 18 breaths/min, and temperature 37°C. His acetaminophen level is 50 µg/mL. Liver function test results are total bilirubin 1.0 mg/dL, alanine aminotransferase 100 IU/L, aspartate aminotransferase 85 IU/L, and alkaline phosphatase 110 IU/L0. Which one of the following interventions is most appropriate?
   a. Check the Rumack-Matthew nomogram to determine the need for N-acetylcysteine.
   b. Continue supportive care and monitor liver function test results.
   c. Initiate N-acetylcysteine therapy.
   d. Administer lactulose,

   Answer: c. The indications for a full course of N-acetylcysteine in this patient are the presence of any acetaminophen level and elevated transaminases in a patient with multiple ingestions of acetaminophen over time. The Rumack-Matthew nomogram is of no help in this situation because it was developed for single acute ingestions in patients who present within 24 hours. Continuing with supportive care and monitoring without administering N-acetylcysteine would likely result in continued worsening of hepatic injury. The liver injury is not sufficient at this point to cause hepatic encephalopathy, so lactulose to improve mental status would not be helpful.
3. A 65-year-old woman is admitted to the intensive care unit (ICU) with hypotension. Her husband found multiple empty pill bottles at home. Her regular medications include extended-release verapamil, lisinopril, and pravastatin. On arrival to the ICU vital signs are blood pressure 78/40 mm Hg, heart rate R 38 breaths/min, respiratory rate 16 breaths/min, temperature 93°C. Normal saline solution (1 L) is administered and calcium chloride 1 g is administered twice with no improvement of blood pressure. Which one of the following is the next best intervention?
   a. Transcutaneous pacing
   b. IV atropine
   c. Lipid emulsion
   d. High-dose insulin

   Answer: d. High-dose insulin therapy is recommended as the next intervention for calcium channel blocker toxicity if calcium is ineffective. Although atropine is often administered, it is usually ineffective. Transcutaneous pacing may increase the heart rate but not the blood pressure because hypotension is usually due to the negative inotropic effects of the drug. Lipid emulsion is an option for those patients who may be refractory to high-dose insulin but it is not recommended as an initial intervention.

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Hypothermia, Hyperthermia, and Rhabdomyolysis

ZOULFICAR KOBEISSI AND CHRISTOPHER B. MCFADDEN

CHAPTER OUTLINE

Hypothermia
- Epidemiology
- Definition
- Heat Regulation
- Clinical Presentation
- Laboratory Evaluation
- Management
- Prognosis

Hyperthermia
- History and Incidence
- Pathogenesis
- Predisposing Factors
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- Specific Hyperthermic Syndromes

Malignant Hyperthermia
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Rhabdomyolysis
- Epidemiology
- Pathophysiology
- Clinical Presentation
- Specific Treatment Requirements

Hypothermia

Cold exposure has been recognized as a cause of death since ancient times. In the year 492 BC, the Persians were sailing to launch their attack against the Greeks when they encountered bad weather and lost about 300 ships and 20,000 soldiers. Herodotus wrote "…[Some were dashed by the rocks, and some of them did not know how to swim and perished for that cause, others again by reason of *cold*."

To recognize hypothermia, it must be possible to measure a temperature. The first thermometer for clinical use was invented in 1612. It was a foot long and required 20 minutes to register a temperature. The invention of the mercury thermometer by Fahrenheit in 1714 made the tool more practical. However, it was not until the late nineteenth century that the thermometer became a clinical tool. This use was established after the invention of a small thermometer that only required 5 minutes to obtain a temperature (1866) and after Carl Wunderlich's publication (1868), which presented data on nearly 25,000 patients and analyzed temperature variation in 32 diseases. In the early 1900s, temperature was routinely measured and physiologic experiments started to appear. By the 1930s to 1940s, therapeutic hypothermia for malignancy and anesthesia was investigated. By the middle of the twentieth century, accidental hypothermia was established as a disease entity.[1]

This section discusses the epidemiology, definition, pathophysiology, clinical diagnosis, clinical manifestations, and management of hypothermia. Despite some similarities in pathophysiologic mechanisms, accidental hypothermia and induced hypothermia should not be compared, as accidental hypothermia occurs unexpectedly and is uncontrolled.

Epidemiology

Accidental hypothermia continues to be a public health problem. The Centers for Disease Control and Prevention reports that between 1999 and 2011, a total of 16,911 deaths in the United States (an average of 1301 per year) were attributed to excessive natural cold.[2]

Approximately 50% of all hypothermia-related deaths occur in persons older than 65 years of age. The age-adjusted mortality rate is three times higher for men than it is for women. In blacks and other races, the mortality rate is higher than that of whites.[2,3] Blacks have decreased heat production and lower rectal temperatures in response to cold exposure.[4] Other populations at risk include the elderly, people with preexisting chronic medical conditions, and people with alcoholism and drug intoxication.[2,3,5] Emerging populations include wilderness enthusiasts and winter sport participants.[6]

Despite advances in medical care, hypothermia remains a challenge to health care providers, with in-hospital mortality rate reaching 40%[7] and an overall mortality rate ranging from 17% to 80%.[8] The prompt recognition and appropriate management play a key role in improving outcomes.

Definition

Hypothermia is defined as a core body temperature lower than 35°C (<95°F). It has been further classified by severity according to the degree by which the core temperature has decreased from baseline into mild, moderate, and severe. Mild hypothermia is defined by a core body temperature of 32°C to 35°C (90°F–95°F). Moderate hypothermia reflects a core body temperature of 28°C to 32°C (82°F–90°F). Severe hypothermia is a core body temperature of less than 28°C (<82°F). Some reports refer to severe hypothermia below 30°C. In trauma patients, hypothermia carries a poorer prognosis. In this case, the definition is even more conservative, with severe hypothermia starting below 32°C. This subclassification has important implications regarding the anticipated physiologic changes and subsequently the use of appropriate therapeutic modalities.[9,10]

Heat Regulation

Body temperature is regulated through a balance between heat production and heat dissipation.[11] Heat production occurs mostly from the metabolic activity of energy-consuming processes within the viscera, namely, the heart, liver, and brain. Heat production in these organs is estimated to be between 40 and 60 kcal/m^2 per hour. Normally heat production is increased by food intake and muscle activity. Different stresses such as fever, infection, and cold exposure also increase heat production.

Heat loss occurs through different forms. Radiation cooling (infrared emissions) accounts for approximately 60% of heat loss. It occurs primarily from the head and unisolated parts of the body. Conduction (direct transfer of heat to an adjacent cooler object) and convection (direct transfer of heat to convective air currents) account for around 10% to 15% of heat loss. Evaporation from the skin and respiratory tract accounts for 25% to 30%. Conduction is an important mechanism in immersion accidents because thermal conduction of water is 30 times that of air. Convection is important in windy conditions by removing the warm isolating layer of air around the body.[6,10,11]

Upon cold exposure, the hypothalamus initiates mechanisms for heat conservation and heat production. Heat conservation is achieved by peripheral vasoconstriction, reducing heat conduction to the skin, and behavioral responses such as wearing more clothes and seeking a warmer environment. Heat production is achieved through stimulation of muscular activity via shivering, which can increase the basal metabolic rate by two to five times. A nonshivering thermogenesis occurs via increased levels of catecholamines and thyroxine.[12] This coordinated physiologic response occurs typically for temperatures between 32°C and 35°C. It lasts only for a few hours, after which muscle fatigue and glycogen depletion ensue. As the core temperature drops below 32°C (90°F), shivering thermogenesis abates, and nonshivering thermogenesis slows. By temperatures below 20°C to 24°C, the different mechanisms of heat production completely fail.[13]

Clinical Presentation

Etiologic Factors (Fig. 66.1)

Factors that predispose to hypothermia are related to impaired thermoregulation, increased heat loss, and decreased heat production. A combination of these factors is often noted in a hypothermic patient.

1. *Impaired thermoregulation* is of critical importance in the elderly, mentally ill, and patients with chronic medical conditions such as Parkinson disease, stroke, multiple sclerosis, and diabetes mellitus. Such populations often use multiple medications, including anxiolytics, antidepressants, phenothiazines, barbiturates, opioids, antipsychotics, oral antihyperglycemics, β-blockers, and α-blockers. These drugs can cause further impairment in thermoregulation.[14] In addition, the elderly and chronically ill may exhibit maladaptive behavior (decreased mobility and inability to communicate effectively), which increases the chance of remaining in an environment with prolonged cold exposure.[14]
2. *Increased heat loss* can be environmental or nonenvironmental.
   a. Hypothermia commonly occurs during winter weather and in cold climates. People with inadequate insulation and continued cold exposure are especially at risk.
   b. Patients with dermatologic dysfunction, such as burns, psoriasis, and exfoliative dermatitis, can have increased heat loss.
   c. Large amounts of unheated IV fluid resuscitation, whether crystalloids or blood, coupled with unheated humidified oxygen, predispose hospital and trauma patients to greater heat loss.
   d. Conditions that cause vasodilation should be highlighted in this category and include alcohol, anesthesia, and toxins released in disease entities such as sepsis.
3. *Decreased heat production* is noted in some specific types of disorders:
   a. Endocrine dysfunction such as hypopituitarism, hypothyroidism, hypoadrenalism, and hypoglycemia.
   b. Malnutrition and starvation, which cause decreased insulative subcutaneous fat and are often associated with hypoglycemia.
   c. Conditions that alter the level of consciousness, causing decreased shivering mechanism. Drugs such as phenothiazines and tricyclic antidepressants as well as alcohol can induce impairment of shivering.[6]

Diagnosis

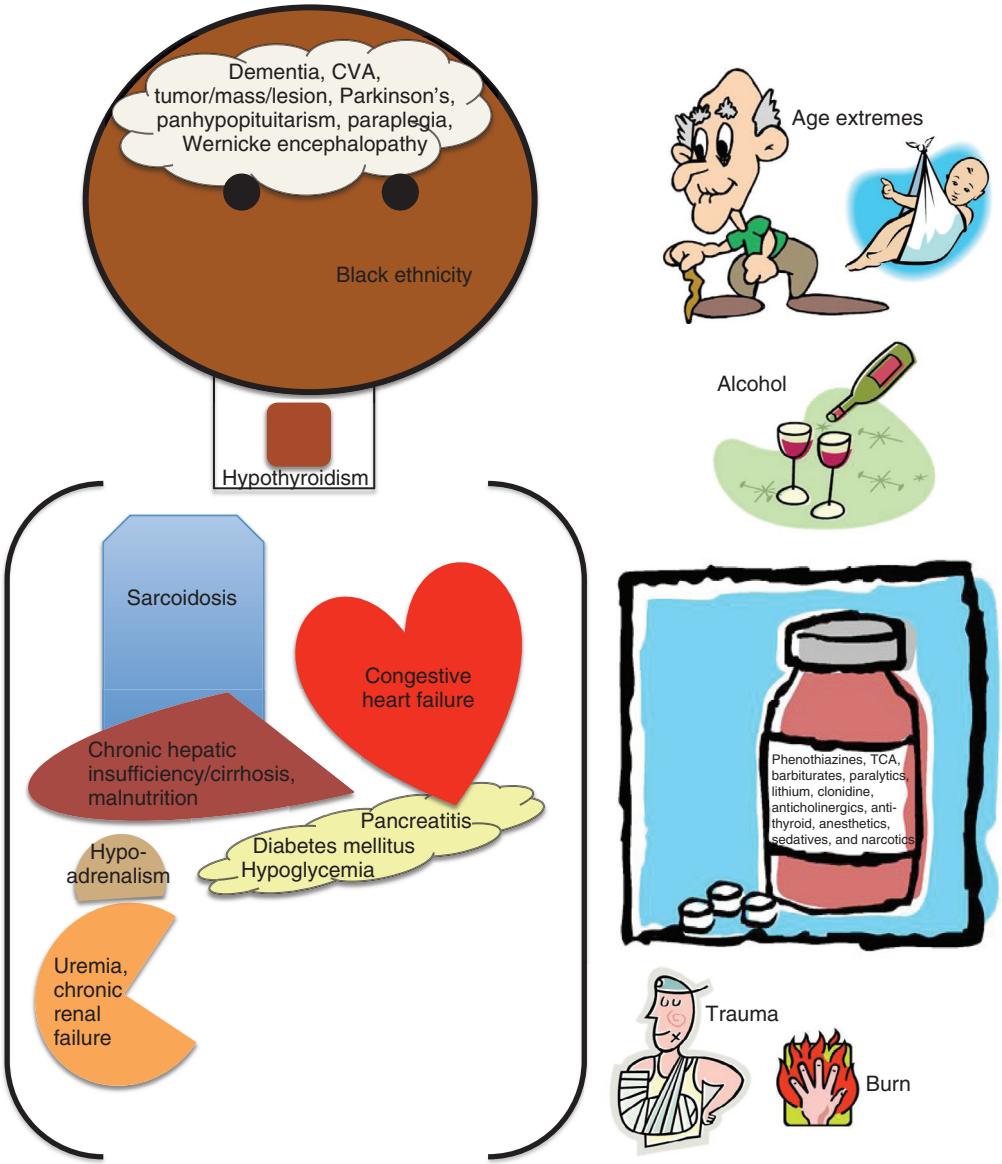
Diagnosis via rectal, esophageal, or bladder probe should be performed using a thermometer capable of measuring temperatures as low as 25°C (77°F). The most accurate recommended thermometer is the esophageal probe inserted into the lower one-third of the esophagus, an average of 24 cm below the larynx in adults. It should be noted that standard clinical thermometers do not register below 34.4°C (94.4°F).[15] Combined methods for temperature monitoring may allow better detection of further changes.

End-Organ Manifestations (Fig. 66.2)

Almost every organ in the body is affected by hypothermia.[16] The initial mechanisms mimic intense sympathetic stimulation, which fades as body temperature drops. Although hypothermia is divided into three stages, it is important to note that the physiologic changes follow a continuum.[16]

Cerebral Effects

Hypothermia is associated with progressive decrease in neuronal metabolism between 35°C and 25°C. This is a protective effect of hypothermia and allows tolerance to periods of cardiocirculatory collapse in contrast with the normothermic state.[6,17,18] Neurologic symptoms begin with mild hypothermia. Between 34°C and 35°C, loss of fine motor skills, lack of coordination, dysarthria, and amnesia take place. Ataxia and apathy are noted around 33°C.[19] Below 32°C, progressive decrease in level of consciousness and pupillary dilation develops. Cerebrovascular autoregulation is lost below 25°C. Deep tendon reflexes diminish and flaccid muscular tone takes place below 27°C. By 23°C, corneal and oculocephalic



• **Fig. 66.1** Diseases and factors associated with hypothermia. *CVA,* Cerebrovascular accident; *TCA,* tricyclic antidepressant. (Reprinted with permission of Zoulficar Kobeissi, MD.)

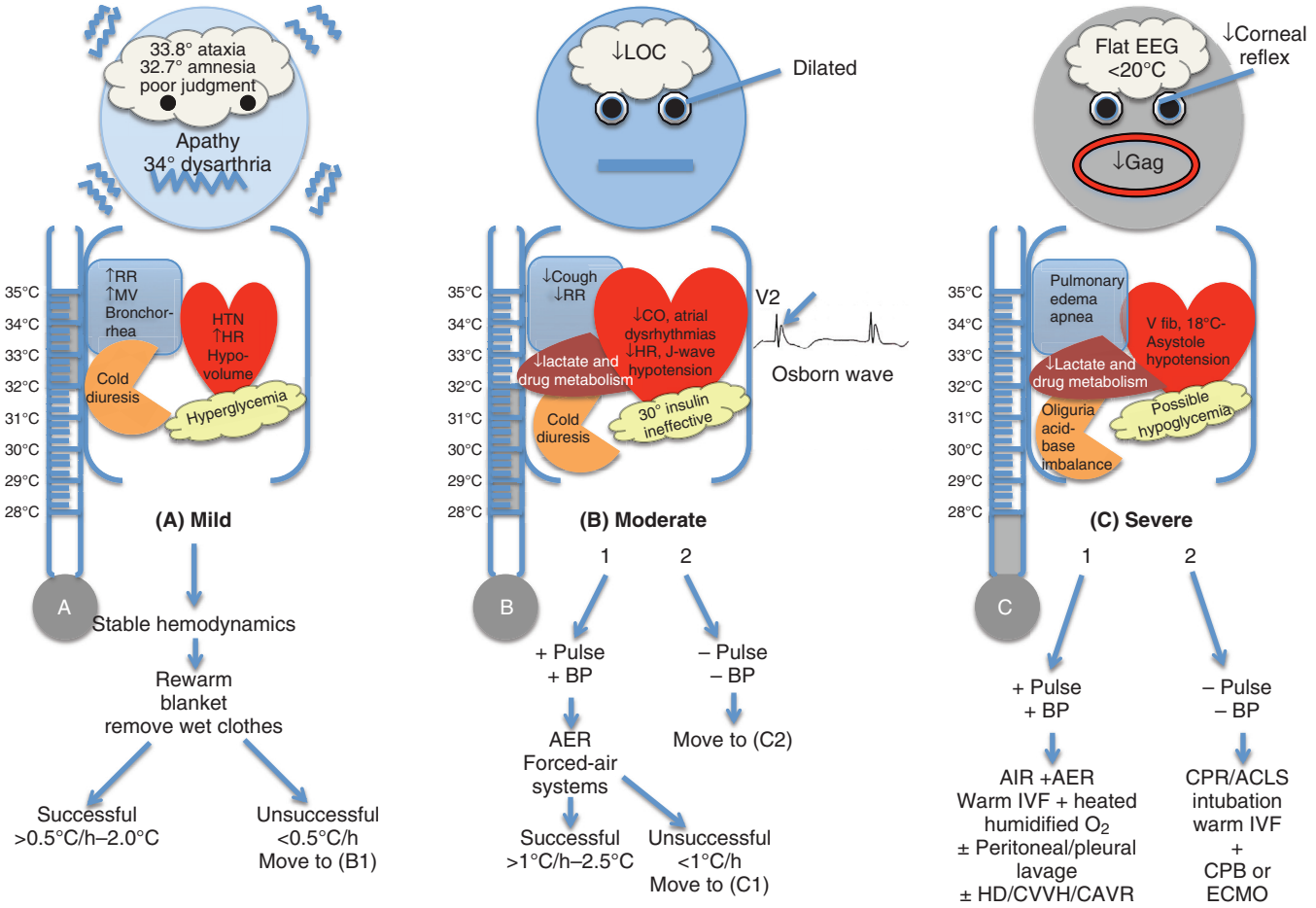
reflexes are absent. The electroencephalogram pattern flattens at 19°C to 20°C. The lowest temperature reported for an adult survival with hypothermia is 13.7°C.[6,15,20] Therefore one has to be very careful in assessing brain death when a patient remains hypothermic.[8]

Cardiovascular Effects

The initial response (34°C–36°C) includes increased heart rate, blood pressure, and carbon dioxide secondary to elevated catecholamine production and peripheral vasoconstriction, resulting in increased in oxygen consumption.[6] A core temperature decrease of as little as 0.3°C is associated with a 7% increase in oxygen consumption. The increase in oxygen requirement results in anaerobic metabolism, acidosis, and significant cardiopulmonary stress, further worsening the abnormal physiology of hypothermia.[16] Below 34°C, progressive bradycardia and decrease in cardiac output and blood pressure take place. Below 28°C, 50% of patients show bradycardia with a 50% decrease in heart rate. Bradycardia is chiefly related to progressive decreased spontaneous depolarization of pacemaker cells. The conduction system is also affected, with prolongation initially noted in the PR interval, then QRS complex, then QT intervals.[21] Atropine is ineffective. The myocardium becomes irritable. As temperature falls lower than 32°C, atrial fibrillation is common, usually preceding ventricular fibrillation that may occur spontaneously when temperature falls below 28°C (82°F). Asystole usually occurs at temperatures less than 25°C.[22]

Respiratory Changes

Early in hypothermia (34°C–36°C) the respiratory drive is stimulated. The minute ventilation increases in response to increased oxygen consumption and CO_2 production. Below 33°C, respiratory depression takes place. Minute ventilation decreases. Depressed cough reflex and ciliary action coupled with increased production of mucus (bronchorrhea) increase the risk of atelectasis and aspiration. Noncardiogenic pulmonary edema has also been reported.[23,24]



• **Fig. 66.2** Hypothermia: clinical presentation and treatment approach. *ACLS,* Advanced Cardiac Life Support; *AER,* active external rewarming; *AIR,* active internal rewarming; *BP,* blood pressure; *CAVR,* continuous arteriovenous rewarming; *CO,* cardiac output; *CPB,* cardiopulmonary bypass; *CPR,* cardiopulmonary resuscitation; *CVVH,* continuous venovenous hemofiltration; *ECMO,* extracorporeal membrane oxygenation; *EEG,* electroencephalogram; *HD,* hemodilution; *HR,* heart rate; *HTN,* hypertension; *IVF,* intravenous fluids; *LOC,* level of consciousness; *MV,* minute ventilation; O_2, oxygen; *RR,* respiratory rate; *V fib,* ventricular fibrillation. (Reprinted with permission of Zoulficar Kobeissi, MD.)

Renal Changes

The initial response to hypothermia includes increased renal blood flow secondary to an increase in blood pressure and cardiac output, inducing diuresis. As hypothermia progresses below 32°C and cardiac output declines, renal blood flow and glomerular filtration rate decrease, resulting in acute renal failure. Urinary output persists in this stage, known as cold diuresis. In cold diuresis, impaired renal tubular sodium reabsorption maintains ongoing urinary flow. This response explains why hypothermia patients may present with profound intravascular volume depletion.[6,16,25]

Gastrointestinal Changes

Ileus, bowel wall edema, depressed hepatic detoxification, punctate gastric erosions, and rarely hemorrhagic pancreatitis are among the gastrointestinal manifestations of hypothermia.[16]

Laboratory Evaluation

Laboratory evaluations should be obtained to assess metabolic status and organ dysfunction. The following are common laboratory findings during hypothermia. They usually change with rewarming and require frequent monitoring.

Arterial Blood Gases

As temperature decreases, the oxyhemoglobin dissociation curve shifts to the left. For every 1°C drop in temperature, pH increases by 0.015, partial pressure of arterial oxygen (PaO_2) decreases by 7.2%, and partial pressure of carbon dioxide ($PaCO_2$) decreases by 4.4%. Because all arterial blood gas (ABG) samples are warmed to 37°C (98.6°F) when measured, the pH appears lower and the PaO_2 and $PaCO_2$ appear higher than the patient's actual values. Most knowledge on acid-base status during hypothermia comes from cardiovascular surgery reports. Although most literature does not recommend correction of temperature to guide therapy, the use of corrected values should be strictly individualized.[26–28]

Complete Blood Cell Count

Hemoconcentration, an increase in hematocrit secondary to a decrease in plasma volume, is common (2% for each 1°C-decrease in temperature). An initial low hemoglobin suggests acute

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hemorrhage or preexisting anemia. White blood cells may decrease; therefore any history suggestive of infection should prompt treatment with antibiotics in high-risk groups such as the elderly, neonates, and the immunocompromised.[29]

Coagulation Factors

Hypothermia induces inhibition of coagulation factors. It also induces thrombocytopenia secondary to bone marrow suppression and splenic and hepatic sequestration, as well as reduction in platelet adhesions and aggregation. Prolonged bleeding time and clotting times are common. Coagulation tests in the laboratory are performed at temperatures below 37°C. If results are normal, they may not negate the presence of underlying hypothermia-induced coagulopathy. The key treatment in this condition is rewarming, not supplementation of coagulation factors.[30,31] Rewarming, however, increases the clotting response. Clinicians should use caution during this process, as patients are more susceptible to negative cardiovascular events.[4]

Blood Urea Nitrogen/Creatinine/Electrolytes

As mentioned earlier, acute renal failure with intravascular volume depletion and decreased renal perfusion is encountered. This is usually associated with higher levels of blood urea nitrogen (BUN) and creatinine (Cr) secondary to decreased clearance. Recurrent evaluation of electrolytes is essential during rewarming because no consistent pattern is present. Either hypokalemia or hyperkalemia may complicate the course of hypothermia and should be corrected promptly. Hypothermia masks the usual electrocardiogram changes seen in normal hyperkalemia.[6,8,16]

Blood Glucose

Hyperglycemia is initially noted as hypothermia inhibits insulin release and insulin uptake by membrane receptors at temperatures below 30°C. It is further exacerbated by increased catecholamines. Insulin at these temperatures is ineffective. Exogenous insulin should be avoided, as it may cause rebound hypoglycemia during rewarming.[32]

Other Laboratory Abnormalities

Hyperamylasemia is common and may be related to a preexisting pancreatitis or pancreatitis induced by hypothermia. Hyperamylasemia correlates with the severity of hypothermia. Variable elevation in creatine phosphokinase levels may reflect underlying rhabdomyolysis.

Electrocardiography Changes

All intervals—PR, QRS, and QT—are prolonged secondary to hypothermia-induced slowed impulse conduction through potassium channels. When body temperature decreases below 33°C (91.4°F), the J (Osborn) wave may be noted as a positive deflection in the left ventricular leads at the junction of the QRS complex and ST segment in 25% to 30% of patients. The presence of this wave is not pathognomonic and has no prognostic implication. The magnitude of the Osborn wave is associated with the degree of severity of hypothermia.[12,21]

Management (See Fig. 66.2)

The lack of a standardized hypothermia treatment protocol among hospitals is still a challenge. The severity of hypothermia, clinical findings, and comorbid conditions of the patient are important factors for determining the aggressiveness of resuscitation techniques. Once hypothermia is confirmed, assessment and treatment of the critically ill patient should take place simultaneously. Some patients with hypothermia and cardiac arrest achieved an almost complete recovery despite prolonged resuscitation with a temperature as low as 13.7°C. Patients with moderate or severe hypothermia should be resuscitated until adequate rewarming is achieved before declaring efforts as unsuccessful.[33–35]

Initial Stabilization

Removal of wet clothing and moving the patient to a warm environment for protection against continued heat loss are essential. Rough movements of the patient's body during physical assessment should be avoided as it could precipitate serious cardiac arrhythmias. Continuous monitoring of cardiac status and core temperature should be established without delay. Similar to any emergency situation, airway, breathing, and circulation should be evaluated promptly in the hypothermic patient.

Airway/Breathing Support

Chest rigidity and decreased diaphragmatic movement impede adequate ventilation. Oxygenation may be insufficient secondary to underlying aspiration or pulmonary edema. Supplemental oxygen should be provided to alert patients with intact airway reflexes pending full assessment of oxygenation status. Hypothermic patients with apnea, deteriorating mental status, or loss of protective reflexes should undergo endotracheal intubation. The oropharyngeal route is preferred. Jaw maneuvering could be difficult in this category of patients secondary to muscle rigidity. Neuromuscular blocking agents do not have a role as they are ineffective at temperatures below 30°C. Intubation with a smaller endotracheal tube may be attempted. Intubation is unlikely to induce dysrhythmias in hypothermic patients.[8]

Cardiocirculatory Support

Volume Resuscitation

Most patients with moderate to severe hypothermia have volume depletion. Continuous warmed IV fluids (40°C–42°C) should be administered. Peripheral large-gauge catheters are the preferred route of administration. The femoral vein is the preferred site if a central line is anticipated. Volume status should be monitored continuously during rewarming, as peripheral vasodilation and hypotension are likely to occur.[36] Most patients with moderate to severe hypothermia suffer from volume depletion. Continuous warmed intravenous (IV) fluids (40°C–42°C) should be administered. Peripheral large-gauge catheters are the preferred route of administration. The femoral vein is the preferred site if a central line is anticipated. Volume status should be monitored continuously during rewarming, as peripheral vasodilation and hypotension are likely to occur.[36]

Cardiac Resuscitation

Patients with moderate to severe hypothermia should undergo a thorough evaluation, looking for signs of cardiac output or peripheral blood flow. Echocardiography and Doppler ultrasound can be used for this purpose. Cardiopulmonary resuscitation should be performed immediately if no pulse or a nonperfusing rhythm (ventricular fibrillation or asystole) is established.[37–39]

Defibrillation. The hypothermic heart may be unresponsive to cardioactive drugs, attempted electric pacing, and defibrillation. Most arrhythmias other than ventricular fibrillation tend to convert spontaneously with rewarming. Sinus bradycardia does not require pacing or pharmacologic intervention. Ventricular fibrillation or

tachycardia without a pulse requires initial defibrillation with maximum energy.

The European Resuscitation Council 2015 guidelines recommend limiting defibrillation to three attempts until the core temperature reaches above 30°C. Defibrillation is reattempted after every 1°C- to 2°C-increase in core temperature or when temperature rises above 30°C to 32°C.[37–39]

Cardioactive Drugs. The antiarrhythmic and vasoactive drug efficacy in moderate to severe hypothermia is not well determined. It is mainly based on animal studies. Both the American Heart Association and the European Resuscitation Council continue to recommend not to use adrenergic drugs for temperatures below 30°C. According to the American Heart Association 2010 guidelines, it may be reasonable to consider administration of a vasopressor during cardiac arrest according to the standard Advanced Cardiac Life Support algorithm concurrent with rewarming strategies. Isolated use of antiarrhythmics does not appear to be beneficial. Caution should be exercised not to administer these drugs repeatedly, as toxic accumulation can occur secondary to decreased metabolism. As normothermia is approached (>35°C), standard drug protocols are used.[37–39]

Additional Support

A nasogastric or orogastric tube should be placed in patients with moderate to severe hypothermia to relieve gastric distention, which might help reduce vomiting and aspiration secondary to gastric dysmotility. A urinary catheter is also essential to monitor urine output and assess volume resuscitation efforts. Intraarterial catheters for pressure monitoring should be used selectively. A Doppler ultrasound device may be necessary. Pulse oximetry is unlikely to be accurate given the poor perfusion to the extremities.

Rewarming Methods

There are several methods of rewarming. Selection depends on the severity of hypothermia and the clinical condition of the patient. Controlled clinical studies and interventional studies are limited, and evidence-based protocols are lacking. Absence of a developed protocol led to the use of a wide variety of treatment strategies, depending on the expertise and previous exposure of the clinical teams and hospital resources.[40]

Passive External Rewarming

Passive external rewarming is the method of choice for hemodynamically stable patients with mild hypothermia (>32°C), adequate physiologic reserve, and intact mechanism of shivering. Treatment includes placement of patients in a warm environment, removal of wet clothing, and application of insulating materials, such as blankets, to prevent heat loss. This method is expected to raise core temperature by 0.5°C to 2.0°C per hour.[6] If unsuccessful, active rewarming is initiated.

Active Rewarming

Active External Rewarming. Active external rewarming (AER) is applied to patients with a core temperature between 86°F and 92°F (30°C–34°C) without potential compromise of airway or hemodynamic status. It involves one or a combination of techniques, including warming blankets, heating pads, radiant energy, and forced heated air systems. Few complications (such as thermal injuries in the form of skin burns) have been reported using these methods. "After drop" is a phenomenon that was reported as a complication of AER. When the extremities and the trunk are warmed simultaneously, cold acidemic blood returns to the central circulation from the periphery secondary to vasodilation, causing a paradoxical decrease in core temperature. This drop worsens acidemia, precipitating hypotension and arrhythmias that can be fatal. Therefore it is advised to apply rewarming strategies to the trunk before the extremities.[41,42]

Estimated rates of rewarming using this method ranges from 0.8°C with heating blankets up to 2.5°C per hour with the forced air rewarming systems. This forced air system is the most widely used by clinicians because it is easy and effective.[41,42]

Active Internal Rewarming. Active internal rewarming is used for patients with moderate to severe hypothermia (<86°F or 30°C) with adequate hemodynamics, in conjunction with AER.[43] Methods include administration of warmed IV fluids (40°C–42°C) and warmed humidified air (40°C–45°C) through a mask or endotracheal tube. IV fluids alone are not adequate but prevent further heat loss. It is estimated that an average 1 L crystalloid (40°C–42°C) infusion for a 70-kg person will increase the temperature by 0.3°C. Rewarming by heated oxygen by endotracheal tube is more effective than a face mask. A total rate of 1°C to 2.5°C per hour is anticipated by this method.[15,43,44] Gastric bladder and colonic irrigation are of limited value secondary to their small surface area.

If rewarming is inadequate, more aggressive methods include peritoneal and pleural lavage. In pleural irrigation, two large-bore (≥36F) thoracotomy tubes are used. One tube is placed at the midclavicular line and is connected to saline solution at 42°C (107.2°F). The other tube is placed at the posterior axillary line and is connected to a chest tube drainage.[45]

Peritoneal lavage and dialysis are achieved by placement of a peritoneal catheter (8F) into the peritoneum and infusing 10 to 20 mL/kg of warmed 42°C isotonic fluid. The fluid is kept in the peritoneal cavity before it is removed.[15]

Extracorporeal Methods of Rewarming

This approach is the most effective method in raising core body temperature.

Hemodialysis. Hemodialysis is appropriate for patients with severe hypothermia and accompanying hyperkalemia and renal failure. The benefit is that hemodialysis is widely available and practical. It is portable and efficient. The rewarming rate ranges between 2°C and 4°C per hour, but it requires the absence of circulatory collapse.[46,47]

Continuous Arteriovenous Rewarming. Continuous arteriovenous rewarming has the ability to maintain circulation, correct hypoxia, and replenish intravascular volume without the need for systemic anticoagulation. The rate of rewarming ranges between 3°C and 4°C per hour and requires a systolic blood pressure of at least 60 mm Hg to be performed.

Continuous Venovenous Hemofiltration. Continuous venovenous hemofiltration (CVVH) has also been reported to achieve successful rewarming. It is widely available, can be performed with lower blood pressure, but provides slow rewarming rates (1°C–3°C per hour). It does not provide full circulatory support, and volume resuscitation is necessary when cardiac output is inadequate. Chest compressions and ventilation must be continued until the return of spontaneous circulation. However, it may prove to be an alternative to continuous arteriovenous rewarming when limited by profound hypotension.

Cardiopulmonary Bypass. Cardiopulmonary bypass (CPB) is the standard of care for patients with severe hypothermia, apnea, and cardiac arrest or hemodynamic instability. It provides rapid rewarming rates (8°C–12°C per hour) while maintaining oxygenation, circulation, and rapid correction of metabolic derangements.

However, the need for CPB in hypothermic trauma patients may be limited secondary to the need for systemic anticoagulation. In addition, the expert teams required for CPB make the implementation somewhat challenging.[6,15,38] Portable CPB systems are available.

Venoarterial Extracorporeal Membrane Oxygenation. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) has become the preferred method of rewarming for hypothermia less than 28°C with cardiac arrest.[48,49] The advantages of VA-ECMO over CPB include increasing availability, the ability to be continued for several days for cardiopulmonary support even after rewarming, and a lower heparinization requirement. The lower anticoagulation requirement makes VA-ECMO preferable for trauma patients. The VA-ECMO system can provide the same rate of rewarming as CPB (8°C–12°C per hour) and does not require a sternotomy.[35,38]

Endovascular Temperature Control Device. Endovascular temperature control device has been reported in recent years as another tool for rewarming in patients with severe hypothermia. It is generally placed in the emergency department for out-of-hospital survivors of cardiac arrest with return of spontaneous circulation to induce therapeutic hypothermia. It can also be used to warm patients with accidental hypothermia. Because the same device is used in both sets of patients, the operation of the equipment is familiar to both the emergency department and ICU staff. The only procedure required to place this device is a central venous catheter, which is less invasive than CPB or ECMO.[35]

Prognosis

The results of different reports on the outcome of patients with moderate to severe hypothermia have varied. Multiple confounding factors exist that make it difficult to predict survival. Older age, lower core body temperature, indoor exposure, submersion, trauma, toxin ingestion, prehospital hemodynamic status, BUN and potassium levels, the need for intubation, and presence or absence of asphyxiation are significant predictors of outcome. For patients undergoing CPB for hypothermia and hemodynamic instability, favorable factors for survival are associated with younger age, higher arterial pH, lower $PaCO_2$, lower serum potassium levels, and the absence of asphyxia and suffocation.[18] Many patients die even after achieving adequate rewarming secondary to multiorgan failure. Recognizing its detrimental outcome, an important approach should pursue prevention. In general, hypothermia is a preventable condition. Public health education and preparedness should be directed toward populations at risk.

Hyperthermia

History and Incidence

Innumerable military campaigns throughout history were lost as a result of heat illness, long before the enemy ever raised a weapon. In modern times, the Israeli Six-Day War during the late 1960s provides the best example of the ravages of heat illness. The Israeli army had forced water consumption policies, by the clock, including strict disciplinary measures for evidence of heat injury due to negligence. By contrast, the Egyptian army did not have well-enforced policies. In the end, the Israeli army's heat injury statistics were negligible, but more than 50% of the Egyptian soldiers in the same locale had heat illnesses that rendered them unable to effectively perform their expected tasks.

Heatstroke and hyperthermia have been identified as the environmental diseases least frequently monitored by epidemiology systems in the United States. Serious heat illness has received considerable recent attention owing to catastrophic heat waves in the United States and Europe, the deaths of high-profile athletes, and military deployments. The exact incidence of heatstroke in the United States is unknown. The Centers for Disease Control and Prevention reported that between the years 1987 and 1988, 1092 death certificates listed excessive heat as either a primary or a secondary cause.[50] It is suspected that a number of other heat-related severe illnesses and deaths occur each year that are attributed to other causes. Guidelines from the National Association of Medical Examiners suggest that in cases in which the measured antemortem body temperature at the time of collapse was 105°F (40.6°C) or higher, the cause of death should be certified as heatstroke or hyperthermia. Deaths also may be certified as heatstroke or hyperthermia with lower body temperatures when cooling has been attempted before arrival at the hospital or when the clinical history includes mental status changes and elevated liver and muscle enzymes.[51]

Pathogenesis

Heatstroke is a complex syndrome of end-organ dysfunction initiated by hyperthermia that occurs when heat accumulation in the body overwhelms heat-dissipating mechanisms. The diagnosis of heatstroke should be considered in patients with core body temperatures greater than 41°C, or in patients with a core temperature of 40.6°C and concomitant mental status changes. Because anhidrosis is a late finding and sweating may be observed in severely hyperthermic patients, diaphoresis should not be considered a discriminatory finding. Heatstroke traditionally is subdivided into exertional and nonexertional causes. Box 66.1 outlines examples of diseases and conditions within each of these categories. To understand the pathogenesis of heatstroke, the systemic and cellular responses to heat stress must be appreciated. These responses include thermoregulation (with acclimatization), an acute-phase response, and a response that involves the production of heat shock proteins.

Thermoregulation

At basal metabolic levels, less than 100 kcal of metabolic heat is generated per hour. However, when physical activity increases, heat production may rise as high as 900 kcal/hr. This level of heat production is capable of raising the core body temperature by 1°C every 5 to 8 minutes. Heat is dissipated via evaporation, conduction

• BOX 66.1 Conditions and Diseases Associated With Heatstroke

Exertional Causes

Environmental: high ambient temperatures/humidity

Physiologic: lack of physical conditioning, inadequate acclimatization, or overexertion

Nonexertional Causes

Environmental: high ambient temperatures/humidity, lack of air conditioning, lack of shrubbery/trees around dwelling, height of home above ground level

Physiologic: age older than 65 years, alcoholism, congestive heart failure, renal failure, diabetes mellitus, chronic obstructive pulmonary disease, dementia, schizophrenia, cystic fibrosis, thyrotoxicosis, hypokalemia, dehydration

Drugs: alcohol, antidopaminergics, anticholinergics, amphetamines, β-blockers, butyrophenones, cocaine, diuretics, hallucinogens, tricyclic antidepressants

or radiation, and convectional losses. Cutaneous vasodilation results in heat loss through all of these physical mechanisms except evaporation. Unfortunately, when the ambient temperature exceeds body temperature, only evaporative losses associated with perspiration actually dissipate heat. Perspiration can produce a maximum rate of heat loss of approximately 400 to 650 kcal/hr in acclimatized persons. When heat production exceeds this threshold, body temperature quickly begins to rise.

Acclimatization

Acclimatization is a physiologic term that collectively describes various adaptive responses to repeated heat stress. Many of these responses are directed at conserving plasma volume. They include decreased total sweat sodium concentration and nonreflexively increased aldosterone secretion. In addition, acclimatized people tend to drink greater volumes of water and have measurable increases in extracellular fluid volume beyond that of nonacclimatized persons. Ultimately, maximum cardiac output and stroke volume increase, while maximum heart rate and oxygen consumption decrease (improved efficiency per unit of metabolic work expended).[52] Similarly, the net amount of heat generated per unit of work expended also decreases.

Acute-Phase Response

The acute-phase response, involving endothelial cells, leukocytes, and epithelial cells, protects body tissues from heat-induced tissue injury. A variety of immunomodulatory and inflammatory cytokines are released in response to increased endogenous or environmental heat, including interleukin (IL) 6 (IL-6), tumor necrosis factor α (TNF-α), IL-10, IL-12, and interferon.

Heat Shock Response

Cells respond to heat by production of inducible heat shock proteins that help induce a state of tolerance to heat stress. These proteins function as molecular chaperones that bind to partially folded or misfolded proteins and thereby prevent their irreversible denaturation. Heat shock proteins also may help regulate the baroreceptor reflex response during heat stress, abating hypotension and bradycardia.

Predisposing Factors

The epidemiology of heatstroke parallels that of hypothermia—nonexertional heatstroke is seen in elderly, alcoholic, or otherwise debilitated patients in urban areas. By contrast, exertional heatstroke develops in otherwise healthy people who overexert themselves in exceedingly hot or humid conditions. Like hypothermia, heatstroke most often develops in patients with impaired thermoregulation. Antidopaminergic drugs, alcohol, and primary central nervous system (CNS) disorders are common denominators in many patients.[52] A number of environmental and socioeconomic conditions have been associated with heatstroke in recent years.[53,54] A lack of air conditioning and a lack of trees or shrubbery around homes are commonly observed in patients presenting with heatstroke. People who are apartment bound, particularly those on higher floors, also appear to be at higher risk during summer heat waves. Finally, elderly patients not only have diminished temperature perception but also do not produce the same volume of sweat, placing them at higher risk for the development of heatstroke.

Many drugs—"recreational" and prescription—are associated with an increased risk of hyperthermia and deserve further emphasis. Cocaine causes generalized sympathetic activation and loss of response to environmental cues. It is rapidly becoming a leading cause of heatstroke in many urban emergency departments. β-Blockers, on the other hand, have been implicated in heatstroke through a drug-mediated direct decrease in sweat gland production. Diuretics decrease baseline circulating plasma volume, leading to decreased sweat production. Hypokalemia decreases sweat gland output as well, and barbiturates can even cause sweat gland necrosis. When a heat wave arrives in an urban area, any one or several of the foregoing factors combined can lead to outbreaks of heat injury.

Presentation and Clinical Manifestations

Nonexertional heatstroke may manifest insidiously.[55] An urban setting and the recognized presence of a heat wave may be the best available diagnostic clues. Some form of CNS dysfunction is nearly universal in patients with nonexertional heatstroke. The spectrum of dysfunction ranges from increased irritability and confusion to stupor and coma. Hyperpyrexia often is the most specific physical finding. In many cases, the presentation of an elderly patient with an altered mental status, irritability, and a high fever suggests sepsis. However, epidemiologic associations, concurrent debilitating disease, and the impact of medications that limit thermoregulation should be considered before limiting therapy to empiric antibiotics and antipyretic medications.

Exertional heatstroke typically occurs more suddenly and with a more self-evident clinical history.[56] Severe dehydration, anhidrosis, and extreme hyperpyrexia are common in external heatstroke. Affected persons appear hyperdynamic, with tachycardia, increased cardiac output, and peripheral arterial vasodilation. CNS dysfunction is somewhat less common in this patient subset. Initially, thermoregulation is intact in patients with exertional hyperthermia. At high core body temperatures, however, metabolic activity overwhelms normal heat dissipation mechanisms, and clear-cut disruption of normal thermoregulation may then appear. Hyperthermia is further accelerated by the loss of effective sweating for evaporative heat dissipation. Myocardial dysfunction with depression of left ventricular ejection fraction also has been described after heatstroke, which resolves with treatment.[57]

In addition to alterations of consciousness, hallucinations, focal neurologic deficits, various cranial nerve abnormalities, and opisthotonos are well described. Seizures occur in more than half of these patients and may be related strictly to core body temperature or to concomitant disorders of free water–electrolyte balance. Decerebrate posturing also is rarely observed in some patients without other known mechanisms of acute brain injury. Many patients may have residual defects, such as dementia, personality changes, focal deficits, cerebellar changes, or pyramidal findings. Nevertheless, many patients also proceed to complete recovery, suggesting that early findings should not deter acute management.[54]

Diagnostic Approach

In addition to CNS dysfunction, rhabdomyolysis is a frequent feature of exertional hyperthermia. Manifestations sometimes include tender, edematous muscles and "cola-colored" urine, but the condition more commonly is defined by elevation in total creatine kinase (CK), serum aldolase, uric acid, or serum potassium (alone or in combination). Hyperkalemia in this situation may be life-threatening.

Acute renal failure occurs in up to one-third of patients with heatstroke.[58] It is considerably more common in patients in whom rhabdomyolysis is a feature (i.e., with myoglobinuria or urate

nephropathy). However, direct heat injury and renal hypoperfusion also may contribute. Acute tubular necrosis in heatstroke typically manifests with oliguria, nonnephrotic range proteinuria, and abundant granular cast formation.

Evidence of hepatocellular injury is present to some degree in essentially all patients with heatstroke and is attributed principally to a direct toxic effect of hyperthermia on hepatocytes.[59] Elevation of serum transaminases is a cardinal feature of this toxicity and often is observed within 30 minutes of syndrome onset. So prevalent is this finding that the absence of transaminitis should cast serious doubt on the diagnosis of heatstroke. Histologic changes including centrilobular necrosis have been observed within 24 hours of heat injury and evolve over the ensuing days. Transaminase and lactate dehydrogenase levels typically peak on the third or fourth hospital day, and depending on the extent of injury, these changes may be accompanied by increased alkaline phosphatase levels, hyperbilirubinemia, and a prolonged prothrombin time. Overall, fulminant hepatic necrosis is rare; however, hepatic insufficiency contributes to late morbidity and death in patients who survive the initial resuscitation.[60] Prolongation of coagulation times also may be due to disseminated intravascular coagulation (DIC). Although clinical DIC also is rare, it is a marker of poor prognosis when present. Clinical manifestations of DIC range from isolated laboratory abnormalities to generalized bleeding. In patients with heatstroke, DIC may exacerbate hepatic injury and is associated with the development of acute respiratory distress syndrome (ARDS). In fact, the codevelopment of DIC and ARDS in patients with heatstroke is predictive of a high mortality rate (>75%). Qualitative coagulation function (including platelet function) also may be impaired by heat injury. The clinical effects of these impairments are variable.

A range of electrolyte abnormalities related to renal failure and dehydration in heatstroke victims has been well described and includes hyponatremia, hypocalcemia, hypokalemia (hyperkalemia in patients with acute tubular necrosis or rhabdomyolysis), hypophosphatemia, and hypomagnesemia. Of these, hyponatremia and free water excess may produce severe neurologic effects including central pontine myelinolysis, which has been reported in patients with heatstroke who receive aggressive prehospital resuscitation with hypotonic solutions. Serum osmolality should be carefully monitored during volume resuscitation, and IV solutions should be modified accordingly. Severe lactic acidosis is especially common in patients with exertional heat injury.[61] Finally, arterial blood gas results are influenced by temperature in a fashion opposite that described with hypothermia (Box 66.2).

• BOX 66.2 Temperature Correction Factors for Arterial Blood Gas Specimens[a]

ABG Component Correction Factor

$pH + 0.015 (37 - T_c)$
$Pao_2 - 0.072 (37 - T_c) \times Pao_2$
$Paco_2 - 0.044 (37 - T_c) \times Paco_2$

Example

A patient presents with a core temperature of 32°C with the following ABG values: pH 7.12, $Paco_2$ 52 mm Hg, and Pao_2 52 mm Hg. Corrections for temperature are as follows:

$pH = 7.12 + [0.015 (37 - 32)] = 7.195$
$Pao_2 = 52 - [0.072 (37 —32) \times 52] = 33.28$ mm Hg
$Paco_2 = 52 - [0.044 (37 - 32) \times 52] = 40.56$ mm Hg

These corrections also may be used for hyperthermia.

[a]*Arterial blood gas values not corrected for temperature in significantly hypothermic patients yield falsely low pH and falsely elevated $Paco_2$ and Pao_2 values.*
Pao_2, *Partial pressure of oxygen;* $Paco_2$, *partial pressure of arterial carbon dioxide;* T_c, *core temperature.*

Approach to Management

Duration of extreme hyperpyrexia is the single most important determinant of morbidity and fatality in all patients with heatstroke (both exertional and nonexertional). Therefore expeditious cooling should be initiated simultaneously with other basic and advanced life support modalities. Indeed, a review of outcome data for heatstroke victims during the Chicago heat wave of 1995 suggested that computed tomography imaging of the brain contributed little to patient management and simply delayed efforts to rapidly cool the patient.[62]

On-site cooling offers an attractive potential advantage in large sporting events where a significant number of exertional heat strokes can be anticipated. Data from the Indianapolis half marathon would support the feasibility of such a plan.[63] Between 2005 and 2012, 22 of 32 (69%) patients who developed heat stroke were initially treated on-site. For those treated on-site core temperatures ranged from 102.4°F to108.5°F, and 41% had hypotension with none below a systolic blood pressure of 70 mm Hg. The majority were treated with cold water immersion and the remainder with ice packs, cooled IV solutions, and cold towels. Of these patients, 9% were released home, 6 were referred to a local emergency department and released, and 3 were admitted to the hospital (1 to the intensive care unit [ICU]).

The same can be said for leveraging emergency medical services teams for earlier initiation of cooling. There is wide variation in prehospital medicine practices in the treatment of exertional heatstroke, leading to creation of a consensus statement on prehospital care.[64] A similar approach has been taken by the National Athletic Trainers' Association with release of a portion statement on external heat illnesses.[65]

Supportive Measures

Intravascular volume restoration must be individualized. In general, patients with exertional hypothermia are severely hypovolemic. Hemodynamic monitoring has demonstrated that patients may manifest two distinct responses to heatstroke: (1) a hyperdynamic response with an elevated cardiac index and depressed systemic vascular resistance and (2) a hypodynamic response with depressed cardiac index and elevated systemic vascular resistance.[58] Although the hypodynamic response may be more common in older patients with preexisting medical conditions and classic heatstroke, severe hyperthermia can lead to myocardial dysfunction even in young, healthy adults without preexisting cardiac disease. Overzealous volume resuscitation in this setting can produce significant pulmonary congestion. The rapid restoration of an adequate perfusion pressure without pressor support is a reasonable goal, and if this is achieved, further volume resuscitation should proceed at a more measured pace. Pulmonary artery catheterization is recommended early in the clinical course for patients with unclear cardiovascular physiology. Finally, isoproterenol traditionally has been considered the inotrope of choice for patients with severely depressed myocardial performance. Its lack of α-activity ensures that heat dissipation is not impeded. Dobutamine may be a more rational choice, however, because it has considerably fewer myocardial irritant and arrhythmogenic properties.

Seizures are treated according to standard guidelines. Benzodiazepines are used for acute, ongoing convulsive activity. Dilantin

is useful for added control or prophylaxis; however, hypotension with rapid IV infusion should be anticipated. Barbiturates also are effective antiseizure drugs but should be reserved as second-line therapeutic agents because of their theoretical impediment to sweat formation and heat dissipation.

Acute renal failure should be approached aggressively in patients with rhabdomyolysis. Intravascular volume repletion should be promptly accomplished, with continued infusion of volume to produce forced diuresis. Mannitol or loop diuretics may be of value to maintain appropriate urine output. Hyperkalemia management may be challenging. The clinician should not hesitate to administer glucose, insulin, and calcium in patients with electrocardiogram changes. Subsequent sodium polystyrene sulfonate (Kayexalate) dosing may also be required.

Cooling Measures

Effective heat dissipation depends on the rapid transfer of heat from the core to the skin and from the skin to the external environment. In persons with hyperthermia, transfer of heat from the core to the skin is facilitated by active cutaneous vasodilation. Therapeutic cooling techniques are therefore aimed at accelerating the transfer of heat from the skin to the environment without compromising the flow of blood to the skin, which can be accomplished by increasing the temperature gradient between the skin and the environment (for cooling by conduction) or by increasing the gradient of water vapor pressure between the skin and the environment (for cooling by evaporation), as well as by increasing the velocity of air adjacent to the skin (for cooling by convection).

Core body temperature should be rapidly cooled to a goal of 38°C to 39°C. The most effective approaches to lowering the core temperature are immersion and evaporative methods. Of these, efficacy data related to ice water immersion modalities historically have been better defined, with observed cooling rates of up to 0.13°C per minute. Similar efficacy has been noted with cool water immersion as well, which should be less uncomfortable for both patient and staff members. Unfortunately, water immersion is not practical for many critically ill patients. Monitoring and treatment for arrhythmias, seizures, and other sequelae are problematic while the patient is immersed in a tub.

Evaporative techniques are quite effective and allow the ICU patient to be placed on a bed or other supportive surface and treated accordingly. The patient is repeatedly wetted with tepid water (not alcohol) or sprayed with water mist while warm air from a fan is blown across the body surface. Evaporative cooling by this method has shown a faster cooling rate in a canine model that is as effective as aggressive peritoneal lavage cooling, reaching rates as high as 0.32°C per minute.[66] An aggressive approach to cooling the heatstroke victim, whatever the approach, is most important. Other adjuncts to cooling include rectal, intraperitoneal, and gastric lavage with iced saline solution. These techniques are effective at rapidly lowering core temperature but are cumbersome and generally unnecessary and may lead to unwanted iatrogenesis.

Efforts to cool a patient should be discontinued when the core temperature falls to 38°C to 39°C. At that point, a continued fall by 1°C or 2°C is expected. Dantrolene sodium has been used in some patients but was found to be ineffective in a double-blinded randomized study.[67,68] Chlorpromazine may be useful in patients in whom shivering develops during active cooling efforts; however, if neuroleptic malignant syndrome (NMS) is in the differential diagnosis (and it often is), meperidine may be a better option than an antidopaminergic agent in patients with normal renal function.

Specific Hyperthermic Syndromes

Malignant hyperthermia (MH) and NMS deserve special emphasis because of their potentially catastrophic impact on critically ill patients, particularly when they are not promptly recognized. MH is associated with use of certain anesthetic agents and can lead to profound skeletal muscle contraction and the subsequent development of life-threatening hyperthermia and other complications. NMS is caused by a variety of antipsychotic drugs and also leads to sustained muscular contraction and hyperthermia.

Malignant Hyperthermia

MH develops in approximately 1 of 15,000 patients who undergo surgical procedures requiring general anesthesia. The vast majority of cases are associated with either halothane or succinylcholine use; however, a variety of other drugs also have been implicated. Box 66.3 outlines these agents by type. Unlike in heatstroke, endogenous heat production is solely responsible for the observed hyperpyrexia. MH constitutes a true medical emergency because of the rapid tempo at which severe sequelae evolve. Better recognition of this syndrome and modern treatment techniques, however, have reduced mortality rates from 70% to approximately 10% in recent years.

Pathogenesis

MH results from a rapid, sustained increase in myoplasmic calcium ion (Ca^{2+}) levels in response to halogenated anesthetics and depolarizing neuromuscular blocking agents. Susceptibility to MH results from mutations in calcium channel proteins that mediate excitation-contraction coupling, with the ryanodine receptor calcium release channel representing the major locus. The mode of inheritance appears to be autosomal dominant, with variable penetrance. The phenomenon occurs in persons who have

• BOX 66.3 Anesthetics Associated With the Development of Malignant Hyperthermia and Neuroleptic Malignant Syndrome

Malignant Hyperthermia

Volatile Anesthetics

Cyclopropane, diethyl ether, enflurane, ethylene, halothane, isoflurane, methoxyflurane, sevoflurane

Muscle Relaxants

Succinylcholine, decamethonium

Neuroleptic Malignant Syndrome

Phenothiazines

Fluphenazine, chlorpromazine, levomepromazine, thioridazine, trimeprazine, trifluoroperazine, prochlorperazine

Butyrophenones

Haloperidol, bromoperidol, droperidol

Dibenzoxepine

Loxapine

Dopamine-Depleting Drugs

α-Methyltyrosine, tetrabenzamine

Dopaminergic Agent Withdrawal

Levodopa-carbidopa, amantadine

a mutation in the ryanodine type 1 receptor, resulting in a defective protein in the skeletal muscle sarcoplasmic reticulum membrane.[69] The uncontrolled rise in the myoplasmic Ca^{2+} concentration disables the troponin inhibition of actin and myosin, resulting in uncontrolled muscle tetany. This surge in muscle metabolic activity causes thermogenesis to increase exponentially and is rapidly followed by total body rigidity and extreme hyperpyrexia.

Numerous familial myopathies (such as Evans myopathy, King-Denborough syndrome, and central core disease) have been associated with the reaction.[70,71] Curiously, this genetic predisposition does not translate into the predictable development of MH. That is, an initial challenge with an anesthetic drug that leads to MH does not consistently predict whether or not MH will occur with future exposures to the same drug. Measured contraction in caffeine or halothane preparations of muscle biopsy specimens is the most reliable predictor of risk for MH.

Presentation

MH is characterized by the triad of (1) severe hyperthermia, (2) muscle rigidity, and (3) metabolic acidosis. MH usually is an acute and rapidly progressive process; however, many reports suggest that the syndrome may vary considerably in severity and rate of progression. In the anesthesia setting, capnography may provide the earliest clue of impending MH, as end-tidal carbon dioxide rises in response to the increased metabolic rate. Clinical harbingers of impending MH include masseter muscle rigidity or trismus and tachycardia, which is reported to occur in more than 95% of patients.[70] Cyanosis, increased blood pressure, and increased respiratory rate all may be observed with the onset of the reaction as the hypermetabolic response is triggered.

Muscle rigidity may explosively progress from localized masseter contraction to diffuse rigidity of skeletal muscle groups. When uninterrupted, this process will lead to progressive, severe hyperthermia. Extreme hyperpyrexia is considered a late finding in MH. Mortality risk has been related to peak core body temperature, reflecting both MH severity and delayed recognition. With progressing rigidity, a mixed metabolic and respiratory acidosis may occur, along with a variety of other electrolyte abnormalities, including hyperkalemia, hypercalcemia, and hypermagnesemia. Severe chest wall rigidity may even prevent adequate mechanical ventilation, leading to life-threatening hypoxemia and hypoventilation. Rhabdomyolysis is reflected in elevated CK levels, usually greater than 1500 units/L and often greater than 10,000 units/L. Myoglobinuria may produce acute tubular necrosis with oliguric renal failure and severe DIC. High fever may result in myocardial dysfunction, pulmonary edema, and cerebral edema.

Diagnosis

Susceptibility to MH can be identified unequivocally only by an in vitro muscle test. Fascicles of muscle obtained from the thigh by biopsy are exposed to halothane and separately to increasing concentrations of caffeine in vitro. The muscle contractures are increased in persons who are susceptible to MH. This test is now widely used to identify susceptibility to MH in patients who have had a reaction to inhaled halogenated anesthetics or suxamethonium that is suggestive of MH. If the test results in the propositus are positive, testing can be offered to first-degree relatives for genetic counseling. Patients whose biopsied muscle demonstrates a contracture to 3% halothane of 0.5 g or more and a contracture to 2 mmol/L caffeine of 0.2 g or more are considered to be susceptible to MH.[72] An in vitro contracture test is the gold standard for diagnosing susceptibility to MH. Two different protocols are used. European laboratories use the protocol devised by Ellis in Leeds with incremental doses of halothane up to 2% and incremental doses of caffeine. In the United States, a single dose of 3% halothane and incremental doses of caffeine are used. The two protocols yield essentially the same results.[73]

Treatment

By far, the most important measure for MH is the immediate cessation of any suspected triggering agents. If anesthesia must be maintained, nontriggering agents should be used. Agents considered safe in MH include barbiturates, narcotics, benzodiazepines, and propofol, to name only a few. Nondepolarizing neuromuscular blockers such as vecuronium or atracurium, although also considered safe in these patients, will do nothing to abort the MH reaction because the primary disease resides within the skeletal muscle cell itself—beyond the neuromuscular junction.

In addition to discontinuing offending agents, sodium dantrolene should be administered. Sodium dantrolene initially was tested as an antimicrobial; however, dantrolene was found to produce muscle weakness by blocking the Ca^{2+} efflux from the sarcoplasmic reticulum. The agent is capable of reversing the MH reaction by lowering myoplasmic Ca^{2+} concentrations. The onset of action usually is within 2 to 3 minutes, with initial responses including muscle relaxation, decreasing heart rate, and decreasing core body temperature. Muscle weakness may follow drug administration, but this should never limit proper therapy. After the initial response, dantrolene may be dosed orally for 24 to 48 hours. Late recurrences of MH have been reported if inadequate dantrolene dosing occurs. IV preparations of dantrolene contain significant amounts of mannitol, which may produce a subsequent osmotic diuresis. Although this reaction may be desirable in patients with rhabdomyolysis, volume and electrolyte management should take this effect into account.

Systemic cooling may be best achieved in these complex patients with evaporative techniques, cooling blankets, cold saline solution infusion, or ice packs. Because of its similar actions on myoplasmic Ca^{2+} concentration, procainamide was the drug of choice for this syndrome before the advent of dantrolene therapy. Cardiac dysrhythmias not responding to electrolyte correction may be safely treated with procainamide or lidocaine. Numerous reports suggest that IV calcium may be safely infused for toxic hyperkalemia. Diltiazem and verapamil may interact with dantrolene to produce hyperkalemia; therefore these agents should be avoided. Although the effects of MH on cardiac muscle remain unclear, some authors advocate that cardiac glycosides also should be avoided because they increase intracellular Ca^{2+} concentration.

Neuroleptic Malignant Syndrome

NMS is an idiosyncratic reaction to neuroleptic drugs and other antidopaminergic agents.[74] A number of drugs that are known to be associated with NMS are listed in Box 66.3. NMS is characterized by muscle rigidity and altered mental status, followed by autonomic instability and hyperthermia. However, temperature elevations generally are less extreme than in MH and are not as life-threatening.

NMS is reported to occur in up to 2% to 3% of all patients receiving neuroleptic medications. The reaction typically develops within a few days of initiating therapy and almost always appears within the first 30 days. Curiously, NMS also occurs rarely in

some patients after many years of a stable dosing regimen. Of importance, NMS also can occur in response to the withdrawal of central dopaminergic agonists such as bromocriptine or levodopa-carbidopa.

Pathophysiology

Some investigators suspect that the genetic predisposition to MH also defines patients at risk for NMS, but most work has failed to demonstrate a relationship between NMS and altered sarcolemmal membrane calcium permeability. Unlike in MH, patients with NMS appear to have both increased heat production and impaired central thermoregulation, compromising heat dissipation. In these patients, a decrease in central dopaminergic tone also results in extrapyramidal signs of skeletal muscle rigidity and tremor and may account for alterations in mental status owing to effects in the mesolimbic system and mesocortical pathways.[75] Finally, even though altered central thermoregulation may contribute to hyperthermia in NMS, rapid resolution of fever after administration of neuromuscular relaxing agents or dantrolene suggests that hyperthermia is due primarily to increased heat generation by skeletal muscle rigidity.

In intubated patients who have sustained multisystem trauma and are supported by mechanical ventilation, fever and tachycardia are not uncommon and mental status changes cannot be adequately evaluated.[76] Rhabdomyolysis is not uncommon in this population. It may be difficult to elucidate a history of neuroleptic medications and heightened vigilance is required.

Presentation

NMS should be considered when fever, muscular rigidity, catatonia, or dystonia occur in the setting of neuroleptic drug administration. Recent reviews have suggested the following criteria for the diagnosis of NMS: treatment with neuroleptics within 7 days; hyperthermia with core temperatures above 38°C; muscle rigidity; exclusion of other systemic or drug-related illness; and any five of the following: altered mental status, tachycardia, hypertension or hypotension, tachypnea or hypoxia, diaphoresis or sialorrhea, tremor, incontinence, CK elevation or myoglobinuria, leukocytosis, or metabolic acidosis.[75,77]

Altered mental status commonly precedes the onset of other symptoms and may manifest as confusion or agitation. More severe cases may progress to obtundation or coma or may manifest as a mute catatonia that is difficult to differentiate from lethal catatonia. Muscle rigidity typically involves the neck, shoulders, and limbs but may compromise ventilation if chest wall involvement is severe. Other neuromuscular findings are diverse and may include dysarthria, dyskinesias, ataxia, or tremors.

Autonomic findings typically include diaphoresis, hypertension, and tachycardia. However, hypotension may develop in some patients. Fever is a late finding and usually occurs in the range of 38°C to 42°C. When fever exceeds 42°C, it may cause end-organ damage like that seen in other hyperthermia syndromes.

Rhabdomyolysis occurs often, though it usually is of a milder caliber than that observed in MH or exertional heatstroke. Elevations in serum transaminases, BUN, and serum Cr often are seen, as well as a leukocytosis.

Treatment

When NMS is suspected, the offending drug should be discontinued immediately and supportive measures initiated. Volume resuscitation, physical measures for cooling, and monitoring of cardiopulmonary and renal parameters should be instituted immediately. Pharmacologic options for the treatment of NMS are more numerous than for other hyperthermia syndromes, because they may be directed toward restoring central dopaminergic tone or reducing peripheral rigidity until the neuroleptic effects subside.

Dopamine agonists such as bromocriptine, amantadine, and levodopa-carbidopa have been successfully used in NMS.[75,78] These agents act to directly increase central dopaminergic tone, thereby antagonizing the various effects of neuroleptic dopamine blockade. Regimens include bromocriptine or amantadine for up to 10 days before tapering. If a levodopa-carbidopa combination is used, it should be dosed four times a day owing to its shorter half-life. Some authors advocate avoiding central dopamine agonists if the diagnosis is unclear or if psychosis remains in the differential diagnosis, to avoid acutely exacerbating the psychotic state or contributing to a lethal catatonia.

Sodium dantrolene has been successfully used in numerous small series. The muscle relaxation that occurs helps to reduce temperature and decrease the sequelae of prolonged rigidity. Neuromuscular blockers also are effective at decreasing skeletal muscle tone, and in patients with high fever and autonomic instability, these agents offer a rapid means of establishing therapeutic effects. Combinations of central dopamine agonists and peripheral-acting agents have not as yet demonstrated a significant advantage over either treatment alone. Electroconvulsive therapy has been used in a number of reports, but its advantages over supportive care alone have not been adequately assessed.[78] Furthermore, the need for anesthesia presents an additional hazard that may complicate management in these patients.

Airway-protective reflexes should be vigilantly assessed because dystonia and impaired bulbar functions increase the risk of gastric aspiration in patients with NMS. Morbidity and mortality risks in these cases often arise from pulmonary complications, such as aspiration, pneumonia, ARDS, or pulmonary embolism. Cardiac complications such as arrhythmias or myocardial infarction in more fulminant cases also contribute to fatality in these patients. As in all of the hyperthermia syndromes, worsening rhabdomyolysis and acute renal failure have been identified as signs of poor prognosis.

Rhabdomyolysis

Rhabdomyolysis is a pathologic state in which the necrosis of muscle cells, through trauma, toxins, medications, or other causes, leads to an excess of intracellular solutes in the extracellular compartments. Target organ damage can range from minimal to severe depending on the degree of necrosis; the main consequences are metabolic abnormalities and acute kidney injury (AKI). Our understanding of the pathophysiology of rhabdomyolysis has evolved with an emphasis on early diagnosis and treatment, often in the setting of major catastrophes. The first report in the English literature, describing four cases of crush injury in Britain during World War II, was recently republished.[79]

Epidemiology

The incidence of rhabdomyolysis is dependent on the population undergoing analysis and the diagnostic criteria being used. It is recognized as a major cause of fatality after severe musculoskeletal injury from trauma.[80] Following the 1999 Marmara earthquake in northwestern Turkey, 8.9% of hospitalized patients required

renal replacement therapy for crush-related injuries.[81] Recently a particular focus has been the ability of the HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) inhibitor class of medications to cause rhabdomyolysis. Though likely a class phenomenon and rare overall, the incidence of rhabdomyolysis is not equivalent for all medications and is increased with the addition of other specific agents, particularly gemfibrozil, other fibrates, or cyclosporine.[82,83] Additional causes of rhabdomyolysis are listed in Box 66.4.[84–89] One recent review noted exogenous toxins, both prescribed and illicit, to be responsible for nearly 50% of cases.[90] In particularly, cocaine and 3,4-methylenedioxymethamphetamine, more commonly referred to as ecstasy, can cause muscle injury leading to rhabdomyolysis.[91,92]

Two additional scenarios that have received significant attention include "propofol infusion syndrome" and the potential for patients with sickle cell trait (SCT) to develop rhabdomyolysis. Both of these situations occur in younger patients. Propofol is rarely associated with a syndrome of metabolic acidosis and rhabdomyolysis. Risk factors include high-dose infusions over a prolonged period and a young age.[93–96] SCT with subsequent rhabdomyolysis owing to exertional sickling is now recognized as a cause for sudden deaths in young patients during strenuous workouts, in particular, football.[97–103] SCT was recently noted to be associated with exertional rhabdomyolysis in a population of U.S. Army soldiers.[104] The epidemiology of rhabdomyolysis is limited by a lack of uniformity regarding the critical value in CK elevation needed to make the diagnosis. Threshold values above which rhabdomyolysis may occur vary and have ranged from 1000 to 10,000 units/L, though 5000 to 10,000 units/L are most common.[105] From an intensivist's perspective, CK elevations less than 5000 units/L should not lead to myoglobin-induced renal failure unless clear additive causes such as volume depletion, sepsis, or radiocontrast are also present.

• BOX 66.4 Causes of Rhabdomyolysis[a]

Trauma/crush injuries
Prolonged immobilization
Electrical injury
Excessive muscular activity
- Excessive exertion especially in sickle cell trait patients
- Malignant hyperthermia
- Neuroleptic malignant syndrome

Infections
- Bacterial infections, in particular, those involving organisms causing pneumonia, muscle inflammation (pyomyositis), or sepsis
- Viral infections including those due to human immunodeficiency virus, influenza virus, coxsackievirus, and Epstein-Barr virus

Medications[b]
- 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors
- Gemfibrozil
- Paraphenylenediamine (hair dye)
- Phenothiazines
- Theophylline

Toxins
- Cocaine
- Carbon monoxide
- Amphetamines including *N*-benzylpiperazine-based medications
- Alcohol
- *Tricholoma equestre* (wild mushrooms)
- Hemlock
- Animal venoms

Metabolic myopathies[138]
- Carnitine palmitoyl transferase deficiency
- Mitochondrial respiratory chain deficiencies
- McArdle disease
- Phosphofructokinase deficiency

[a]*In addition to the causes listed here, risk factors include excessive heat, hyponatremia, hypophosphatemia, and hypokalemia.*[139–142]
[b]*Additional medications have been associated with rhabdomyolysis.*[84,143]
HMG-CoA, *3-Hydroxy-3-methyl-glutaryl-coenzyme A.*

Pathophysiology

The primary event in rhabdomyolysis is muscle cell necrosis resulting in the accumulation of sodium and calcium intracellularly; disruption of the cell membrane and excessive requirements for adenosine triphosphate accelerate this insult.[106,107] As muscle cells undergo necrosis, intracellular substances are released and include potassium, uric acid, phosphorus, lactic acid, and myoglobin. Under normal circumstances, haptoglobin binds any free myoglobin, thus prohibiting filtration across the glomerulus. As the haptoglobin binding is overwhelmed, free myoglobin is filtered and injures renal tubular cells. This process involves free radical toxicity. Additional causes include volume depletion, renal vasoconstriction, and tubular obstruction.[84,108,109] Myoglobin and urinary tubular-protein casts are more prone to precipitation at a lower pH in experimental models. As a result, inducing an alkaline diuresis has been thought to be beneficial in cases of rhabdomyolysis.[110]

Research has suggested that it is the reperfusion of ischemic muscle as much as the ischemia itself that produces a high burden of oxygen-derived free radicals with subsequent cellular lipid membrane injury.[111] As renal function worsens, particularly when accompanied by intravascular volume depletion and renal failure, patients cannot excrete the high load of metabolites associated with muscle death, especially potassium.

Myoglobin release occurs across a spectrum of physical injuries from moderate exercise to lethal crush injuries. Myoglobinemia was noted in 39% of a cohort of Marine recruits, illustrating the frequency of mild muscle cell necrosis with strenuous exercise.[112] Obviously, not all such injuries lead to AKI. Beyond the actual amount of muscle necrosis, the development of AKI is most dependent on the degree of volume depletion present during the initial insult and the rapidity with which it is restored. Many of the syndromes that lead to the development of rhabdomyolysis, such as very strenuous exercise, crush injuries, or intoxications, are accompanied by volume depletion.

Clinical Presentation

Patients with rhabdomyolysis present with a variety of symptoms. Often there is a history of injury, weakness, or muscle pain. Dark red or brown urine may or may not be present, depending on the amount of muscle necrosis and delay from injury. Frequently, the history is limited because of altered sensorium; clues include unexplained acidosis, hyperkalemia, hyperuricemia, hypocalcemia, elevations in CK not consistent with myocardial infarction, and unexplained renal failure. Recurrent presentations warrant an evaluation for a metabolic myopathy.[113] Screening for rhabdomyolysis, through serial CK measurements, may be worthwhile in high-risk obese patients (body mass index >56 kg/m^2) undergoing gastric bypass surgery.[114] The obese population is also more at risk for rhabdomyolysis after trauma and aggressive CK monitoring may be helpful in this population.[115]

In most instances, serum CK will increase during the initial 48 hours of hospitalization. In a retrospective review of patients admitted to an ICU with rhabdomyolysis, defined as a CK level greater than 10,000 units/L, significantly higher CK levels were associated with renal failure.[116] In the group with renal failure, the mean CK levels were 47,194 and 55,366 units/L at admission and peak, respectively; in the group without renal failure, the same levels were 17,531 and 28,643 units/L.

Although myoglobin is the most important protein in terms of nephrotoxicity, serum CK is routinely used in clinical practice as a marker of disease severity. This inconsistency is due to the widespread availability of the CK assay. Myoglobin clearance is not dependent on the kidneys and thus levels peak before CK levels.[117] Consequently, the CK levels being monitored for disease activity may not correlate with the timing of the renal injury. AKI owing to peak CK levels less than 5000 units/L should not be attributed to rhabdomyolysis unless the diagnosis was made substantially after the peak period of muscle cell necrosis; in this scenario, the CK levels will have decreased from a previously undocumented level.

The change of serum Cr in nonrhabdomyolysis oliguric AKI is usually not more than 1 mg/dL per 24 hours. In rhabdomyolysis, Cr enters the intravascular compartment at a higher rate as the result cell lysis, yielding an unusually rapid rise in serum Cr. In an early report, Grossman and associates noted a rise in Cr frequently greater than 2.5 mg/dL per day.[118] Speculation exists that this change in Cr may, in part, be due to the larger than average size in patients affected with rhabdomyolysis.[119] These same authors noted the impressive rate of renal recovery from rhabdomyolysis-induced AKI seen in the majority of patients; this high rate of recovery is now well recognized.

Specific Treatment Requirements

The most important intervention to limit renal complications of crush-related injuries is early and aggressive volume resuscitation. Delays in initiation of IV fluid are associated with a higher frequency of patients requiring renal replacement therapy.[120] The damaged muscle cells provide a large reservoir for fluid sequestration; as a result large volumes of IV fluids have to be given and, ideally, should be instituted as early as possible, even on-site before victims of crush injuries are freed.[86,121]

A debate exists in the medical literature regarding the ideal type of volume resuscitation. As previously mentioned, alkaline diuresis has been shown in animal models to decrease the formation of myoglobin casts and subsequent AKI.[110] Similarly, mannitol is an agent favored for its proposed ability to scavenge free radicals and to reduce tissue swelling owing to osmotically induced fluid removal from damaged muscle.[122,123] These treatments have not been validated in well-designed, prospective trials. Retrospective studies suggest variable benefits with the addition of mannitol or alkaline diuresis over normal saline solution alone.[124,125] In addition, there are potential risks to volume expansion with bicarbonate-based solutions or mannitol. They include the increased risk of calcium-phosphate complex formation and hypocalcemia from an increase in pH. A hyperosmolar state may occur if mannitol is used in a state of impaired kidney function. Finally, mannitol may *increase* the risk of renal failure in certain populations.[126] Risk factors for mannitol-induced AKI include kidney dysfunction, high-dose mannitol therapy, and use of cyclosporin A. In summary, volume expansion irrespective of the type of agent is the most important treatment modality. The focus on adequate diuresis is appropriate but presumes myoglobin-induced renal damage is ongoing. Intensivists often encounter patients whose myoglobin load is falling and whose renal insult has already occurred. Although the Cr level may continue to rise, the onset of oliguria suggests limited benefit from further aggressive volume resuscitation, presuming adequate intravascular volume has been restored. In fact, given the good prognosis of AKI, overzealous volume resuscitation risks pulmonary compromise.

Historically, extremely aggressive volume resuscitation was pursued with an initial goal diuresis of up to 12 L/day, presuming intact renal function. Less aggressive volume resuscitation may be equally protective though data are lacking. The focus on diuresis downplays the importance of establishing and maintaining adequate intravascular volume. Central venous pressure or other means to monitor intravascular pressure may be more useful to determine adequate resuscitation. It is also likely that the rapidity with which volume status is restored, irrespective of the type or quantity of diuresis, is the key determinant. Unfortunately, these guidelines are poorly studied in a prospective format.

In the setting of AKI requiring renal replacement therapy, the ideal modality is the one most easily accessible, assuming hemodynamic stability. Options include hemodialysis, peritoneal dialysis, and continuous modalities. Although continuous renal replacement modalities provide the best theoretical protection from ongoing metabolic and volume complications, its superiority has not been verified in rigorous trials. In cases associated with large-scale injuries such as earthquakes, the remaining infrastructure often dictates which dialytic modality can and should be provided.[80,127] Historically, peritoneal dialysis has not been considered adequate in its ability to remove the large solute load present with rhabdomyolysis.[128] Nonetheless, if it is the only available modality, its potential role in managing rhabdomyolysis may be improved with more frequent exchanges. It should be noted that no traditional renal replacement method has the capability to remove myoglobin because of its size. However, considering the rapid extrarenal clearance of myoglobin, it is unclear if therapy focused on myoglobin clearance will provide any superiority over current care. A novel approach recently evaluated the use of super high-flux (SHF) membranes to clear myoglobin during continuous venovenous hemofiltration.[129,130] The authors demonstrated a fivefold increase in myoglobin removal but did acknowledge the potential for the removal of albumin, clotting factors, and protein-bound medications. A randomized study is currently under way to evaluate the potential for an extracorporeal therapy device, coupled to a continuous venovenous hemofiltration machine, to remove myoglobin.[131]

Hypocalcemia is common in rhabdomyolysis and may provide challenging management choices. Calcium entry into necrotic muscle cells often causes profound hypocalcemia. Calcium supplementation should be reserved for those patients with symptomatic hypocalcemia as hypercalcemia is a frequent finding during disease recovery.[132] In addition, rapid increases in serum pH through the administration of IV bicarbonate may worsen hypocalcemia. Rasburicase has been reported to reduce hyperuricemia in young patients with rhabdomyolysis.[133]

Additional issues include close monitoring for limb ischemia owing to compartment syndromes induced by muscle damage and subsequent fluid sequestration. Intracompartmental pressure monitoring may predict the need for intervention, although research has suggested additional factors—most importantly hypotension and the difference between mean arterial pressure and intracompartmental pressures—influence whether compartment syndrome develops.[134] The history, logic, and disappointing results of early and aggressive fasciotomy have recently been described.[135] Mannitol

is postulated to "decompress" intracompartmental edema in acute muscle compartment syndromes. Animal data support an acute reduction in intracompartmental pressures[136]; long-term tissue protection and human outcomes have not been validated. High-dose corticosteroids have been proposed as a treatment option for refractory cases of rhabdomyolysis but prospective studies are lacking.[137]

In summary, rhabdomyolysis is a frequent, treatable disorder. Extensive metabolic research has yielded a number of clues about the cause of AKI during rhabdomyolysis. Therapy should emphasize aggressive and early volume resuscitation. Renal replacement therapy may be necessary to assist in managing the metabolic complications of patients; patients have a good prognosis for recovery of rhabdomyolysis-induced AKI.

Key Points

- Populations at risk for hypothermia include the elderly, people with preexisting chronic medical conditions, and people with alcoholism and drug intoxication. Emerging populations include wilderness enthusiasts and winter sport participants.
- All intervals—PR, QRS, and QT—are prolonged secondary to hypothermia-induced slowed impulse conduction through potassium channels.
- Patients with moderate or severe hypothermia should be resuscitated until adequate rewarming is achieved before declaring efforts as unsuccessful.
- The diagnosis of heatstroke should be considered in patients with core body temperatures greater than 41°C.
- Severe dehydration, anhidrosis, and extreme hyperpyrexia are common in external heatstroke.
- Myocardial dysfunction with depression of left ventricular ejection fraction also has been described after heatstroke that resolves with treatment.
- Acute renal failure occurs in up to one-third of patients with heatstroke.
- Intravascular volume restoration must be individualized. In general, patients with exertional hyperthermia are severely hypovolemic.
- The most effective approaches to lowering the core temperature are immersion and evaporative methods.
- By far, the most important measure for MH is the immediate cessation of any suspected triggering agents.
- NMS is characterized by muscle rigidity and altered mental status, followed by autonomic instability and hyperthermia.
- Dopamine agonists such as bromocriptine, amantadine, and levodopa-carbidopa have been successfully used to treat NMS.
- Rhabdomyolysis is unlikely to lead to renal failure with a creatine kinase level below 5000 units/L unless volume depletion or another kidney insult is present.
- Aggressive volume resuscitation is more important than the type of volume replacement given to reduce the risk of myoglobin-induced AKI in cases of rhabdomyolysis.
- Alkaline-based volume resuscitation may worsen hypocalcemia.
- Rhabdomyolysis-associated AKI, including cases requiring renal replacement therapy, has a good prognosis.

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Review Questions

1. Which of the following is the most correct statement regarding heat regulation?
   - **a.** Heat conservation is achieved by peripheral vasodilation.
   - **b.** Heat production is achieved through shivering and continues irrespective of the severity of hypothermia.
   - **c.** No shivering thermogenesis is achieved via increased levels of growth hormone.
   - **d.** The hypothalamus plays a central role in heat regulation upon cold exposure.

   Answer: d. Upon cold exposure, the hypothalamus initiates mechanisms for heat conservation and heat production. Heat conservation is achieved by peripheral vasoconstriction, reducing heat conduction to the skin, and behavioral responses such as wearing more clothes and seeking a warmer environment. Heat production is achieved through stimulation of muscular activity via shivering, which can increase the basal metabolic rate by two to five times. A nonshivering thermogenesis occurs via increased levels of catecholamines and thyroxine. This coordinated physiologic response occurs typically for temperatures between 32°C and 35°C. It only lasts for few hours, after which muscle fatigue and glycogen depletion ensue. As the core temperature drops below 32°C (90°F), shivering thermogenesis abates, and nonshivering thermogenesis slows down. By temperatures below 20°C to 24°C, the different mechanisms of heat production completely fail.
2. Which of the following clinical scenarios describes a patient most likely to be predisposed to hypothermia?
   - **a.** 79-year-old man hospitalized taking haloperidol (Haldol) with acute onset of agitation and muscle rigidity
   - **b.** 45-year-old well-nourished woman running a marathon in June
   - **c.** 28-year-old woman hospitalized in the emergency department with tachycardia, weight loss, and sweating
   - **d.** 75-year-old man with Parkinson disease and psoriasis and taking metoprolol for hypertension walking in the wilderness in January

   Answer: d. The first patient is at a risk of neuroleptic malignant syndrome with is associated with hyperthermia. The second patient could be at risk of heat stroke, which is associated with hyperthermia, although less likely owing to the fact that she is active and can make sound judgment to access water and shelter. The third patient should be evaluated for possible hyperthyroidism, which is associated with hyperthermia. The last patient has multiple risk factors for hypothermia including impaired thermogenesis because of age, Parkinson disease, and use of β-blockers. Increased heat loss occurs as the result of cold weather and psoriasis.
3. Which of the following is the most accurate statement regarding cardiac resuscitation during hypothermia?
   - **a.** The hypothermic heart is adequately responsive to vasoactive medications.
   - **b.** Any heart rate below 50 beats/min should be paced.
   - **c.** Ventricular fibrillation without a pulse requires initial defibrillation with maximum energy.
   - **d.** Adrenergic drugs should be used for temperatures below 30°C according to the usual Advanced Cardiac Life Support protocol.

   Answer: c. See the "Cardiac Resuscitation" section.
4. A 28-year-old athlete who was hit by an avalanche was rescued and brought to the emergency department pulseless with a temperature of 28°C. In addition to the ABCs (airway, breathing, circulation), which is the most correct statement regarding management?
   - **a.** Continue cardiopulmonary resuscitation (CPR) and initiate hemodialysis (HD).
   - **b.** Continue CPR and initiate continuous venovenous hemofiltration (CVVH).
   - **c.** Continue CPR and initiate venoarterial extracorporeal membrane oxygenation (VA-ECMO).
   - **d.** Continue CPR and initiate cardiopulmonary bypass (CPB).

   Answer: c. Choices a. and b. require the absence of circulatory collapse. The advantages of VA-ECMO over CPB include the increasing availability of the technology, the ability to be continued for several days for cardiopulmonary support even after rewarming, and its lower heparinization requirement. The lower anticoagulation requirement makes VA-ECMO preferable for trauma patients. The VA-ECMO system can provide the same rate of rewarming as CPB (8°C–12°C per hour) and does not require a sternotomy.[35,38]
5. A 22-year-old male presents to the emergency department complaining of diffuse cramps and decreased urine output for the past 24 hours. He is a body builder and has been increasing his training regimen over the past week. He has had poor oral intake for 2 days with intermittent vomiting. Vitals signs are as follows: pulse 110 beats/min, blood pressure 112/84 mm Hg, temperature 96.2°F, and respiratory rate 22 breaths/min. He weighs 90 kg. Laboratory test results are notable for creatinine 3.6 mg/dL, potassium 5.8 mmol/L, and bicarbonate 20 mmol/L. His urine shows trace protein, specific gravity of 1020, large blood on dipstick of urine and 0 to 5 red blood cells on microscopy. A creatine kinase (CK) level is 62,000 units/L. Despite 3 L of intravenous fluid (IVF) he remains oliguric. Which of the following statements is the most correct?
   - **a.** Mannitol is appropriate to stimulate urine output.
   - **b.** Hemodialysis will likely be needed to control hyperkalemia.
   - **c.** Calcium infusion for hyperkalemia is contraindicated because of eventual rebound hypercalcemia with rhabdomyolysis.
   - **d.** Adequate initial volume resuscitation in this condition is typically around 30 mL/kg IV crystalloid.

   Answer: b. This case presents a scenario of exertional rhabdomyolysis with oliguric acute kidney injury and hyperkalemia. The case illustrates the potential severity at initial presentation of rhabdomyolysis. In light of the patient's low urine output and the expectation that hyperkalemia from muscle cell injury may worsen, dialysis should be considered as an early intervention in this case. Beyond other forms of volume resuscitation and avoidance of offending agents, limited therapeutic options exist. Mannitol is contraindicated in oliguric AKI because of the risk of consequent hyperosmolality. Calcium may be given for emergent hyperkalemia, but a higher threshold should exist for replacement of calcium owing to hypocalcemia in the setting of rhabdomyolysis. Finally, IVF resuscitation often needs to be much larger than other critical illnesses because damaged muscle cells sequester IVF.
6. A 35-year-old male presents with exertional rhabdomyolysis and despite very evaluation showed no evidence of compartment syndrome. He is hemodynamically stable. Laboratory studies include an arterial blood gas analysis showing a pH of 7.28 and a potassium level of 5.2 mmol/L. His lactate level is 3.2 mmol/L. He is scheduled for an additional dialysis session

this day. After an initial decrease in CK, the level is now rising. Which one of the following is most important at this time?

a. Administration of 1 ampule of bicarbonate for lactic acidosis
b. Repeat evaluation for compartment syndrome
c. Increased IVF administration
d. Administration of mannitol

Answer: b. The patient now shows the possible development of compartment syndrome in part related to fluid sequestration despite an initial negative evaluation. Intracompartmental pressure monitoring should be repeated. In the presence of tissue ischemia with stable hemodynamics, the administration of IVF will not be helpful and may be harmful. Bicarbonate administration may be similarly harmful because of the potential to raise pH excessively, especially as dialysis will raise pH independently. Finally, mannitol is contraindicated in states of oliguric kidney failure.

7. A 64-year-old female is hospitalized for recent falls. Her blood pressure on admission is 80/40 mm Hg, which improves with 2 L of IVF. You are consulted for rhabdomyolysis and acute kidney injury. She has a history of coronary artery disease (prior coronary artery bypass grafting), hypertension while using lisinopril 20 mg/daily, and osteoarthritis. She takes atorvastatin 10 mg/day and ibuprofen 400 mg/day. Laboratory results on admission are as follows: potassium 4.6 mg/dL, creatinine 1.8 mg/dL (baseline 0.8), and CK 1800 units/L. Her urinalysis shows 1+ protein, specific gravity of 1.030, and no blood. Which of the following is the most correct statement?

a. CK levels are not related to the level of muscle trauma.
b. Her acute kidney injury is due to rhabdomyolysis.
c. Atorvastatin should not be continued at discharge.
d. Renal vasoconstriction from volume depletion, use of an angiotensin-converting enzyme (ACE) inhibitor, and use of a nonsteroidal antiinflammatory drug (NSAID) are the likely cause of her acute kidney injury (AKI).

Answer: d. This case shows a female presenting with AKI from volume depletion. Her renal function is impaired by the volume depletion with ACE inhibitor and NSAID use. It is unlikely this level of CK elevation will induce acute kidney injury; typically CK levels less than 5000 units/L should lead one to consider other diagnoses of AKI. The lack of blood in her urine and high urine specific gravity support volume depletion and not rhabdomyolysis as the cause of her AKI. As a result, continuation of her atorvastatin is not contraindicated at discharge. Although the cause of AKI in rhabdomyolysis is myoglobin-induced renal tubular damage, CK levels are routinely used as marker of muscle injury as they are more frequently measured than myoglobin. The one important caveat to this is CK levels may not peak until several days after muscle injury, so levels should continue to be monitored until they decline.

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Performance Improvement and Severity Scores in Critical Care

CHRISTA SCHORR AND SEAN R. TOWNSEND

CHAPTER OUTLINE

Critical Care Performance Improvement
- Background
- Quality Improvement Landscape
- Quality Improvement Interventions in Critical Care
- Practice Management: Clinician-Family Communication
- Intensive Care Unit Staffing: Intensivist-Led Team Model

Culture Transformation and Organizational Learning

Critical Care Scoring Systems
- Severity of Illness Scoring Systems
- Scoring System Use in Performance Improvement
- Model Development, Validation, Calibration, and Discrimination
- Overview of Prediction Models
- Organ Dysfunction Scoring Systems
- Scores for Early Detection of Critical Illness
- Scoring Systems for Specific Conditions

Summary and Conclusions

Critical Care Performance Improvement

An intensive care unit (ICU) at the most basic level has an obligation to continuously evaluate the quality of care delivered. Outcomes are primarily used to validate effectiveness and quality. However, another approach is to examine the processes producing those results.[1] Striving to improve quality of care is the foundation for performance improvement (PI). PI includes identifying and remedying deficiencies in processes and implementing new processes to provide better patient care and improved clinical outcomes. Clinicians' drive to provide the best possible care for ICU patients in a safe environment is shaping the standard in critical care delivery. Critical care service programs are evolving to include services beyond the walls of the ICU. Services may be provided in emergency departments, step-down units, and by outreach teams that consult for urgent issues and provide initial support for patients in unstable condition on the hospital wards. An essential component of the health care system, intensive care services require dutiful attention to operations to ensure high-quality care and continuous PI wherever critical care is delivered.

Background

In 1999 the Institute of Medicine (IOM) of the National Academies of Sciences, Engineering, and Medicine published a landmark report, *To Err Is Human: Building a Safer Health System.* The National Academies bring together committees of experts in all areas of scientific and technologic endeavor to address critical national issues and provide advice to the federal government and the public. The IOM report was widely hailed as groundbreaking in view of its documentation of the ways in which the health care system harms patients. Some of the findings about the American health care system included the following: (1) tremendous gaps exist between medical knowledge and practice; (2) adverse events harm patients far too often; (3) too many people do not receive the care they need; and (4) the system propagates waste by permitting fragmentation of care and utilization inefficiencies.[2] In *To Err Is Human*, the IOM also estimated that despite incurring costs that are 40% greater than those for the next most expensive nation in terms of health care, 44,000 to 98,000 Americans die each year as a result of errors in their health care.[2]

In 2003 in an exhaustive review of nearly 7000 patient charts across all regions of the United States, McGlynn and colleagues reported that the average defect rate, defined as the percent of cases in which care consistent with 439 indicators of quality was not delivered, approached 45% nationally.[3] Stated otherwise, patients receive the care indicated slightly more than one-half of the time. These investigators concluded that the deficits identified in adherence to recommended processes for basic care posed a continuing immediate danger to the health of the American public. These findings were unfortunately reaffirmed in 2010 when Landrigan and colleagues found high rates of adverse events even among hospitals that had participated in efforts to reduce patient harm.[4]

Donabedian Framework

Building on work begun by Donabedian, the IOM published *Crossing the Quality Chasm: A New Health System for the 21st Century* in 2001. The report outlined fundamental changes that must be made to improve health care in the United States. Donabedian had described three components of quality care—structure, process, and outcome—each of which must be addressed to effectively control and manage quality in health care settings.[5] He proposed that each overarching concept of control should be monitored using specific tools (Table 67.1). The IOM report also refined Donabedian's seven attributes of high-quality health care,

TABLE 67.1 Relationship Between Quality Areas and Management Tools With Their Relative Importance

	MANAGEMENT TOOLS		
Quality Area	Standards	Guidelines	Indicators
Structures	+++	+	+
Processes	++	+++	++
Results/outcomes	+	++	+++

Reproduced from Frutiger A, Moreno R, Carlet J, et al. A clinician's guide to the use of quality terminology. Working Group on Quality Improvement of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1998;24:860–863.

proposing instead six primary aims: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity.[6]

Quality Improvement Landscape

Based on formidable critiques of the quality of the U.S. health care system, a variety of organizations either willingly have taken up the challenge to improve health care or, through legislation, have been empowered to improve the delivery of health care in the United States. All of these efforts have led to creation of agencies or activities with relevance to the ICU.

Agency for Healthcare Research and Quality

The mission of the Agency for Healthcare Research and Quality (AHRQ) mission is to provide safe, high-quality, accessible, equitable, and affordable health care in association with the U.S. Department of Health and Human Services (HHS) and other partners to ensure that evidence is understood and used.[7] Funding for health care safety and quality improvement research may be acquired through grant applications to the AHRQ. The Comprehensive Unit-Based Safety Program (CUSP) is an example of quality improvement work, supported by AHRQ, to decrease hospital-acquired infections. CUSP methods reduced central line–associated bloodstream infections by 41%, saving 500 lives and avoiding millions in excess costs.[8]

AHRQ's associated functions have changed over the years. The 2010 Patient Protection and the Affordable Care Act (ACA) assigned comparative effectiveness research to a new independent nonprofit agency, the Patient-Centered Outcomes Research Institute (PCORI). Additionally, delivery and system innovations were moved from AHRQ to the Centers for Medicare and Medicaid Innovation.

Patient-Centered Outcomes Research Institute

Established by Congress through the ACA, the PCORI receives 80% of its funding from the Patient-Centered Outcomes Research (PCOR) Trust Fund to support research and operations. A total of $210 million was provided for years 2010 through 2012.[9] From 2013 through 2019 the PCOR Trust Fund will receive $150 million annually. Research funding began in 2012 with an estimated 1110 project awards provided through 2016.[9]

The PCORI's structure is aimed toward projects that improve patient and caregiver health decisions. Research programs focused on several national priorities, including comparing prevention, diagnosis, and treatment for a variety of people; approaching health care access; and communicating and disseminating information.[10]

Centers for Medicare and Medicaid Innovation

The Innovation Center, established by Congress through the ACA as an agency within the Centers for Medicare and Medicaid Services (CMS), was created to test models that improve care, lower cost, and advance quality payment models.[11] Several of the initiatives of the Centers for Medicare and Medicaid Innovation include accountable care organizations, primary care, and initiatives to accelerate the adoption of best practices.[11] In 2016 CMS announced the Million Hearts: Cardiovascular Disease Risk Reduction Model to improve risk assessment for cardiovascular disease.[12] This model is an example of an initiative to speed the adoption of best practice in preventing 1 million heart attacks and strokes over 5 years.

Another example is the Partnership for Patients initiative that began in 2011, focused on making hospital care safer by decreasing preventable hospital-acquired infections and improving care transitions in a reliable and efficient manner. This effort reduced hospital-acquired conditions by 21% over a 5-year period resulting in $28 billion in cost savings.[13] The success led CMS to award $110 million in ACA funds to continue improvements in patient safety.[14] In 2016 more than 4000 hospitals across 16 Hospital Improvement Innovation Networks (HIINs) organizations were contracted to engage in national initiatives to reduce patient harm and 30-day readmissions.[15] Some focuses of critical care highlighted by HIINs in their work include reducing adverse drug events, improving airway safety, maintaining antibiotic stewardship, promoting a culture of safety, and reducing sepsis mortality.[16]

National Quality Forum

Created in 1999, the National Quality Forum (NQF) is a private, not-for-profit membership organization formed to promote and implement a national strategy for health care quality measurement and reporting.[17] The multistakeholder group seeks to improve American health care through endorsement of consensus-based national standards for the measurement and public reporting of health care performance data. Working with a broad base of health care interests including governmental agencies, insurers, and various medical associations, the NQF has prevailed on hospitals to report compliance rates with their measures.[17] Approximately 300 NQF-endorsed measures are used in both private and state programs. The Pulmonary and Critical Care portfolio includes 13 endorsed measures. Areas of measurement include asthma management, mortality in patients with chronic obstructive pulmonary disease or pneumonia, and more generally, critical care mortality, and length of stay.[18] NQF's Infectious Disease portfolio includes the #0500 Severe Sepsis and Septic Shock: Management Bundle endorsed in 2012 and again in July 2017.[19]

The Joint Commission

The Joint Commission (JC), founded in 1951, evaluates, accredits, and certifies nearly 21,000 health care organizations and programs in the United States.[20] Commonly misunderstood to be a governmental agency, the JC is an independent not-for-profit organization that contracts with CMS to accredit health care organizations. The JC seeks to continuously improve the safety and quality of care not only through enforcing standards that lead to Medicare accreditation, but also by promoting quality improvement initiatives. [21]

In particular, the JC has opened the Center for Transforming Healthcare (CTH) aiming to tackle critical quality and safety

problems in health care. The center aims to achieve "high reliability" in health care, typically described as achieving extraordinarily low error rates as observed in nuclear power plant operations, aircraft carriers, commercial aviation, and so on.[22] To achieve these ends, the CTH has adopted Rapid Process Improvement as a methodology to drive change in health care. The approach emphasizes the importance of both change management as exemplified in Six Sigma process improvement, and Lean production tools aimed at increasing value and eliminating waste.[23] Using this approach, the JC has partnered with hospitals to dramatically reduce harm and improve quality in several critical care areas, including reducing sepsis mortality, hand-off communications, hand hygiene, and venous thromboembolism prevention. The CTH has published toolkits known as Targeted Solutions Tools to help hospitals achieve high reliability in several of these areas.[24]

Quality Improvement Interventions in Critical Care

Devotion to collecting, disclosing, and comparing safety and quality metrics is essential to improve critical care practice. Intervention-specific quality improvement initiatives in critical care have developed with many organizations committing resources to implement such initiatives. Some of the strategies for ICU quality improvement benefit from standardized measures available through the NQF and others; however, as practitioners take notice of the growing imperative to change the way critical care is delivered, many cutting-edge initiatives are moving forward without a consensus on which quality indicators should be applied.

The Society of Critical Care Medicine (SCCM) Task Force report recommends a stepwise approach to quality improvement, along with strong motivation, interdisciplinary team collaboration, and engaged leadership.[25] Clinicians interested in quality should understand the structure-process-outcome model, recognizing that structure, the way we organize care, is often the most difficult to change.[25] Process and outcomes, what we do or fail to do, and results we achieve may be easier measures; both have advantages and disadvantages worthy of evaluation.[25]

In 2012 the European Society of Intensive Care Medicine (ESICM) Task Force on Safety and Quality sought to identify a set of indictors that could be used to measure quality and improvement performance in any ICU around the world.[26] Nine indicators were proposed, including three regarding ICU structure, two process related, and four outcome measures (Box 67.1).[26] These indicators and other critical care quality measures are often aligned with strategies that advance more general goals such as developing a culture of safety and harm prevention.

Shewhart Model for Process Improvement

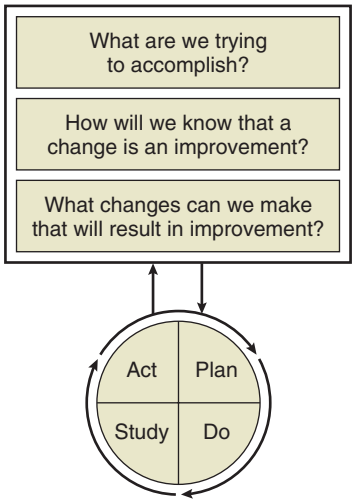
Critical care quality improvement initiatives, such as those advocated by SCCM or ESICM as already described, have typically been executed in the setting of collaborative efforts among several hospitals. Collaboration among hospitals was initially widely championed by the Institute for Healthcare Improvement (IHI) and adapted later by other groups. The IHI developed shared learning programs to improve care through various ICU collaboratives. The precise mechanisms of implementation for these initiatives vary, but most quality improvement initiatives encourage the use of small-scale experiments to test new ideas. The principle calls for organizations to make the process of scientific prediction a part of routine work and was first advanced in 1931 by Walter Shewhart, a pioneer in industrial quality control. Shewhart advocated the use of iterative "plan-do-check-act" cycles to systematically test new ideas, evaluate their results, and, if successful, implement them.[27] The IHI Model for Improvement has promoted a similar structure to accelerate improvement with the "plan-do-study-act" cycle (Fig. 67.1).[28] Organizational components include forming the team, establishing aims and measures, followed by selecting, testing, implementing, and spreading changes.[29]

• BOX 67.1 Proposed Set of Indicators to Measure Quality and Improvement in Any Intensive Care Unit

Indicator Number	Indicator Description	Indicator Type
1	ICU achieves national requirements to provide intensive care.	Structure
2	Consultant level Intensivist available 24 h a day.	Structure
3	Maintain a system to monitor adverse events for each patient.	Structure
4	Provide routine multidisciplinary clinical ward rounds.	Process
5	Standardize handover procedure (chart documentation) for discharging patients.	Process
6	Reporting and analysis of standardized mortality ratio using a calibrated severity of illness score.	Outcomes
7	Evaluate ICU readmission rates within 48 h of ICU discharge.	Outcomes
8	The rate of central venous catheter–related blood stream infection.	Outcomes
9	The rate of unplanned endotracheal extubations.	Outcomes

ICU, Intensive care unit.

Adapted from Rhodes A, Moreno RP, Azoulay E, et al. Prospectively defined indicators to improve the safety and quality of care for critically ill patients: a report from the Task Force on Safety and Quality of the European Society of Intensive Care Medicine (ESICM). Intensive Care Med. *2012;38:598–605.*



• Fig. 67.1 Institute for Healthcare Improvement model for quality improvement. (From Langley GL, Nolan KM, Nolan TW, et al. *The Improvement Guide: A Practical Approach to Enhancing Organization Performance.* San Francisco: Jossey-Bass; 1996.)

Prevention of Health Care–Associated Infections

Health care–associated infections (HAIs) are associated with poor outcomes and increased health care costs, with a large number of these infections acquired in the ICU setting. The risk of developing an HAI includes but is not limited to exposure to venous and urinary catheters and ventilators. National initiatives to reduce HAIs have demonstrated impressive results. Large-scale improvement campaigns such as AHRQ's *On the CUSP: Stop BSI* (bloodstream infections) and *On the CUSP: Stop CAUTI* (catheter-associated urinary tract infection) have attracted attention from policymakers.[30] Insights from these national improvement projects provide steps for future quality improvement programs to be more efficient and effective. Nevertheless, spreading innovation and adoption of best practices nationally remain fraught with delays.

Prevention of Ventilator-Associated Events

Reducing complications in high-risk mechanically ventilated patients requires a multidisciplinary approach and high rates of adherence to recommended evidence-based interventions. Ventilator-associated events include ventilator-associated pneumonia (VAP), peptic ulcer disease, gastrointestinal bleeding, aspiration, venous thromboembolic events, and obstacles to managing secretions. Despite variability in clinical definitions to establish valid criteria to diagnose VAP, institutions have devoted considerable effort to combating VAP rates. The Centers for Disease Control and Prevention (CDC), however, has offered a clinical definition of VAP that requires patients to be mechanically ventilated for more than 48 hours and satisfy a minimum of one radiographic, one systemic, and two pulmonary criteria.[31]

The prototypical collaborative effort to decrease VAP rates has been use of the "ventilator bundle" initially promulgated by the IHI more than a decade ago. The IHI ventilator initiative was initially launched to describe a pattern of best practices for ventilated patients, not to decrease VAP rates. Nevertheless, routine use of the ventilator bundles have been shown to reduce VAP rates.[32] A contemporary version of the ventilator bundle includes standard head of the bed elevation to between 30 and 45 degrees, provision of routine oral care with 0.12% chlorhexidine, implementation of peptic ulcer disease and deep vein thrombosis prophylaxis, as well as inclusion of elements A, B, and C from the "ABCDEF bundle."[33] The ABCDEF bundle is aimed at reducing delirium and improving pain management and outcomes for adult ICU patients.[34] Elements of the ABCDEF bundle include the following:

- **A** Assess, prevent, and manage pain
- **B** Both spontaneous awakening trials and spontaneous breathing trials
- **C** Choice of analgesia and sedation
- **D** Delirium: Assess, prevent, and manage
- **E** Early mobility and exercise
- **F** Family engagement and empowerment

Prevention of Central Line–Associated Bloodstream Infection

Prevention of central line–associated bloodstream infections (CLABSIs) has been a national priority in critical care quality improvement. The CDC has produced a standard measure that defines prevention of these infections as part of the National Healthcare Safety Network's patient safety component protocol.[35]

A typical approach to preventing CLABSIs includes four elements of care: proper hand hygiene, use of chlorhexidine for skin antisepsis, routine application of maximal barrier precautions, and optimal site selection. In a 2014 systematic review, CLABSI prevention quality improvement interventions such as care bundles and checklists were effective in risk reduction.[36] The *On the CUSP: Stop BSI* collaborative study included 1071 ICUs from 792 hospitals to prevent CLABSI rates in adult ICUs, with a unit-level mean goal of less than 1 case per 1000 catheter days.[37] Berenholtz and colleagues demonstrated a decrease in mean CLABSI rates from 1.96 cases per 1000 catheter-days at baseline to 1.15 cases in the 16- to 18-month follow-up period. These results suggest that most U.S. ICUs can achieve CLABSI reductions below the national average.[37]

Prevention of Catheter-Associated Urinary Tract Infections

Urinary tract infections are one of the most common HAIs in the ICU, primarily attributable to indwelling urinary catheters. Before the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) catheter-associated urinary tract infection (CAUTI) guideline revision in 2009, data from 1990 to 2007 showed a significant decline in national CAUTI rates among 367 facilities representing 1223 adult ICUs.[38] Depending on the type of ICU evaluated (e.g., medical, surgical, neurological) a 19% to 67% reduction in symptomatic urinary tract infection was noted; with regard to asymptomatic bacteriuria, a reduction of 29% to 72% was observed.[38] The various strategies and interventions that led to this reduction informed the HICPAC guideline revision in 2009. These include appropriate urinary catheter use, consideration of alternatives to indwelling urethral catheterization in selected patients, performing proper aseptic technique during urinary catheter insertion, following proper catheter maintenance techniques, and integration of a formal hospital quality improvement program with necessary surveillance strategies.[39]

Deploying Rapid Response Teams

The rapid response team (RRT)—sometimes referred to in the literature as a medical emergency team (MET)—is a team of nurses and other health care professionals (respiratory therapists, pharmacists, emergency department personnel, and others) who bring critical care expertise to the bedside. The teams may or may not include physicians. The essential concept is intervening to prevent harm when nursing staff and in some institutions a family member is urgently concerned about a patient's well-being. The key goal is to act before "failure to rescue" occurs and a patient has had a cardiac or respiratory arrest.[40] The team provides bedside evaluation, treatment, and if indicated, triage to a higher level of care such as the ICU or operating room.[41]

Increased interest in hospital quality and outcomes has resulted in many hospitals developing and implementing RRTs. Evidence supporting RRT adoption is mixed. Nevertheless, many hospitals have detected the need to have such a team to respond to urgent patient issues when physicians or house staff may not be readily available. In a randomized controlled study of 23 Australian hospitals, 11 hospitals functioned as usual and 12 introduced a MET system. The investigators concluded that although the introduction of the MET system led to an increase in calls to the team, it did not substantially affect the incidence of cardiac arrest, unplanned ICU admissions, or unexpected death.[42] A meta-analysis review of seven RRT studies in adults aimed to reduce cardiopulmonary arrest rates yielded mixed results. Together the seven studies

showed that implementation of an RRT in adults was associated with a 33.8% reduction in cardiopulmonary arrests outside the ICU.[43] Methods to identify deteriorating patients earlier may include an educational program, additional staffing of nurse practitioners or increasing nurse staffing to prevent deterioration, and educating caregivers to recognize the signs of deterioration may be alternatives to RRTs.[44] Additional research to assess the benefits or detrimental effects of using or not using an RRT/MET compared with other preventative designs is needed.

Resuscitation and Treatment for Sepsis or Septic Shock

The Surviving Sepsis Campaign (SSC) has been the principal driver in evidenced-based sepsis quality improvement for nearly 2 decades. The SSC was created in 2002 jointly by the SCCM and ESICM. At its inception, the campaign's aim was to change clinical practice with the development of practice guidelines and an associated PI program. The group published evidence-based guidelines for the treatment of severe sepsis and septic shock first in 2004 and subsequently in 2008, 2013, and 2017.[45–48]

Partnering with the IHI, the SSC became a global PI program after publication of the 2004 guidelines.[49] The program included the development of sepsis bundles, educational materials, recruitment of participating hospitals, and a secure database for data collection and monitoring of process and outcome measures. The initial campaign results from 15,022 subjects at 165 international sites reported a significant increase in bundle compliance and unadjusted mortality rate decrease from 37% to 30.8% over a 2-year period.[50] Subsequent analysis of 29,470 patients from 218 community, academic, and tertiary care hospitals in the United States, South America, and Europe over 7.5 years showed that increased compliance with sepsis bundles (based on the 2004 SSC guidelines) was associated with a 25% relative risk reduction in mortality, and with every 10% increase in bundle compliance, a 4% reduction occurred in hospital and ICU length of stay.[51]

These initial publications led to the development of a sepsis measure submitted to the NQF for evaluation as a validated performance measure. As noted earlier, the NQF endorsed the measure as part of its infectious disease portfolio in 2012 and again in July 2017.[52] After the initial endorsement, the measure was adopted by CMS as the first sepsis quality measure, SEP-1, in the United States. The adoption of the measure by CMS was driven in part by an observed doubling in the number of hospital stays for this diagnosis between 2000 and 2008.[53]

In 2015 the CMS released the Sepsis Bundles Project National Hospital Inpatient Quality Measures (SEP-1) early management bundle for severe sepsis/septic shock. Collection and scoring of these quality metrics were mandated to begin in late 2015. The sepsis metrics in these 3- and 6-hour bundles were essentially the same as the 2012 SSC bundles metrics. However, with the publication of the ProCESS (Protocolized Care for Early Septic Shock) and ARISE (Australasian Resuscitation in Sepsis Evaluation) trials demonstrating that successful resuscitation of septic shock could be accomplished without a central venous catheter, SEP-1 did not require central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) measurements.[54,55] Instead a reassessment of intravascular volume and tissue hypoperfusion after initial fluid bolus was required. This reassessment could include either a focused physical examination or any two of the following elements: (1) measuring CVP, (2) measuring $ScvO_2$, (3) performing cardiovascular ultrasound, or (4) ascertaining the effect of fluid bolus or passive leg raise on cardiac output.[56]

Almost coincident with the NQF measure endorsement, hospitals in New York were directed by the New York State Department of Health (NYS DOH) to follow and submit patient level data on evidence-informed protocols for early identification and treatment for patients with sepsis and septic shock. Among 49,331 patients, longer times to complete the 3-hour bundle (obtain blood cultures before initiating antibiotic treatment, measure serum lactate level, and administer broad-spectrum antibiotics) and longer time to antibiotic administration were associated with increased risk-adjusted in-hospital mortality.[57] Conversely, in this study a longer time to complete a required fluid bolus was not associated with lower mortality, although the authors indicated this finding may have resulted from confounding by indication.[57] Overall, sepsis protocols that include early identification and rapid treatment continue to contribute to improvement in patient outcomes and avoidable deaths.

Establishing Multidisciplinary Rounds

Surveys of institutional perceptions of the state of safety in ICUs have led to the establishment of multidisciplinary rounds.[58] Multidisciplinary rounds enable all members of the team caring for critically ill patients to gather formally and offer their expertise as cases in the ICU are reviewed. Multidisciplinary rounds have been established in critical care units with various structures, either nurse-led or physician-led, meeting daily or regularly during the week. Experience implementing multidisciplinary rounds suggests that although initial meetings may be wide-ranging and unstructured, they can become a vital adjunct to patient care. Specifically, these rounds provide an opportunity for disciplines to share their knowledge of patient care needs and focus the entire care team on common goals. These rounds are a mainstay of the effort to change the culture of ICUs from compartmentalized care based on a single discipline's knowledge to a more holistic approach integrating the talents of the many services caring for critically ill patients.[59]

Incorporating a mnemonic—for example FAST HUG—to address essential components of care for the critically ill is a simple method to improve teamwork while addressing quality metrics.[60] FAST HUG includes identification of key aspects of care including *F*eeding, *A*nalgesia, *S*edation, *T*hromboembolic prophylaxis, *H*ead-of-bed elevation, stress *U*lcer prevention, and *G*lucose control.[60] Updates to this mnemonic have been proposed such as FAST HUGS BID, which includes additional components, *S*pontaneous breathing trial, *B*owel function, removal of *I*ndwelling catheters and *D*e-escalation of antimicrobials and other pharmacotherapies.[61] FAST HUGS BID was a further modification aimed at the surgical patient in the ICU.[62] In one of the authors' institutions, the mnemonic FASTER FLAGG (*F*eeding, *A*nalgesia, *S*edation, *T*hromboembolic prophylaxis, *E*xtubation candidate, *R*estraint orders, *F*oley catheter removal, *L*ine removal, *A*ctivity, *G*lucose control, and *G*oals of care) is used by the nursing staff daily during both multidisciplinary rounds and in daily chart documentation. Standardizing a method to discuss routine patient care issues with the multidisciplinary team can help frame daily goals of care, address potential adverse events, and lead to improved patient outcomes.

Daily ICU Patient Goals Assessment–Quality Rounds

Daily goals assessment allows all parties involved in the care of patients to formally keep track of plans established on either patient care rounds or multidisciplinary rounds and to verify their completion. This typically has been achieved in critical

care units by using a daily goals worksheet completed by the rounding team.

As one example, a study conducted in a surgical oncology ICU assessed ICU length of stay and percent of ICU residents and nurses who understood the goals of care for patients in the ICU. Comparing baseline and postimplementation of a daily goals worksheet, less than 10% of residents and nurses understood the goals of care for the day at baseline compared with greater than 95% after implementation.[63] After implementation of the ICU daily goals worksheet, a reduction in ICU length of stay from a mean of 2.2 days to 1.1 days was observed.[63]

Effective quality patient care rounds include a multidisciplinary team with defined roles and a standardized structure with a goal-oriented approach that includes a checklist.[64] Barriers to quality patient rounds include poor information retrieval and documentation, long rounding times, and perceptions of not being valued by rounding physicians.[64] For example, improvements were sustained for 2 years in one trauma ICU using a checklist as part of rounds along with noted improvements in measures of preventative care and assessments of culture change.[65]

Practice Management: Clinician-Family Communication

Protocols, guidelines, and toolkits have improved process and outcomes in numerous areas of critical care. Translation of these techniques to advance communication with family members of the critically ill is dependent on coordination between clinicians and family members. Such coordination is frequently not an explicit goal.[66] Discussions with family members geared toward shared decision making and goal-oriented care plans are important in promoting patient- and family-centered care.

Clinician-family meetings are intended to share information related to the patient's condition and prognosis and to allow the family to discuss care preferences, family concerns, and goals of treatment.[67] Early effective communication with patients and family members is imperative in shared decision making as they are an integral part of the care in the critically ill.

The American College of Critical Care Medicine (ACCM) Task Force 2004–2005 recognized the need for clinicians to develop a care plan and partner with patients and family members to improve outcomes.[68] In a unified policy statement the ACCM and American Thoracic Society define shared decision making as a collaborative process that allows patients, or their surrogates, and clinicians to make health care decisions together, taking into account the best scientific evidence available, in addition to the patient's values, goals, and preferences.[69] Adjustments in the decision-making model may be appropriate to fit the situation, patient, and family.[69]

Family members often act as surrogate decision makers for the critically ill, which reportedly has been linked to anxiety, depression, and fatality. Methods to decrease stress include clinicians adapting to the family preference in decision making using a stepwise approach progressing toward improved decision making for the critically ill patient.[66,70]

Ideally clinician-family conferences should be conducted within 72 hours of ICU admission. A brief meeting prior to the conference has been suggested to improve the family experience with future conferences. Increased family satisfaction has been reported when clinicians spend more time listening than talking. Clinical-family communication has been summarized in a mnemonic called VALUE and is used as a framework for communication (Box 67.2). Lautrette et al. reported that application of the VALUE conference approach resulted in significant reduction in family symptoms of anxiety, depression, and posttraumatic stress disorder 90 days after the patient's death.[71] Long-term sustainability of the VALUE-grounded communication approach may be facilitated with point-of-care daily reminders, including a family communication item on the daily goals checklist, progress note templates, and maintenance of placards in each patient room.[72] Documentation of the pertinent conference details and treatment goals are essential to assist future clinician-clinician and clinician-family communication throughout the patient's ICU and hospital stay.

• BOX 67.2 VALUE: A Five-Step Approach to Improving Communication in Intensive Care Unit With Families of Deceased Patients

V	Value and appreciate statements by family members.
A	Acknowledge family emotions.
L	Listen to the family.
U	Understand who the patient was as a person.
E	Elicit questions from the family.

From Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. *2007;356:469–478.*

Intensive Care Unit Staffing: Intensivist-Led Team Model

A structural change in ICU care that may lead to improvement in the quality outcomes includes the establishment of an intensivist-led ICU service in medical ICUs. Although in other ICUs, such as neurosurgical units or pediatric units, it is commonly expected that the attending physician is an intensivist trained in that specialty, this has not been the rule in medical ICUs. Typically mixed medical-surgical ICUs in the United States are "open" in that any physician on staff may admit patients to the ICU and intensivists are available for consultation. The literature suggests that "closed" ICUs in which only medical intensivists care for medical patients may be associated with decreased morbidity and mortality rates and length of stay.[73] In a before-and-after cohort study, implementation of the Leapfrog ICU physician staffing model resulted in decreased ICU length of stay, lower rates of VAP and CLABSI, and significant cost savings.[74]

Despite early literature supporting "closed" ICUs and more recent ICU physician model results, barriers to implementation exist, including perceived loss of control for some physicians, administrative perceptions of high costs of implementation with few financial benefits, and concern for limited availability of board-certified intensivists.[75] However, many executive and ICU leaders identify quality of patient care as the main motivating factor for implementing an all-intensivist ICU staffing model.[75] Pronovost et al. suggest avoiding the terms "open" versus "closed" when referencing intensivist staffing and suggest adopting a team-based approach whereby the intensivist partners with the primary physician in care delivery.[75] Coupling the team-based approach with a culture of quality, safety, and accountability can improve quality performance and outcomes.

Culture Transformation and Organizational Learning

The ultimate goal of clinical quality improvement work of any sort remains that of creating a culture of enduring change that can absorb new initiatives and sustain gains earned in prior improvement efforts. Underscoring the long-term strategy of ICU culture change in describing improvement initiatives cannot be overestimated. If insufficient attention is paid to the context in which improvement efforts are set into motion, an environment unfamiliar with testing changes and hostile to deviations from routine will hinder the success of the project itself. To this end, as clinical initiatives are advanced, concern must be maintained for executing projects to encourage collaboration and cooperation among the persons who work in the ICU. Typically these strategies involve crafting of change teams, devising and testing protocols to incorporate the concerns of the front-line users of the protocols, and adapting to local cultural needs and traditions while incorporating new ideas. In the course of this work, colleagues cease contemplating their work as discrete projects that can be finalized. Instead, they learn to constantly revise protocols and strategies in response to feedback from the front-line users. If these ideals are maintained in the rollout of key initiatives and structural changes, often a change in mindset from an organization of independent actors to one in which collaborative efforts promote organizational learning can take hold. Unfortunately, no scientific procedure is available to guide the way in making such cultural transformations gracefully. The talents of committed and patient people are essential.

Critical Care Scoring Systems

Severity of Illness Scoring Systems

Severity of illness scores were introduced in critical care in the 1980s to describe and classify critically ill patient populations. The early instruments were developed to stratify patients based on severity and predict outcome based on a set of variables and an equation model. Models primarily included data combinations from three areas: demographics, such as age and gender; chronic health conditions; and acute physiology, such as laboratory values and vital signs obtained within the first 24 hours of ICU admission. Some of the updated prediction models included principal diagnosis, operative status, and origin before ICU admission.

Mortality prediction models are commonly used in clinical trials to measure severity of illness at admission and for stratification of baseline clinical characteristics.[76] In clinical practice, ICU scoring systems are generally used to assess performance. Historically, the three most commonly used scoring systems in adult ICUs included the Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Probability Model (MPM), and the Simplified Acute Physiology Score (SAPS).[77,78] Updates to these early scoring systems occurred in the 1990s and again in mid-2000s. A comparison of these three major scoring systems is presented in Table 67.2.

Scoring System Use in Performance Improvement

The purpose of severity scoring systems in PI is to evaluate ICU populations and identify opportunities to improve quality of care and efficiency. However, scoring systems are used in only approximately 10% to 15% of ICUs in the United States.[76] Limited use may be partly due to the expense associated with data collection, including cost for software, training, and support and availability of knowledgeable staff. Concern about the accuracy of ICU scoring systems may also contribute to limited clinical application.[76]

Severity scoring models encompass a combination of diagnostic, physiologic, or demographic variables to predict patient outcomes. Scoring models may perform well in mortality predictions yet the role for benchmarking and PI may be somewhat restricted. Without ICU performance data, clinicians and administrators have a narrowed view in their ability to realistically describe, compare, and improve the quality of care for their critically ill patient population. As a matter of accessibility, often administrative data inform committees regarding ICU quality and performance. Data, based on assigned International Classification of Diseases (ICD) coding, can be appropriate to provide an overview of outcomes and resource utilization centered on diagnosis and length of stay. However, administrative data alone may not adequately quantify severity of illness or mortality risk.

Although severity scoring systems and prediction models are worthwhile tools, they too have limitations. Updates are often required because of the ultimate model deterioration that occurs over time. Reasons for model weakening were partially due to variations in patient characteristics at time of presentation, accessibility to treatment, an increase in mean aged and chronically seriously ill patients, and the growing number of immunocompromised patients.[78,79] Furthermore, errors in prediction models caused by differences in patient selection and lead time bias may support the addition of new variables for consideration in future model revisions.

Model Development, Validation, Calibration, and Discrimination

Early severity of illness scoring model development, including the selection of variables and weights, was based on clinical judgment through a panel of experts. Instrument advances ensued among all three scoring systems (APACHE, MPM, and SAPS) with logistic regression techniques for model development and performance validation with measures of calibration and discrimination. Model development is generally achieved using large databases collected from many ICUs. Validation, in a sample other than that used for model development, may be completed with a new cohort or randomly dividing the existing database. Calibration can be evaluated using the formal goodness-of-fit tests, which evaluate the estimated probability of death to actual patient mortality.[80] A well-calibrated model exists when the number of observed and expected patient deaths is similar. Model discrimination uses the area under the receiver operating characteristic (ROC) curve to measure the accuracy of the model to differentiate patients who live or die, based on the mortality probability estimates. A ROC of 0.50 is no better than a flip of a coin. Thus model developers normally seek a ROC area that exceeds 0.70.[80]

Overview of Prediction Models

APACHE

The prototype APACHE system included weighting for 34 potential physiologic measures, using the worst value during the initial 24 hours after ICU admission, which provided an acute physiology

TABLE 67.2 General Severity Scores and Outcomes Prediction Models

Characteristic	APACHE	SAPS	APACHE II	MPM[a]	APACHE III	SAPS II	MPM II[b]	SAPS 3	APACHE IV	MPM_0 III
Year	1981	1984	1985	1988	1991	1993	1993	2005	2006	2007
No. of countries	1	1	1	1	1	12	12	35	1	1
No. of ICUs	2	8	13	1	40	137	140	303	104	135
No. of patients	705	679	5815	2783	17,440	12,997	19,124	16,784	110,558	124,855
Selection of variables and their weights	Panel of experts	Panel of experts	Panel of experts	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression	Multiple logistic regression
Variables										
Age	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Origin	No	No	No	No	Yes	No	No	Yes	Yes	No
Surgical status	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic health status	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Physiology	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute diagnosis	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
No. of variables	34	14	17	11	26	17	15[c]	20	142	16 (+1)
Score	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Mortality prediction	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a]These models are based on previous versions, developed by the same investigators (Lemeshow S, Teres D, Pastides H, et al. A method for predicting survival and mortality of ICU patients using objectively derived weights. *Crit Care Med.* 1985;13:519–525; and Lemeshow S, Teres D, Avrunin JS, et al. A comparison of methods to predict mortality of intensive care unit patients. *Crit Care Med.* 1987;15:715–722).
[b]The numbers presented are those for the admission component of the model ($MPM\ II_0$). $MPM\ II_{24}$ was developed using data for 15,925 patients from the same ICUs.
[c]$MPM\ II_{24}$ uses only 13 variables.
APACHE, Acute Physiology and Chronic Health Evaluation; *ICUs,* intensive care units; *MPM,* Mortality Probability Model; *SAPS,* Simplified Acute Physiology Score.
From Moreno R. Severity of illness scoring systems. In: Parrillo, JE, Dellinger RP, eds. *Critical Care Medicine: Principles of Diagnosis and Management in the Adult.* Philadelphia: Elsevier; 2013:1288.

score (APS).[81] The original model was revised in 1985 creating APACHE II. Measures were simplified to include just 12 physiologic variables, the addition of weighted points for age and chronic health conditions, and the major reason for ICU admission based on a list of 50 operative and nonoperative diagnoses.[82] APACHE II scores were used to stratify patients for new therapy and evaluate resource utilization and efficiency.[82] Six years later a third validation was available in APACHE III, which offered options for an APACHE III score and predictive equations that may be linked to disease classification and patient location.[83] A new variable to APACHE III was location before ICU treatment, as patients transferred to the ICU from areas other than the emergency department have a slightly higher increased risk of death.[83] The current version, APACHE IV, was remodeled in 2006, which included the addition of new variables and a different statistical model.[79] APACHE IV offers hospital mortality predictions and is a suggested tool for benchmarking ICU performance in the United States.[79]

MPM

The Mortality Probability Model (MPM_0) was developed as an assessment of acuity and to predict hospital mortality.[84] Data on ICU admission and variables after 24 hours in the ICU were used to create a model to predict hospital mortality. Revisions to MPM occurred in 1993 (MPM II) and again in 2007 (MPM III).[85,86] MPM_0 characterized patients close to the time of admission and was based on age and 15 binary variables measured within 1 hour of ICU admission, whereas MPM_{24} included data within the first 24 hours of the ICU stay. Revised in 1993 using an international sample of patients, MPM_0 II is based on measurements obtained within the first hour of ICU admission.[85] In a 2007 updated model (MPM_0 III), code status was added to the variables captured in MPM_0 II, providing a more accurate comparison of observed versus expected outcomes.[86]

SAPS

Created in 1984, the SAPS used 14 easily identifiable variables, collected during the first 24 hours after ICU admission, to classify patients at risk for death.[87] The 1993 revision to build SAPS II included 17 variables and used logistic regression to assign weights to the variables, rather than clinical judgment as used in the older system.[88] The SAPS III admission score is based on data collected at ICU admission (±1 hour) consisting of 20 variables.[89]

All of the prediction models are subject to deterioration and require recalibration over time. Future use of large national and international data sets along with advances in computer science technology systems may aid in acceleration of this recalibration process. However, proceeding with caution is vital as data management systems capturing frequent changes in physiologic variables may alter the accuracy of the model.[90]

Organ Dysfunction Scoring Systems

Organ dysfunction/failure may be considered a process that can begin as mild dysfunction to progression of complete organ failure.[91] For some critically ill patients, a second or third organ failure may ensue, resulting in multiple-organ failure, a major cause of morbidity and mortality.[91] Several scoring models were developed to evaluate the presence and severity of organ dysfunction and include the Multiple Organ Dysfunction Score (MODS), the Sequential Organ Failure Assessment (SOFA), and the slightly more complex Logistic Organ Dysfunction System Score (LOD) (Table 67.3).

MODS is a scale to measure the severity of organ dysfunction in six organ systems: respiratory, renal, cardiovascular, hematologic, hepatic, and neurologic.[92] Each organ system is scored from 0 to 4 (0 is normal and 4 is the most severe dysfunction). The worst

TABLE 67.3 Organ Dysfunction/Failure Scoring Systems

Organ System	MODS[a]	SOFA[b]	LOD[c]
Respiratory	Pao_2/Fio_2 ratio	Pao_2/Fio_2 ratio Mechanical ventilation	$Paio_2/Fio_2$ ratio Mechanical ventilation
Cardiovascular	Pressure-adjusted HR	MAP Use of vasoactive agents	SAPS HR
Renal	Creatinine	Creatinine Urinary output	Creatinine Urinary output Urea
Hematologic	Platelets	Platelets	Platelets WBCs
Neurologic	GCS	GCS	GCS
Hepatic	Bilirubin	Bilirubin	Bilirubin Prothrombin time

[a]Data from Marshall JC, Cook DA, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med.* 1995;23:1638–1652.
[b]Data from Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.* 1996;22:707–710.
[c]Data from Le Gall JR, Klar J, Lemeshow S, et al. The ICU Scoring Group: the logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA.* 1996;276:802–810.
Fio_2, Fraction of inspired oxygen; *GCS,* Glasgow Coma Scale; *HR,* heart rate; *LOD,* Logistic Organ Dysfunction; *MAP,* mean arterial pressure; *MODS,* Multiple Organ Dysfunction Score; *Pao_2,* partial pressure of arterial oxygen; *SAPS,* Simplified Acute Physiology Score; *SOFA,* Sequential Organ Failure Assessment; *WBCs,* white blood cells.
From Moreno R. Severity of illness scoring systems. In: Parrillo JE, Dellinger RP, eds. *Critical Care Medicine: Principles of Diagnosis and Management in the Adult.* Philadelphia: Elsevier; 2013:1296.

score during the 24-hour period is used to calculate the overall score (0–24). A high MODS correlates to a higher mortality risk.[92]

Similar to MODS, SOFA counted the same six organ systems applying a score of 0 to 4 for each system.[91] One major difference between the two scoring systems is how the cardiovascular score is calculated. For the SOFA score, cardiovascular dysfunction/failure is based on the use of vasoactive agents.[91] MODS requires a calculation for pressure-adjusted heart rate which is the heart rate times the right atrial pressure (CVP) divided by the mean arterial pressure (MAP).[92] Higher SOFA scores and increases over time were associated with worse outcomes.

Unlike the MODS and SOFA scoring systems, the LOD score was designed to be measured only once in the first 24 hours of ICU admission, rather than repeated measures on subsequent ICU days.[93] The maximum LOD score is 22 with an individual organ score of 0 to 5 for renal, neurologic, and cardiovascular; 0 to 3 for pulmonary and hematologic; and 0 or 1 for hepatic.[93]

Organ dysfunction scores provide an objective measure arising from a potentially life-threatening insult. Application of these scores on ICU admission or on sequential ICU days can be used as a valuable prognostic tool. However, as safety and quality move toward early recognition and timely appropriate response to clinical deterioration regardless of location, scoring systems to identify patients at risk for clinical deterioration are becoming more commonplace among hospital care teams.

Scores for Early Detection of Critical Illness

Critical illness preceded by acute deterioration, owing to delayed recognition or suboptimal care, in hospitalized patients can put patients at risk of cardiopulmonary arrest, unplanned ICU admission, and poor outcomes.[94] Acute deterioration is often observed with changes in vital signs or alterations in mental status. Reasons for delays are generally confounded by limited resources, provider availability, and inadequate staff expertise to respond to the observed patient abnormalities. To aid in early recognition, real-time early warning scores (EWS) have been developed and used in health care settings as a means to provide prompt assessment and intervention in patients at risk for deterioration.[95] The easy to use bedside EWS tools have been modified to specific groups such as surgical patients and medical patients.[95,96] The Modified Early Warning Score (MEWS) was designed to identify medical patients at risk for deterioration.[97] Additionally, scores to aid in early detection of critical illness have been implemented in the prehospital setting. Developed by the Royal College of Physicians, the National Early Warning Score (NEWS) is a surveillance system for patients presenting acutely to the hospital, generating a clinician alert to assess and respond to acute illness.[98] NEWS is also recommended for use in the prehospital setting by primary care and ambulance services. EWS systems are convenient in identifying patients at risk or currently experiencing acute illness, alerting the clinical team for timely response and treatment.

Scoring Systems for Specific Conditions

Simple and practical scoring models have been developed using large databases to assess severity in specific conditions such as sepsis. For example, the Sepsis Severity Score was an internationally developed score containing 36 variables from 23,438 patients with severe sepsis whose data were entered into the Surviving Sepsis Campaign database.[99] Model development included 90% of the population with 10% applied to the validation model. Logistic regression was used to create a model to predict mortality specifically for severe sepsis patients. The Sepsis Severity Score is a sum of individual values with a median score of 56.3, median score of 55, with a range of minimum and maximum scores of 0 to 130.[99] The model performed well in regard to discrimination and calibration.[99]

Using analysis from several databases, a task force of 19 members from the ESICM and SCCM set out to update the sepsis and septic shock definitions. The authors proposed new sepsis definitions and use of a simple bedside clinical score termed quickSOFA (qSOFA) to identify adult patients with suspected infection who may require escalation of care and are more likely to have worse outcomes.[100] The qSOFA criteria require the patient to have at least two of the following: respiratory rate of 22 breaths/min or greater, altered mental status, or systolic blood pressure of 100 mm Hg or less.[100] Although large data sets were used to develop the new definitions and bedside score, the authors stress that the systemic inflammatory response syndrome criteria may still be useful for identification of infection. Early sepsis identification is key to PI. Conversely, patients meeting qSOFA criteria would indicate late identification and potentially poor outcomes.

Specific scoring systems may be incorporated into decision making to determine appropriate treatment options. For instance, extracorporeal membrane oxygenation (ECMO) among patients with acute respiratory distress syndrome (ARDS) using the PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) mortality risk score may be used to assess appropriateness for therapeutic options in acute lung injury treatment.[101] Schmidt et al. used eight ECMO parameters to develop a mortality risk score in patients with refractory ARDS treated with ECMO.[101] The PRESERVE score ranged from 0 to 14 points with a higher score indicating increased risk of death within 6 months of ICU disscharge.[101] The authors suggest that the PRESERVE score may be a useful tool for ICU physicians to define appropriate ECMO candidates in patients with severe ARDS.

These scoring systems need validation before they are widely used. Nonetheless, as clinical management and therapies advance, disease-specific scoring tools may inform clinicians about prognosis or offer decision support regarding whether or not to initiate highly specialized treatment modalities.

Summary and Conclusions

In the era of cost-effectiveness and high quality, ICUs seek solutions to objectively evaluate the quality of care delivered. Severity of illness scoring systems provide a valuable framework to characterize ICU patients for research, evaluate quality improvement programs and resource use, and benchmark performance. As critical care practice and therapies progress, the accuracy of prognostic models may not have the same level of exactness and subsequently underestimate mortality. Periodic testing and revisions may be needed, especially in diagnostic categories with significant improvements in early diagnosis, treatment, and advances in technological resources.

When selecting a scoring system, consideration should be given to the feasibility of data collection, particularly time to calculate the score and whether the model is openly available. One should

reflect on the patient population, choosing a scoring system based on general (medical) or specific conditions (cardiac surgery). Integrating PI process measures, severity scoring, and outcome measures that include length of stay, readmission, as well as mortality may reflect a more accurate assessment of the ICU quality of care delivered in the existing ICU environment.

Key Points

- High-quality health care consists of structure, process, and outcomes executed by a collaborative model.
- Governing agency missions embrace a patient-centered approach to provide safe, reliable, and efficient health care with specific prominence in critical care.
- Multiple national quality improvement campaigns, aimed at spreading best practices, led to a significant infection reduction in hospital acquired infections.
- Advancement in sepsis performance improvement has evolved to endorsed National Hospital Inpatient Quality Measures with mandated sepsis measure reporting for all U.S. hospitals.
- Structured multidisciplinary rounds using simple tools such as a checklist or a mnemonic to address key aspects of critical care contribute to better-quality ICU care delivery.
- Severity of illness scoring systems are commonly used in critical care research and less frequently in clinical practice to predict outcomes, whereas organ dysfunction scores provide a value to evaluate failure of organs owing to a life-threatening insult.
- Optimizing early warning scores to identify patients at risk for deterioration of their conditions or needed escalation of care has been used both in hospital and prehospital settings as a means of improving outcomes in the acutely critically ill patient.

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Review Questions

1. According to the available literature, which of the following outcomes is most likely true concerning rapid response team (RRT) implementation?
   - **a.** A decrease in intensive care unit (ICU) admissions in some but not all studies
   - **b.** A decrease in incidence of severe sepsis in some but not all studies
   - **c.** A decrease in ST-segment elevation myocardial infarction (STEMI) mortality
   - **d.** RRT does not require education of the bedside providers outside the critical care environment.

   Answer: a. RRTs have been developed as a means to provide and deploy health care providers with critical care expertise to areas of the hospital during the early phase of potential deterioration in a patient's condition. The impact of RRTs, per clinical trials, has yielded mixed results, including a decrease in cardiac arrest and unplanned ICU admissions in some but not all studies (choice a correct). There has not been an impact of RRTs on the incidence of severe sepsis (choice b) or STEMI (choice c). Education for the bedside providers outside the ICU is essential to implement a rapid response team as RRT calls are commonly generated in medical and surgical areas of the hospital (choice d).
2. Which one of the following is most correct concerning prevention of ventilator-associated events (VAEs)?
   - **a.** Ventilator-associated pneumonia (VAP) requires mechanical ventilation for longer than 24 hours.
   - **b.** Bacteremia is a VAE.
   - **c.** Routine oral care is part of the ventilator bundle.
   - **d.** Choice of antibiotic for surgical prophylaxis of the postoperative mechanically ventilated patient is part of the ABCDEF bundle.

   Answer: c. Reducing VAEs in high-risk mechanically ventilated patients includes adherence to evidence-based interventions. The clinical definition of VAP requires patients be supported by mechanical ventilation for more than 48 hours (choice a). VAEs include VAP, peptic ulcer disease, gastrointestinal bleeding, aspiration, venous thromboembolic events, and obstacles to managing secretions (choice b). Routine oral care with 0.12% chlorhexidine is included in the ventilator bundle as an element to prevent VAEs (choice c correct). Antibiotic administration is not an element of the ABCDEF bundle. The A in the ABCDEF bundle is linked to Assess, prevent, and manage pain (answer d).
3. Which one of the following is true concerning prevention of catheter-associated urinary tract infections?
   - **a.** Consideration of alternatives to indwelling bladder catheter use in selected patients
   - **b.** Daily bladder antibiotic irrigation
   - **c.** Changing bladder catheters every 3 days
   - **d.** Aggressive hydration to increase urine flow

   Answer: a. (CAUTI)
   The Healthcare Infection Control Practices Advisory Committee guidelines include appropriate urinary catheter use, consideration of alternatives to indwelling urethral catheterization in selected patients, performing aseptic technique during catheter insertion, following proper catheter maintenance techniques, and integration of a formal hospital quality improvement program with necessary surveillance strategies (choice a correct). Choices b, c, and d have not been shown to prevent catheter-associated urinary tract infections.

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Ethical Considerations in Managing Critically Ill Patients

JEFFREY P. BURNS AND ROBERT D. TRUOG

CHAPTER OUTLINE

Informed Consent and Decision Making in Critical Care
- What Is the Distinction Between Competency and Decisional Capacity?
- Who Gives Consent?
- Who Obtains Consent and, Ideally, When?
- Is the Physician an Advocate or Neutral Party in the Informed Consent/Decision-Making Process?
- What Treatments May Be Withheld or Withdrawn?
- Who Ultimately Decides When There Are Conflicts About the Goals of Care?

Practical Aspects of Withdrawing Life-Sustaining Treatments in the ICU
- Team Preparation
- Family Preparation
- What Is the Most Compassionate Means of Withdrawing Mechanical Ventilation With the Intention of Allowing the Patient to Die?
- How Should Signs of Apparent Patient Suffering Be Treated After Mechanical Ventilation Is Withdrawn?
- How Much Is Too Much Sedation and Analgesia for the Dying Patient in the ICU After the Withdrawal of Mechanical Ventilation?

Managing critically ill patients raises ethical considerations of some kind in nearly every case. The goal of this chapter is to present a focused review of select essential ethical concepts frequently confronted in the practice of critical care medicine, with a special emphasis on how to address these concerns in daily practice. There are many other helpful resources for those wishing a deeper review of the ethical, philosophical, and legal literature underpinning the concerns raised in this chapter.[1]

Informed Consent and Decision Making in Critical Care

The conceptual foundation of informed consent is that patients have the sole right to determine what will be done with their bodies. This includes a firm constitutional right, at least in the United States, that a competent adult patient has the right to accept or refuse any medical or surgical treatment, even if it is potentially lifesaving. From a long history of famous legal cases in the United States on informed consent for medical procedures, patient in effect give their permission "to be touched" after the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks and benefits associated with each.[2]

Ideally, informed consent is an ongoing process inherent in patient care that builds trust and reduces disappointment if the intended outcome does not result. By this formulation, informed consent is an ongoing discussion about the general issues of managing an illness as well as specific procedures being proposed.

What Is the Distinction Between Competency and Decisional Capacity?

The essential criteria for informed consent are that it is given voluntarily, without coercion; it may be withdrawn at any time; and it is given by a patient who is competent to understand the nature, and carefully evaluate the consequences of the proposed therapy, in light of his or her life preferences and values.

Although "competent" is the term used most commonly to convey the ability of the patient to reason adequately in this context, in fact only a court of law can determine whether a patient remains competent to make medical decisions. As a practical matter for clinicians in the intensive care setting, the question is framed in terms of whether the patient has "decisional capacity" to give informed consent. One usually does not need a lawyer or a psychiatrist to determine that a patient has or does not have decisional capacity; in most cases this is a determination that experienced, board-certified intensivists can make on their own.

The legally relevant criteria for assessing decision-making capacity involve whether the patient is able do the following:

1. Communicate a choice, as in clearly indicating a preferred treatment option
2. Understand the relevant information, as in grasping the fundamental meaning of the information communicated by the physician
3. Appreciate the situation and its consequences, as in acknowledging the medical condition and the likely consequences of treatment options
4. Reason about treatment options, as in engaging in a rational process of manipulating the relevant information[3]

Who Gives Consent?

In the intensive care setting the ability of critically ill patients to participate in decision making often fluctuates over the course of their illness trajectory. When patients lack the decisional capacity necessary for informed consent, decisions must be made by a surrogate. Ideally, the patient will have completed an advance directive, indicating the individual that he or she has entrusted with making these decisions. This document is also known as a health care proxy or durable power of attorney for health care decisions. In many states, this document is often supplemented by a living will, which provides that surrogate decision maker with specific information about the values and preferences of the patient with regard to the use of resuscitation and other forms of life-sustaining interventions.

If the patient has not designated a durable power of attorney for health care, then states vary on the procedure to be followed. Some stipulate a specific hierarchy for determining the surrogate, beginning with the spouse, followed by adult children, siblings, and so on. Others allow more flexibility and permit the clinicians to choose a surrogate who knows the patient well and who is invested in promoting the patient's well-being, even if that person is not legally related to the patient. When no surrogates are available, the hospital may seek to have a legal guardian appointed by the court, or in some cases the clinicians may make decisions based on their perceptions of the patient's best interests, often assisted by hospital chaplains or the hospital ethics committee.

Who Obtains Consent and, Ideally, When?

The patient's attending physician is responsible for obtaining the patient's informed consent. Other physicians may assist in this process (i.e., residents, or "house staff"), but it is the responsibility of the attending physician to ensure that those involved in obtaining consent are sufficiently knowledgeable about the procedure to adequately communicate the risks, benefits, and alternatives.

All patients provide a general consent for treatment at the time they are admitted to a hospital, and some hospitals consider this sufficient for all of the diagnostic and therapeutic procedures performed in the intensive care unit (ICU). However, both The Joint Commission and the Centers for Medicare and Medicaid Services now stipulate that best practices are associated with each institution having a written policy on what procedures require a separate and specific informed consent.

What Information Must Be Conveyed in the Informed Consent Process?

The classic formulation of the information that should be conveyed in the informed consent discussion includes the following:

1. Risks and benefits of the proposed procedure
2. Alternatives to the proposed procedure
3. Risks and benefits of alternatives to the proposed procedure
4. Risks and benefits of doing nothing

The Joint Commission emphasizes that the informed consent process is far more than obtaining a signature on the way to the procedure. Ideally, the signature should be merely the final step or culmination of a process during which the patient and the physician have the time to ask and answer questions over a period of time that may involve several conversations.[4]

Research suggests that when informed consent is obtained, the information provided by health care professionals is often unclear or insufficient, leading to misunderstanding, a worse treatment response, and even litigation. Studies in the literature also demonstrate that asking the patient to recount ("teach-back") what they have been told in the informed consent discussion adds to comprehension.[5] Importantly, the teach-back method not only helps to determine whether patients understand the risks, benefits, and alternatives to treatment, but it also helps to focus patients on what's important to them in a given context.

Is the Physician an Advocate or Neutral Party in the Informed Consent/ Decision-Making Process?

Stated another way, what is the ideal physician-patient decision-making relationship in critical care?[6] The surrogate decides independently? The surrogate decides after considering the physician's recommendation? There is "shared" responsibility for decision making? The physician decides after considering the surrogate's opinion? The physician decides independently?

A joint statement by the American College of Critical Care Medicine and American Thoracic Society Ethics Committees recently addressed this issue and endorsed the following recommendations, among several others[6,7]:

1. Shared decision-making is a collaborative process that allows patients, or their surrogates, and clinicians to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values, goals, and preferences.
2. Clinicians should engage in a shared decision-making process to define overall goals of care (including decisions regarding limiting or withdrawing life-prolonging interventions) and when making major treatment decisions that may be affected by personal values, goals, and preferences.
3. Clinicians should use as their "default" approach a shared decision-making process that includes three main elements: information exchange, deliberation, and making a treatment decision.
4. A wide range of decision-making approaches are ethically supportable, including patient- or surrogate-directed and clinician-directed models. Clinicians should tailor the decision-making process based on the preferences of the patient or surrogate.

What Treatments May Be Withheld or Withdrawn?

It is ethical and legal to withhold or withdraw any medical treatment when the patient's family, as informed by a recommendation from the clinical team, determines that the burdens of such treatments outweigh the benefits.

Any medical intervention, from extracorporeal membrane oxygenation and pacemakers to the use of physiologic monitors, may be withheld or withdrawn from the dying patient in the ICU.

Who Ultimately Decides When There Are Conflicts About the Goals of Care?

In the United States there is a firmly established and well-defined legal and ethical consensus that an adult patient with decisional capacity, or the adult patient's legal surrogate if the patient lacks decisional capacity, has the right to refuse any medical and/or surgical intervention, even if his or her physician believes the proposed therapy to be potentially lifesaving treatment. That is, patients have a strong "negative" right to refuse even life-sustaining

treatment—which again in legal parlance is the "right to be free from unwanted bodily touching."

But do patients' or their legal surrogates have an equally strong right to demand any therapy, up to and including potentially life-sustaining treatment? There is no consensus on this point, and the management of requests by patients or surrogates for treatments that clinicians believe should not be administered is controversial.

A joint statement by the American Thoracic Society, American Association for Critical Care Nurses, American College of Chest Physicians, European Society for Intensive Care Medicine, and Society of Critical Care recently addressed this issue and endorsed the following recommendations, among others[6]:

1. Institutions should implement strategies to prevent intractable treatment conflicts, including proactive communication and early involvement of expert consultants.
2. The term "potentially inappropriate" should be used, rather than futile, to describe treatments that have at least some chance of accomplishing the effect sought by the patient, but clinicians believe that competing ethical considerations justify not providing them. Clinicians should explain and advocate for the treatment plan they believe is appropriate. Conflicts regarding potentially inappropriate treatments that remain intractable despite intensive communication and negotiation should be managed by a fair process of conflict resolution; this process should include hospital review, attempts to find a willing provider at another institution, and opportunity for external review of decisions. When time pressures make it infeasible to complete all steps of the conflict resolution process and clinicians have a high degree of certainty that the requested treatment is outside accepted practice, they should seek procedural oversight to the extent allowed by the clinical situation and need not provide the requested treatment.
3. Use of the term "futile" should be restricted to the rare situations in which surrogates request interventions that simply cannot accomplish their intended physiologic goal. Clinicians should not provide futile interventions.

Practical Aspects of Withdrawing Life-Sustaining Treatments in the ICU

Observational studies over the past 2 decades of death in the ICU reveal a strikingly similar pattern; nearly two-thirds of all deaths in adult, pediatric, and neonatal ICUs in North America and Europe follow the withholding or withdrawal of life-sustaining treatments.[8]

The withdrawal of life-sustaining treatment in the ICU with the intention of allowing the patient to die raises difficult and rapidly evolving clinical and ethical decision making more profoundly than nearly any other context. This is especially the case with the abrupt and unpredictable change in patient symptoms as assisted ventilation is withdrawn. Failure of the clinical team to anticipate many different possible patient responses to the cessation of life-sustaining treatment, and especially assisted ventilation, and have in place a flexible and effective plan of care to address changes as they arise, can lead to abrupt decisions that leave both the patient's family and clinicians with lasting emotional distress that optimal and ethical end-of-life care was not provided. How can intensive care clinicians provide care that effectively responds to the evolving physiologic, emotional, and spiritual needs of the patient and their family members in a timely manner, and within an ethical framework consistent with the values of the medical profession and society in which we live?

Many detailed articles in the literature well document comprehensive palliative care for the dying patient. However, the peculiar practical issues in providing palliative care to critically ill patients in the ICU are often not well detailed. The guideline for the withdrawal of mechanical ventilation presented here is adapted from the consensus statement by the American College of Critical Care Medicine.[9]

Team Preparation

Before the withholding or withdrawal of life-sustaining treatments, the attending physician, bedside nurse, and other members of the care team such as clergy and psychosocial experts, should meet to anticipate, plan, and coordinate their efforts during the withdrawal of life-sustaining treatments just as a good resuscitation requires a coordinated team effort.

A guiding concept in determining which treatments to continue and which treatments to withhold or withdraw in this process is that any intervention that appears to promote the patient's comfort or dignity (as well as ameliorate emotional, psychological, or spiritual concerns) should be continued. Those that do not appear to promote the patient's comfort or dignity should be withdrawn.

Family Preparation

Next, anticipatory guidance to prepare the family before the withdrawal of life-sustaining treatments is essential. The attending physician and bedside nurse should meet with the family to provide a brief but clear overview about the process before the withdrawal of life-sustaining treatments, and assurance that symptoms of patient suffering will be treated. Although guiding the family about what to expect cannot alleviate all of their anxiety around the process, failure to guide them at all will surely only increase anxiety and anguish.

Predictions about the patient's clinical course after withdrawal of mechanical ventilation or other forms of life-sustaining treatment are best avoided, as these predictions are often inaccurate and may result in a substantial loss of credibility when expectations about death or the timing of death are in error. The overarching objective at this time is to assure the family that although certain life-sustaining treatments will be withdrawn, care of the patient will never be withdrawn. Thus, in answer to questions about how long the patient might live, for example, it is important to refocus and reassure the family by comments such as "We think it is unlikely that your loved one will survive after the ventilator is withdrawn, but whether he breathes only for a short time or for a very long time we can assure you that we will treat symptoms that appear to be causing him discomfort."

At times it will be necessary for the clinicians to anticipate, ask, and answer concerns or questions that the family appears to be afraid or unable to verbalize. For example, it may be helpful for the attending physician to volunteer, even if not explicitly asked, the comment, "Sometimes after the ventilator is withdrawn patients experience a change in skin color, or unusual breathing noises, and this is to be expected and our job is make sure that your loved one does not experience symptoms of suffering or discomfort. If we see signs of discomfort, we will treat them."

Families should be invited to participate in activities to relieve their loved one's discomfort, such as repositioning, or mouth care, or bathing. They should be encouraged to participate in assessment

of the patient's pain or discomfort, and they should also be encouraged to provide other means of comfort that may have special meaning for them or the patient, such as holding hands, playing favorite music, or wrapping their loved one in a special blanket.

What Is the Most Compassionate Means of Withdrawing Mechanical Ventilation With the Intention of Allowing the Patient to Die?

An artificial airway may be removed (extubation), or the patient may have supplemental oxygen and/or positive-pressure ventilation gradually reduced at some rate determined by the physician when the artificial airway will remain in the trachea through the dying process (a procedure known as "terminal wean").

The method of withdrawal should be guided by the specific circumstances of the patient. For example, a patient likely to experience significant hemoptysis may benefit from a terminal wean with the gradual reduction in the fraction of inspired oxygen and/or ventilator rate at a pace not faster than pharmacologic sedation is administered to treat objective signs of distress from the effects of hypoventilation and hypoxia.

Notably, prior research on alveolar anoxia determined that the most rapid descent into unconsciousness with the least agitation occurs when hypoxia is allowed to progress in the face of normocarbia. On the other hand, when the plan is to extubate the trachea as the mode of mechanical ventilation withdrawal, then it will most commonly be necessary to administer additional analgesia and sedation before extubation in anticipation of respiratory distress that may result from the abrupt removal of assisted ventilation.

How Should Signs of Apparent Patient Suffering Be Treated After Mechanical Ventilation Is Withdrawn?

The abrupt onset of respiratory distress as mechanical ventilation is withdrawn, coupled with the uncertainty on how effectively and how long the patient may be able to breathe without mechanical ventilation, makes dosing medications for symptom relief especially difficult for clinicians. Administering too much sedation will likely compromise effective respirations even further and thus hasten death, whereas administering too little sedation will abandon a dying patient to untreated suffering, often making it difficult to find an appropriate middle ground.

First, palliative measures should be comprehensive and not rely only on medications. Frequent repositioning, mouth care, or massage may be far more effective in providing symptom relief to the dying patient than exclusive reliance on analgesics and sedatives as the foundation of the palliative care plan.

Second, the clinician's obligation is to treat objective signs of discomfort as experienced by the patient. The distress of the family should be addressed by continued reassurance and emotional support. This situation often arises during the evolving and typically unpredictable changes in the breathing pattern of the dying patient. These changes in breathing pattern are not necessarily either easily treated or uncomfortable for the patient. For example, all gasping does not need to be treated with escalating does of sedatives or narcotics; ideally the decision should be determined by a consensus between the family and clinicians at the bedside on whether the patient's activity appears to be causing, or is a manifestation of, suffering.

Third, the current ethical and legal guidelines place importance on the intentions of clinicians in administering analgesics and sedatives at the end of life. Specifically, clinicians should administer doses that are intended to relieve pain and suffering but not intended to directly cause death. One should not, however, give more sedation than what the patient needs to be comfortable (be prepared for the request, "Please, can't we just get this over with?").

How Much Is Too Much Sedation and Analgesia for the Dying Patient in the ICU After the Withdrawal of Mechanical Ventilation?

Although it is not universally accepted, the doctrine of double effect is a common framework to guide clinicians in determining how much is too much sedation and analgesia for the dying patient. The doctrine of double effect states that five conditions must hold for an action to be considered morally acceptable, even if it should hasten the death of another. Those five conditions, in the case of administering sedation or analgesia in the ICU to a dying patient following the withdrawal of mechanical ventilation, are as follows:

1. The action must be morally good or neutral. Most would agree that assuring that a dying patient is treated for pain or suffering is a morally good or neutral action.
2. The good effect is intended. That is, the clinician intends to relieve pain and suffering by administering sedation and analgesia in this context.
3. The bad effect is merely foreseen, but not intended. The clinicians foresee that by administering sedation and analgesia in this context the patient's death may be hastened, but their intention is, or should only be, the relief of pain and suffering and not the patient's death.
4. The bad effect cannot be the means to the good effect. The clinician must not commit an action that is clearly intended to cause the patient's death as the means to stopping or relieving the patient's pain and suffering. For example, by the doctrine of double effect one would not be allowed to administer a neuromuscular blocking agent or a potassium bolus in this context because these agents have no sedative or analgesic properties and thus the only mechanism by which they relieve the patient's suffering is by causing the death of the patient.
5. Proportionality—the good must outweigh the evil permitted. Here the doctrine stipulates it must be better, all things considered, to allow the good effect (action) to be permitted even though some bad consequences (hastening of death) also occur.

What, Then, Is—or Should Be—the Goal of Using Sedatives and Analgesics in This Context?

If one adheres to the doctrine of double effect as a guiding framework in titrating sedatives and analgesics to the dying patient, the goal is only to treat objective signs of discomfort that evolve; it is not to bring about a certain outcome. Stated another way, the target is to make the patient comfortable; the target is not some arbitrary maximum dose and the target is not the death of the patient.

Thus if there are no objective signs of discomfort and the patient breathes effectively after extubation, despite anticipation that death would immediately follow withdrawal of ventilation, there should be no panic among the clinicians that something is wrong or that further sedatives or analgesics must be administered. If the patient is unexpectedly breathing comfortably after extubation, continue all other nonmedication measures of palliative care and provide ongoing and comprehensive support for the family. On the other hand, it may take multiple boluses of escalating doses of sedatives and analgesics to treat clear signs of discomfort after extubation to keep the patient comfortable.

By the doctrine of double effect framework, the frame of mind of the family and of the clinicians before the withdrawal of life-sustaining treatments is that the process of dying will proceed at its own time and place. The response of the clinicians should be based solely on how the patient evolves, and it is not the intention in administering sedatives and analgesics to ensure that a certain outcome evolves.

Intentions are, of course, essentially subjective and private, and thus not easily externally validated. As such, the only way to infer the nature of a clinician's intentions are by self-report and an analysis of his or her actions. Accordingly, documentation of the clinician's intentions in the patient's chart is an important part of providing end-of-life care. Correspondingly, sedation and/or analgesia should be titrated to effect (importantly, some objective sign or symptom suggestive of pain or suffering), and the dose should not be limited solely on the basis of "recommended" or "suggested" doses and the care provided should be clearly documented as such.

The concept of "anticipatory dosing" (as opposed to reactive dosing) should also guide clinicians in the use of sedation and analgesia at the end of life. The rapid withdrawal of mechanical ventilation is an example of the need for anticipatory dosing. At the time of ventilator withdrawal, the clinician can anticipate that there will be a sudden increase in dyspnea. It is not sufficient simply to respond to this distress with titrated doses of an opioid (reactive dosing). Rather, clinicians should anticipate that the abrupt withdrawal of assisted breathing will trigger increased respiratory distress and therefore they should provide adequate sedation or analgesia beforehand (anticipatory dosing). As a general rule, the doses of medication that the patient has been receiving hourly should be increased by twofold or threefold and administered acutely before withdrawing mechanical ventilation.

What Basic Documentation Is Essential?

- A brief description must be placed in the patient's medical record of the decision-making process that led to the withholding or withdrawal of life-sustaining treatment, and the palliative care provided.
- For example, when describing the decision-making process, one should note the date and time of the family meeting, those present, and some statement that conveys that there is "agreement between the family members and the clinician team that the burdens of life-sustaining treatments outweigh any remaining benefit and that the decision has been made to withdraw life-sustaining treatments at this time."
- In describing the palliative care measures provided, it is important to briefly document the rationale used to titrate sedation and analgesia, if administered. For example, "Signs of suffering were noted with the onset of gasping respirations and increased work of breathing after the patient was extubated. Morphine and versed were ordered by Dr. JB and administered by LP RN and titrated to treat these signs of patient suffering. The patient's signs of suffering were relieved after three boluses over 20 minutes and the patient expired at 9:00 a.m."

Key Points

- The conceptual foundation of informed consent is that patients have the sole right to determine what will be done with their bodies. This includes an established constitutional right, at least in the United States, that a competent adult patient has the right to accept or refuse any medical or surgical treatment, even if it is potentially lifesaving.
- Ideally, informed consent is an ongoing process inherent in patient care that builds trust and reduces disappointment if the intended outcome does not result. By this formulation, informed consent is an ongoing discussion about the general issues of managing an illness as well as specific procedures being proposed.
- The legally relevant criteria for assessing decision-making capacity involve whether the patient is able to (1) communicate a choice, as in clearly indicating a preferred treatment option; (2) understand the relevant information, as in grasping the fundamental meaning of the information communicated by the physician; (3) appreciate the situation and its consequences, as in acknowledging the medical condition and the likely consequences of treatment options; and (4) reason about treatment options, as in engaging in a rational process of manipulating the relevant information.
- The classic formulation of the information that should be conveyed in the informed consent discussion are the risks and benefits of the proposed procedure; alternatives to the proposed procedure; risks and benefits of alternatives to the proposed procedure; and risks and benefits of doing nothing.
- It is ethical and legal to withhold or withdraw any medical treatment when the patient, or the patient's legal health care surrogate, as informed by a recommendation from the clinical team, determines that the burdens of such treatments outweigh the benefits. Any medical intervention, from extracorporeal membrane oxygenation and pacemakers to the use of physiologic monitors, may be withheld or withdrawn from the dying patient in the ICU.
- A 2016 joint statement by the American Thoracic Society, American Association for Critical Care Nurses, American College of Chest Physicians, European Society for Intensive Care Medicine, and Society of Critical Care recently addressed the issue of how clinicians should respond to requests for "potentially inappropriate care."[10]
- The practical issues in providing palliative care to critically ill patients in the ICU are comprehensively well outlined in a 2008 consensus statement by the American College of Critical Care Medicine.

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Review Questions

1. Who decides?

A 70-year-old man has a prosthetic aortic valve placed and subsequently requires a pacemaker for third-degree heart block. He is poorly compliant with anticoagulation regimen and has multiple embolic strokes over the next decade, leaving him unresponsive. His wife requests disabling of the pacemaker on the grounds that the patient would not choose to continue living in this condition. The patient's only child has been vigilant at the patient's bedside and he advocates that all life-sustaining treatments be continued. The patient appointed his wife the durable power of attorney for his health care several years before his current neurologic decline.

Which answer is correct?

a. The pacemaker must be continued because "internal" treatments cannot be legally withdrawn.
b. The pacemaker must be continued because stopping it would be euthanasia (illegal).
c. The pacemaker cannot be discontinued without a court order.
d. The pacemaker may be discontinued, as the wife is the patient's legal surrogate.
e. The pacemaker must be continued, but the batteries can be allowed to expire without replacement.

Answer: d. When patients lack the decisional capacity necessary for informed consent, decisions must be made by a surrogate. Ideally, the patient will have completed an advance directive, indicating the individual that he or she has entrusted with making these decisions. This document is also known as a health care proxy or durable power of attorney for health care decisions.

2. Which answer is correct regarding the right to refuse life-sustaining treatment?

a. Patients, or their legally authorized surrogates, have a virtually unlimited right to refuse unwanted life-sustaining treatments.
b. There is a difference between withholding and withdrawing treatment.
c. All treatments may be withheld or withdrawn except extracorporeal membrane oxygenation.
d. All treatments may be withheld or withdrawn except pacemakers.

Answer: a. In the United States there is a firmly established and well-defined legal and ethical consensus that an adult patient with decisional capacity, or the adult patient's legal surrogate if the patient lacks decisional capacity, has the right to refuse any medical and/or surgical intervention, even if the patient's physician believes the proposed therapy to be potentially lifesaving treatment.

3. Which, if any, of the following choices represents excellent end-of-life care?

a. No morphine
b. Morphine followed by potassium chloride
c. Large bolus of morphine before extubation
d. Neuromuscular blocking agent before extubation
e. Titrated administration of morphine

Answer: e. Correspondingly, sedation and/or analgesia should be titrated to effect (importantly, some objective sign or symptom suggestive of pain or suffering), and the dose should not be limited solely on the basis of "recommended" or "suggested" doses and the care provided should be clearly documented as such.

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Delirium, Sleep, and Mental Health Disturbances in Critical Illness

ANNACHIARA MARRA AND E. WESLEY ELY

CHAPTER OUTLINE

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Overview

An admission to the intensive care unit (ICU) is recognized by both the lay public and medical professionals to be a life-threatening event in most circumstances that is immediately made more distressing and sinister by the onset of delirium and severe sleep derangements during the ICU stay. Upon survival, however, these worries are often replaced over the ensuing months and years by mental health disturbances that can be crippling to survivors. We are now aware of the sometimes life-changing ramifications of brain and behavioral disorders sustained by ICU survivors. In the past 15 or so years, data have been published that clearly illustrate a spectrum of acquired or exacerbated "neck-up" disorders that often dismantle the lives of these patients and seriously delay their recovery. Most notable among these disorders is a potentially life-altering "dementia-like" brain injury that occurs in 60% to 80% of ICU survivors that is most often characterized by memory deficits and executive dysfunction. These problems have real-world implications because they diminish patients' ability to work, drive, shop, monitor finances, and remember the names of their friends, relatives, and coworkers. These extremely troublesome neuropsychological deficits are compounded by mood disorders such as major depression and posttraumatic stress disorder (PTSD). These two diagnoses (depression and PTSD) are underdiagnosed despite their occurrence in 20% to 30% and 10% to 20% of ICU survivors, respectively. As a profession, we are just beginning to address the risk factors for these newly acquired diseases.

Having acknowledged the preceding realities of the states of survival of critical illness, it is also true that advances in clinical medicine have resulted in dramatic improvements in survival in a host of medical conditions, such as acute respiratory distress syndrome (ARDS) and sepsis. In general, 1- to 3-month mortality rates for both of these common ICU admission diagnoses in most cohorts are now in the 20% to 35% range, whereas in the 1990s these mortality rates were in the 40% to 60% range. As a result of the increased confidence in survival, both the lay public and health care professionals are now increasingly focused on preservation of cognitive abilities, prevention of functional decline, and the quality of life among patients who survive critical illness.[1–5] The potential of being left cognitively impaired is a major determinant of patients' treatment preferences at the end of life, with 9 of every 10 patients preferring death to severe cognitive impairment.[6] In support of this reality, in a report from the international "Surviving Intensive Care" 2002 Roundtable Conference held in Brussels,[7] the need for future investigations in neurocognitive abnormalities among survivors of intensive care received the strongest recommendation from the international panel of experts. Physicians and health care providers in ICUs are accustomed to recognizing multiple-organ dysfunction syndrome (MODS),[8–11] with therapy focused on the causes and treatment of respiratory, cardiovascular, renal, and hepatic dysfunction. There are increasing data on the syndrome of brain dysfunction during and after the ICU.[12] This chapter focuses on the cognitive and mental health disturbances of critical illness, with emphasis on delirium and sleep disturbances during critical illness, as well as a brief discussion of PTSD, long-term cognitive impairment (LTCI), and depression after critical illness.

Acute Brain Dysfunction or Delirium

Definition

Delirium is defined by American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 5th revised edition (DSM-V),[13] as a disturbance in attention and awareness that develops over a short period of time and tends to fluctuate in severity during the course of a day.

The new DSM-5 criteria shift the core feature of delirium from awareness to attention owing to the recognition that consciousness was difficult to assess objectively. The European Delirium Association and American Delirium Society proposed a more inclusive interpretation of the DSM-5 criteria, suggesting that patients who are not comatose but have impaired arousal, resulting in an inability to engage in cognitive testing or interview, must be understood as effectively having inattention to increase patient safety through broader delirium prevention and identification.[14]

Many different terms have been used to describe this spectrum of cognitive impairment in critically ill patients, including ICU psychosis, ICU syndrome, acute confusional state, septic encephalopathy, and acute brain failure.[15–18] The current consensus of many authorities is to use the unifying term *delirium* and subcategorize according to the level of alertness (hyperactive, hypoactive, or mixed).[19] We take this approach in this chapter.

Prevalence and Subtypes

Although the prevalence of delirium in medical ICU cohort studies has been reported to be between 20% and 80%,[20–22] more general ranges are practical depending on the severity of illness and the delirium detection instrument used, such as 40% to 60% in nonventilated and 60% to 80% in ventilated ICU patients.[23] Unfortunately, because delirium is usually "quietly" manifested by negative symptoms, it remains unrecognized by the clinician in a majority of the patients experiencing this complication,[24,25] and it may be incorrectly attributed to dementia, depression, or just an "expected" occurrence in the critically ill, elderly patient.[24] Peterson and associates reported on delirium subtypes from a cohort of ventilated and nonventilated ICU patients in whom delirium was monitored. They found the rates of these subtypes in the ICU to be 1.6% for hyperactive, 43.5% for hypoactive, and 54.1% for mixed.[26] Pandharipande et al. showed similar results in surgical and trauma patients, in whom hypoactive delirium (64% and 60%, respectively) was significantly more prevalent than the mixed (9% and 6%) or the pure hyperactive delirium (0% and 1%).[27]

Hyperactive delirium, which is rare in the pure form and associated with a better overall prognosis,[28] is characterized by agitation, restlessness, attempting to remove catheters or tubes, hitting, biting, and emotional lability.[19,29] This subtype was in the past referred to by the misnomer "ICU psychosis." Hypoactive delirium, on the other hand, is very common and in many circumstances actually more deleterious for the patient in the long run.[28,30] Unfortunately, it remains unrecognized in 66% to 84% of patients, whether being treated in the ICU, hospital ward, or emergency department.[25,31–33] This delirium subtype is characterized by withdrawal, flat affect, apathy, lethargy, and decreased responsiveness.[28,34,35] Because of the fluctuating nature of delirium, patients may present with a mixed clinical picture or may sequentially experience both of these subtypes. Many critical care providers would have the incorrect impression that hyperactive delirium is far more common, perhaps because affected patients attract attention because of their immediate threat to self and others. Unless routine monitoring for delirium is implemented,[36,37] the majority of delirium episodes, especially the "quiet" (hypoactive) form, will be missed. Another categorization scheme was proposed by Ouimet and colleagues,[38] who evaluated 600 ICU patients for symptoms of delirium and categorized them according to the number of symptoms present. Patients with no symptoms were considered to have "no delirium," those with four or more symptoms to have "clinical delirium," and those with one to three symptoms, to have "subsyndromal delirium.'[39] Subsyndromal delirium has also been associated with worse post-ICU outcomes.[40]

Prognostic Significance

The consequences of this brain dysfunction are important. Delirium itself is a strong predictor of increased length of mechanical ventilation, longer ICU and hospital stays, increased cost, long-term cognitive impairment, and mortality.[41–45] In non-ICU populations, the development of delirium in the hospital is associated with an in-hospital mortality rate of 25% to 33%, prolonged hospital stay, and three times greater likelihood of discharge to a nursing home. It is also an independent predictor of the combined outcome of death or nursing home placement.[42,46–48] Among medical ICU patients, delirium has been shown to be a strong predictor of increased duration of mechanical ventilation, longer length of ICU stay, higher costs, prolonged neuropsychological dysfunction, and even death.[41,42,45,49,50] Ely et al. showed that the majority of ICU delirium cases occurred soon after admission, with an average time of onset between the second and the third day with a mean duration of 3.4 ± 1.9 days. In this study, delirium was the strongest predictor of hospital length of stay, even after adjusting for severity of illness, age, gender, race, and days of psychoactive drug use.[41]

Delirium has been a strong risk factor for mortality.[42,51] Three separate cohort studies have shown that the duration of delirium (in a dose-dependent sort of relationship) is an independent predictor of increased subsequent death, with the most commonly cited finding being that every day a patient spends in ICU delirium portends a 10% higher risk of death even after adjusting for relevant covariates, such as severity of illness, age, psychoactive medication use, and coma.[42,45,51] The relationship between the duration of delirium and mortality was nonlinear, with a greater effect observed earlier in the course of delirium. These data suggest that the harm of delirium may occur early in the course of brain dysfunction for ICU patients.[45] Conversely, Klein Klouwenberg et al. speculated that the increased mortality could be mediated through a prolonged ICU length of stay, rather than a direct effect on the daily risk of death, although longer duration of delirium (>2 days) still had some attributable mortality risk.[52] Nonetheless, a meta-analysis of 28 studies with ICU patients consistently demonstrated a higher a risk of in-hospital death associated with delirium (risk ratio 2.19, 95% confidence interval [CI] 1.78–2.70, $P < 0.001$).[53] In addition, it is now shown that the duration of delirium is an independent predictor of LTCI in general medical and surgical ICU patients who in the past were not suspected of having long-term dementia-like abnormalities.[54]

Pathophysiology

The mechanisms of delirium remain a very promising area of neuroscientific study[55] and likely relate to those factors leading to LTCI, as noted in the following text.

Neurotransmitter Hypothesis

From a neuroscience perspective, delirium is thought to be related to imbalances in the synthesis, release, and inactivation of neurotransmitters modulating the control of cognitive function, behavior, and mood.[28,35] Three of the neurotransmitter systems involved in the pathophysiology of delirium are dopamine, gamma-aminobutyric acid (GABA), and acetylcholine.[17,56,57] Whereas dopamine increases excitability of neurons, GABA and acetylcholine decrease neuronal excitability.[17] An imbalance in one or more of these neurotransmitters results in neuronal instability and unpredictable neurotransmission. In general, an excess of dopamine and depletion of acetylcholine are two major physiologic problems believed to be central to delirium.[58] Other neurotransmitter systems thought to be involved in the development of delirium are serotonin imbalance, endorphin hyperfunction, and increased central noradrenergic activity.[28,56]

Neuroinflammatory Hypothesis

Other factors thought to be mechanistically deliriogenic in ICU patients are inflammatory abnormalities induced by endotoxins and cytokines.[59,60] The inflammatory mediators produced in sepsis, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, and other cytokines and chemokines, initiate a cascade that leads to endothelial damage, thrombin formation, and microvascular compromise.[61] Animal models show that these inflammatory mediators cross the blood-brain barrier,[62] increase vascular permeability in the brain,[63] and result in electroencephalography (EEG) changes consistent with those seen in septic patients with delirium.[64,65] Release of inflammatory mediators may occur from (1) decreased cerebral blood flow, a result of the formation of microaggregates of fibrin, platelets, neutrophils, and erythrocytes in the cerebral microvasculature; (2) cerebral vasoconstriction occurring in response to α_1-adrenergic receptor activity[66]; or (3) interference with neurotransmitter synthesis and neurotransmission.[67]

Impaired Oxidative Metabolism Hypothesis

One hypothesis attempts to explain acute delirium as a behavioral manifestation of a "widespread reduction of cerebral oxidative metabolism resulting in an imbalance of neurotransmission."[68] On the basis of a series of investigations in which they evaluated delirious patients using EEG, Engel and Romano[69] postulated that delirium is a state of "cerebral insufficiency"—that is, a global failure of cerebral oxidative metabolism. Their work showed that delirium is associated with diffuse slowing on EEG, a finding believed to represent a reduction in brain metabolism.

Cholinergic Deficiency Hypothesis

Blass and colleagues[70] offered a possible link between the state of cerebral insufficiency proposed by Engel and Romano[69] and the hypothesis of cholinergic blockade by suggesting that impaired oxidative metabolism in the brain results in a cholinergic deficiency. The finding that hypoxia impairs acetylcholine synthesis supports this hypothesis.[71] This reduction in cholinergic function leads to an increase in the level of glutamate, dopamine, and norepinephrine in the brain. In addition, serotonin and GABA levels are reduced; all of these changes contribute to delirium.

Large Neutral Amino Acid Hypothesis

Changes in the plasma levels of various amino acid precursors of cerebral neurotransmitters may affect their function, thus contributing to the development of delirium.[72] The amino acid entry into the brain is regulated by a sodium-independent large neutral amino acid transporter type 1.[73] The essential amino acid tryptophan, which is the precursor for serotonin, competes with several large neutral amino acids (LNAAs), such as tyrosine, phenylalanine, valine, leucine, and isoleucine, for transport across the blood-brain barrier via the large neutral amino acid transporter type 1 transporter.[73] This competition determines its uptake into the brain.[73] Recently alterations in plasma tryptophan and tyrosine levels were identified as independent risk factors for the transition to clinical delirium.[74] Increased activation of the kynurenine pathway, which is involved in the metabolism of tryptophan and the formation of neurotoxins, has also been linked to fewer days alive and without acute brain dysfunction in critically ill patients.[75] Another amino acid that may play an important role in the pathogenesis of delirium is phenylalanine.[68] Like tryptophan, phenylalanine competes with the other LNAAs (tyrosine, tryptophan, valine, leucine, and isoleucine) for transport across the blood-brain barrier. An increase in the cerebral uptake of tyrosine and phenylalanine compared with the other LNAAs leads to greater availability of precursors for both dopamine and norepinephrine, two neurotransmitters that have been implicated in the pathogenesis of delirium.[68]

Inflammation Hypothesis

It is important to realize that although delirium may occur as a result of perturbations in other organ systems, the brain responds to systemic infections and injury with an inflammatory response of its own that also involves cytokine production, cell infiltration, and tissue damage.[76,77] Reports indicate that local inflammation in the brain and subsequent activation of these central nervous system immune responses are accompanied by manifestations of systemic inflammation,[57,78,79] including production of large amounts of peripherally produced tumor necrosis factor α, IL-10, and interferon-γ.[76,80–82] Thus it is postulated that the brain can become an engine of inflammation, driving the development, resolution, or both, of MODS. Van Gool and associates propose that this self-propelling inflammation, in the context of microglial activation, could help explain the association between delirium and LTCI.[83] Surprisingly, van Gool points out that animal models have shown activated microglia can remain primed for months after injury, allowing ample time for ongoing injury long beyond the period of an ICU stay. These factors should be considered when designing neuroimaging studies in ICU survivors and will serve as fascinating topics for future study.

Neuroaging Hypothesis

Aging is associated with age-related cerebral changes in stress-regulating neurotransmitters, brain-blood flow decline, decreased vascular density, neuron loss, and intracellular signal transduction systems that may render the brain more susceptible to exogenous insults such as acute inflammatory states in the body.[84–87] In addition, the aging brain may mount a more exuberant central nervous system inflammatory response when stimulated by peripheral inflammatory states.[88]

Neuroendocrine Hypothesis

Delirium represents a reaction to acute stress mediated by abnormally high glucocorticoid levels that induce a general vulnerability in brain neurons by impairing the ability of neurons to survive after various metabolic insults.[89] Chronically high levels of physiologic stress are also associated with increased levels of inflammation in the body, connecting the neuroinflammatory and neuroendocrine theories of delirium.[55]

Diurnal Dysregulation Hypothesis

This hypothesis suggests that disruptions to the 24-hour circadian cycle and the usual stages of sleep may lead to the development of delirium.[90] Derangements in melatonin levels may cause delirium owing to its central role in the regulation of the circadian rhythm and sleep-wake cycles.[91,92] Sleep deprivation has been associated with increased levels of inflammatory substances, connecting this hypothesis to the neuroinflammatory theory of delirium.[55]

Network Disconnectivity Hypothesis

According to this hypothesis delirium could represent a variable failure in the integration and appropriate processing of sensory information and motor responses. The clinical forms of delirium, hypoactive versus hyperactive, may be determined by which neural networks break down in response to stressors such as aging, sleep deprivation, infection/inflammation, or medication exposure.[93] How they break down in the face of a particular stressor is thought to be related to the degree of baseline network connectivity and the level of inhibitory tone, mediated by GABA levels in that particular neural network.

None of these theories by themselves explains the full phenomenon of delirium. Rather, it is thought that two or more of these, if not all, act together to lead to the biochemical derangement we know as delirium.[90]

Risk Factors for Delirium

Although non-ICU cohort studies have identified numerous risk factors for the development of delirium,[48] only a few studies have examined these factors in the ICU population. Numerous risk factors for delirium have been identified, including preexisting cognitive impairment, advanced age, use of psychoactive drugs, mechanical ventilation, untreated pain, and a variety of medical conditions, such as heart failure, prolonged immobilization, abnormal blood pressure, anemia, sleep deprivation, and sepsis.[31,42,94–96] Baseline risk factors that predispose patients to a greater degree of vulnerability for delirium include Alzheimer disease, chronic illness, advanced age, and depression.[17,97,98] Dubois and coworkers[95] found that preexisting hypertension and smoking (presumably because of relative hypoperfusion and nicotine withdrawal, respectively) were significantly associated with the development of ICU delirium.[21] A new area of investigation is genetic predisposition to delirium, as the apolipoprotein (Apo) E4 polymorphism. The relationship between ApoE polymorphism and brain dysfunction is still unclear. Some studies found that the ApoE genotype was able to predict delirium that lasted nearly twice as long as patients without the polymorphism.[99,100] On the other hand, a study of older surgical patients who were free of dementia did not find a relationship between the ApoE genotype and either increased risk or protection in postoperative delirium incidence, severity, or duration.[101]

Precipitating and iatrogenic risk factors represent areas of potential modification and, thus, intervention for delirium prevention and treatment. Precipitating factors are hypoxia, metabolic disturbances, electrolyte imbalances, withdrawal syndromes, acute infection (systemic and intracranial), seizures, dehydration, hyperthermia, sleep deprivation, head trauma, vascular disorders, and intracranial space-occupying lesions.[17,97,98]

The average medical ICU patient has 11 or more risk factors for developing delirium. These risk factors can be divided into predisposing baseline (as with underlying characteristics and comorbidities) and hospital-related, or precipitating factors (such as acute illness, its treatment and ICU management) (Table 69.1).[102] Although delirium may be a function of a patient's specific underlying illness, it may also be due to medical management issues and thus may have preventable causes. Of these risk factors, sedative and analgesic medications and sleep deprivation appear to be the leading iatrogenic, and hence possibly preventable, risk factors for delirium. There are conflicting data on the association of anticholinergics, corticosteroids, histamine H_2 antagonists, and anticonvulsants with the development of delirium in ICU patients.[24,103–105]

TABLE 69.1 Selected Risk Factors for Delirium in the Intensive Care Unit

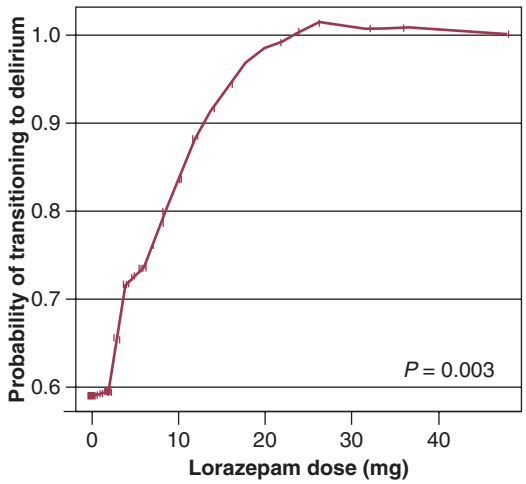
Type of Factor	Risk Factors
Patient Factors	• Age • Baseline comorbid conditions • Baseline cognitive impairment • Genetic predisposition (?) • Acute illness • Sepsis • Hypoxemia[a] • Global severity of illness score • Metabolic disturbances
Iatrogenic or Environmental Factors	• Metabolic disturbances[a] • Anticholinergic medications[a] • Sedative and analgesic medications[a] • Sleep disturbances[a]

[a]Potentially modifiable factor.

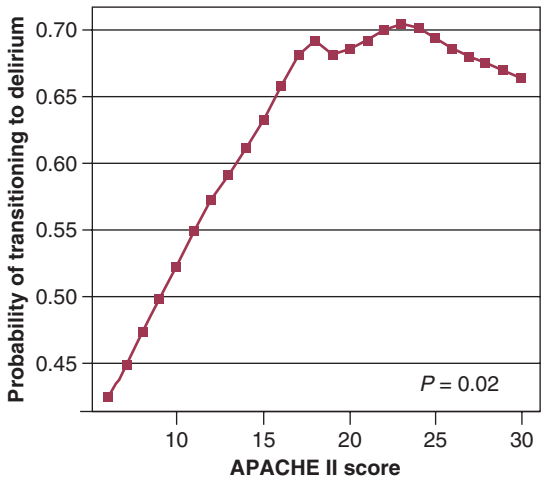
Sedatives and Analgesic Agents Contributing to Delirium

Sedative and analgesic medications are routinely administered to patients undergoing mechanical ventilation, in accordance with widely recognized clinical practice guidelines by the Society of Critical Care Medicine (SCCM),[105,106] to reduce pain and anxiety. Investigations have shown that continuous intravenous sedation is associated with prolonged mechanical ventilation and greater morbidity.[107] Similarly, associations between psychoactive medications and worsening cognitive outcomes have been reported in postoperative patients. Marcantonio and colleagues,[108] studying postoperative patients in whom delirium developed, found an association between use of benzodiazepines and meperidine and the occurrence of delirium. Dubois and coworkers[95] have shown that opiates (morphine and meperidine) administered either intravenously or via an epidural catheter may be associated with the development of delirium in medical/surgical ICU patients. Further comparative research is needed to better understand the role of different type, timing, and dose of opioids in the development of delirium.[109] Studies such as these have generated concern about whether such drugs were actually responsible for the development of delirium or were given as a result of delirium.

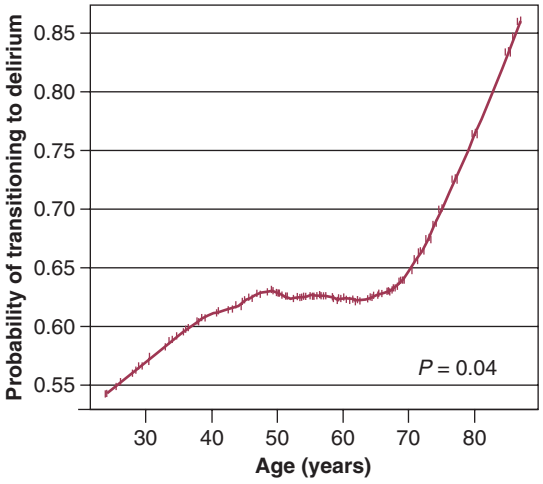
Our group has studied this temporal relationship between the administration of sedatives and analgesics and delirium.[110] To do so, one must make repeated cognitive assessments and must be able to assess the risk factors to which a patient is exposed in between these assessments to study which of these factors is associated with a transition or a change in cognitive status to or from normal, delirium, or coma. In our study, lorazepam was found to



• **Fig. 69.1** Lorazepam dose versus probability of transitioning to delirium. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 hours. This incremental risk was large at low doses and plateaued at around 20 mg/day. (From Pandharipande P, Shintani A, Truman P, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104:21–26.)



• **Fig. 69.3** Severity of illness versus the probability of transitioning to delirium. The probability of transitioning to delirium increased dramatically for each additional point in APACHE II (Acute Physiology and Chronic Health Evaluation II) severity of illness score until it reached a plateau score of 18. (From Pandharipande P, Shintani A, Truman P, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104:21–26.)



• **Fig. 69.2** Age versus the probability of transitioning to delirium. The most notable finding related to age was that the probability of transitioning to delirium increased dramatically for each year of life after 65 years. (From Pandharipande P, Shintani A, Truman P, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104:21–26.)

be an independent risk factor for daily transition to delirium, and fentanyl, morphine, and propofol were associated with higher but not statistically significant odds ratios for such transition (Fig. 69.1).[110] Increasing age and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores were also independent predictors of transitioning to delirium (Figs. 69.2 and 69.3).[110] Similar associations between another benzodiazepine, midazolam, and transition to delirium have been found in another study conducted in our trauma and surgical ICU patients.[23] In addition, Seymour et al. confirmed that benzodiazepines are an independent risk factor for development of delirium during critical illness even when given more than 8 hours before a delirium assessment.[111]

The class of benzodiazepines does not seem to change the risk profile, with both lorazepam and midazolam being significant risk factors for delirium. Because of this, the SCCM ICU Pain Agitation Delirium (PAD) guidelines recommend that nonbenzodiazepine sedative options may be preferred over benzodiazepine-based sedative regimens.[106,112] The GABA-mimetic effect of benzodiazepines and propofol can alter the levels of numerous neurotransmitters believed to be deliriogenic.[67,113] Novel sedative agents that are GABA receptor-sparing (such as the α_2-agonists) may help reduce some of the cognitive dysfunction seen in ICU patients. Data for opioids and delirium are not as consistent as those for the benzodiazepines. Although meperidine has been associated with delirium in most of the published studies, evidence for both fentanyl and morphine has been less convincing.[95,108,114] Morrison and colleagues[114] conducted a prospective observational trial in patients who had undergone hip surgery and found that patients whose pain was well controlled with morphine were less likely to demonstrate delirium than those who received other opioids. These investigations point to the importance of the judicious use of psychoactive medications, with a focus on adequate analgesia.[115] One hopes that ongoing randomized controlled trials will pave the way to the development of sedation and analgesic guidelines for the prevention or reduction of the occurrence of delirium as the result of administration of these psychoactive drugs.

Diagnosis

The development of tools such as the Intensive Care Delirium Screening Checklist (ICDSC)[20] and the Confusion Assessment Method for the ICU (CAM-ICU)[22] has allowed for the rapid diagnosis of delirium in patients by nonpsychiatrists and other health care personnel even while such patients are mechanically ventilated. Several other scales have been developed and validated to diagnose delirium in ICU patients[116] (Delirium Detection Score [DDS], Cognitive Test for Delirium [CTD], Abbreviated Cognitive Test for Delirium, Neelson and Champagne Confusion Scale

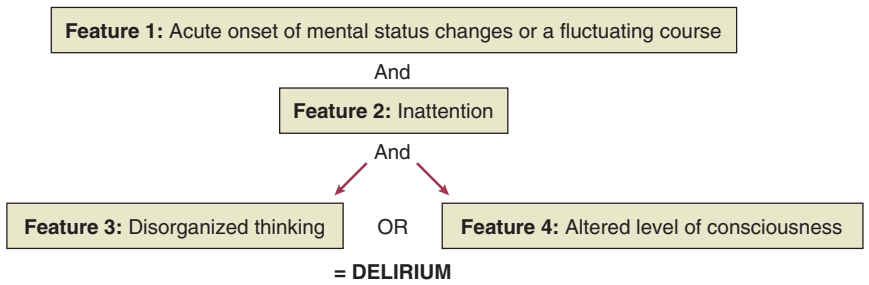
Linking Sedation and Delirium Monitoring:
A Two-Step Approach to Assess Consciousness

Step One: Sedation Assessment
The Richmond Agitation and Sedation Scale: The RASS

Score	Term	Description	
+4	Combative	Overly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
–1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* **(≥10 seconds)**	Verbal Stimulation
–2	Light sedation	Briefly awakens with eye contact to *voice* **(<10 seconds)**	
–3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**	
–4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
–5	Unarousable	No response to *voice or physical* stimulation	

If RASS is –4 or –5, then **Stop** and **Reassess** patient at later time.
If RASS is above –4 (–3 through +4), then **Proceed to Step Two.**

Step Two: Delirium Assessment



• **Fig. 69.4** Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the ICU (CAM-ICU). This sedation scale and delirium instrument can be used together as a two-step approach to assess consciousness and diagnose delirium. Patients are considered to have delirium if they have RASS scores of –3 and higher and are assessed by CAM-ICU as "positive" by having both features 1 and 2 and either feature 3 or feature 4. (Data from references 22, 117, and 118 [available online].)

[NEECHAM], Nursing Delirium Screening Scale [NuDESC]). However, the ICDSC[20] and the CAM-ICU[22] are the tools recommended by the SCCM PAD guidelines for this purpose.[106]

Diagnosis of delirium is a two-step process. The level of arousal is first measured with the use of a standardized sedation scale, like the Richmond Agitation-Sedation Scale (RASS) (Fig. 69.4).[117,118] This is a 10-point scale with scores ranging from +4 to −5, with a score of 0 denoting a calm and alert patient. Positive RASS scores denote positive or aggressive symptomatology ranging from +1 (mild restlessness) to +4 (dangerous agitation). The negative RASS scores differentiate between response to verbal commands (scores −1 to −3) and physical stimulus (scores −4 and −5). If the patient's RASS score is −4 or −5 or the patient is not arousable by verbal commands, no further evaluation for delirium is performed, because the patient is comatose and is unable to be assessed for delirium. For patients who are arousable (RASS scores of −3 and higher), delirium can be assessed by the ICDSC that assesses eight features of delirium: altered level of consciousness, inattention, disorientation, hallucinations, psychomotor agitation/retardation, inappropriate mood/speech, sleep/wake cycle disturbance, and symptom fluctuation. The sensitivity and specificity of this tool are 99% and 64%, respectively.[20] The CAM-ICU, which can be performed in about 60 to 90 seconds,[119] consists of four features that assess the following: acute change or fluctuation of mental status (feature 1), inattention (feature 2), disorganized thinking (feature 3), and an altered level of consciousness (feature 4).

To be diagnosed as delirious, a patient must have a RASS score of −3 or higher, with an acute change or fluctuation in mental status (feature 1), accompanied by inattention (feature 2) and either disorganized thinking (feature 3) or an altered level of consciousness (feature 4). A complete description of the CAM-ICU as well as training materials, including translations and clinical vignettes, can be found at our website (www.icudelirium.org).

Recently a meta-analysis evaluated the accuracy of the CAM-ICU and the ICDSC for the diagnosis of ICU delirium.[116] This investigation included nine studies evaluating the CAM-ICU ($N = 969$ total patients) and four studies evaluating the ICDSC ($N = 361$). The authors calculated the pooled sensitivity of the CAM-ICU to be 80% (95% CI 77.1%–82.6%) and specificity of 95.9% (95% CI 94.8%–96.8%). The pooled sensitivity and specificity of the ICDSC were 74% (95% CI 65.3%–81.5%) and 81.9% (95% CI 76.7%–86.4%). They concluded that both delirium scales can be used as a screening tool, and that the CAM-ICU was an excellent diagnostic tool and the ICDSC had moderate sensitivity and good specificity.[116]

Prevention and Management

Primary Prevention and Nonpharmacologic Approaches

In a trial of 852 general medical patients older than 70 years,[94] implementation of strategies for primary prevention of delirium resulted in a 40% reduction in the odds for development of delirium

(15% in control subjects vs. 9.9% in the intervention patients). The protocol focused on optimization of risk factors via the following methods: repeated reorientation of the patient by trained volunteers and nurses, provision of cognitively stimulating activities for the patient three times per day, nonpharmacologic sleep protocol to enhance normalization of sleep/wake cycles, early mobilization activities and range-of-motion exercises, timely removal of catheters and physical restraints, institution of the use of eyeglasses and magnifying lenses, use of hearing aids and earwax disimpaction, and early correction of dehydration.[94] Unfortunately, this intervention did not show sustained benefit during the 6 months of follow-up.[120] Later studies of delirium were unable to reproduce this success in reducing the incidence of delirium.[121,122]

Milisen and associates[123] and Lundstrom and coworkers[124] studied the impact of the implementation of multifactorial and multidisciplinary educational strategies on duration and severity of delirium in patients cared for by staff who had received delirium-specific education.[129,130] In these studies the implemented programs reduced duration of delirium,[123,124] hospital stay, and mortality rate.[123,124] Cole and colleagues[122] found no difference in delirium rates between patients cared for by an intervention nurse and patients who received standard care. All of these nonpharmacologic "protocolization of care" studies focused on non-ICU patient populations. Clearly such investigations must be designed and conducted in the ICU (rather than simply extrapolated from non-ICU studies).

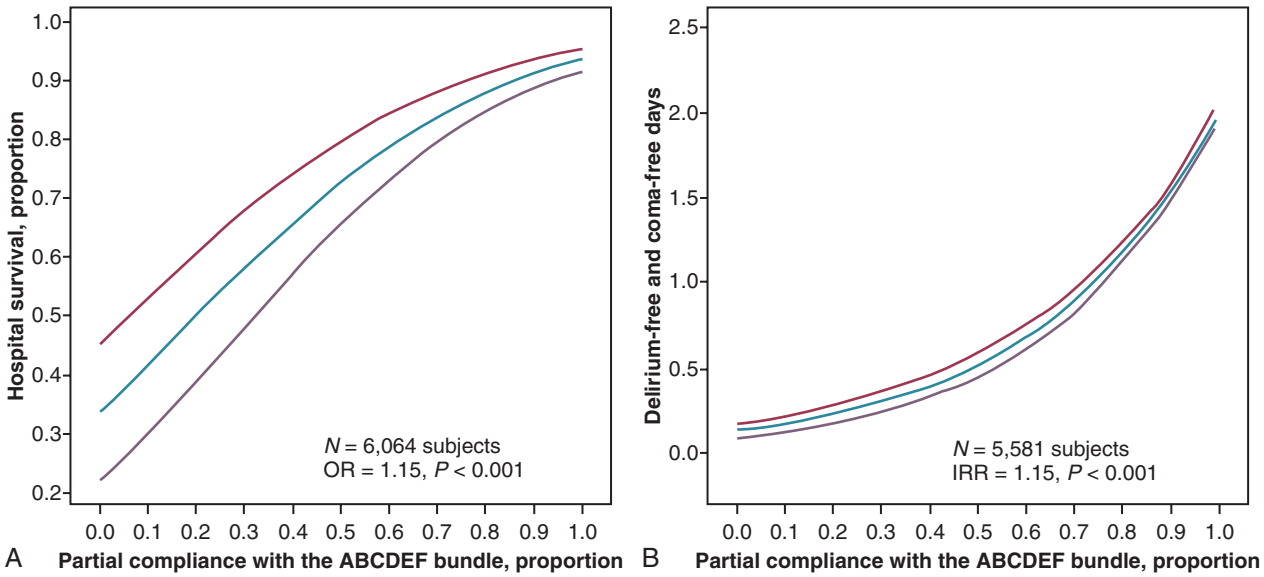
Although primary prevention of delirium is preferred, some delirium is inevitable in the ICU. In patients exhibiting delirium, the basic tenets of patient management, such as restoration of sleep/wake cycles, timely removal of catheters, early mobilization, minimization of unnecessary noise/stimuli, and frequent reorientation, should be applied liberally. Additionally, it should be emphasized that although sedative and analgesic agents have a very important role in patient comfort, health care professionals must also strive to achieve the right balance of administering these drugs through greater focus on reducing unnecessary or overzealous use. Instituting daily interruption of sedatives and analgesics, protocolizing their delivery, and instituting target-based sedation have all been shown to improve patient outcomes, although the studies reporting these results have not specifically looked at delirium rate or duration.[107,125,126] Studies have also shown a benefit for pain control in the prevention of delirium, because pain itself can be a risk factor for the development of delirium.[114,121,123] Family involvement can also be very helpful in reorienting and soothing some patients with delirium. It is important to teach family members about the fluctuating course of delirium as well as how they can detect it. All of these strategies are nicely summarized and operationalized in the evidence-based ABCDEFs of ICU care, which stands for spontaneous Awakening trials, spontaneous Breathing trials, Coordination of care and Choice of sedative, Delirium monitoring and management, Early mobility, and Family engagement. The ICU Liberation Collaborative is a real-world quality improvement initiative being implemented across 76 ICUs designed to strategically engage the ABCDEF bundle through team- and evidence-based care[127] (www.iculiberation.org) (Fig. 69.5). Recently Barnes-Daly et al. showed that, in 6064 patients admitted to 7 community hospitals, higher ABCDEF bundle compliance was independently associated with improved survival and more days free of delirium and coma after adjusting for age, severity of illness, and presence of mechanical ventilation (Fig. 69.6).[128]

Pharmacologic Therapy

Medications should be used for delirium only after adequate attention has been given to correction of modifiable contributing factors (e.g., sleep disturbance, restraints), as discussed previously.

Symptoms Pain, Agitation, Delirium Guidelines	**Monitoring** Tools	**Care** ABCDEF Bundle	**Done**
Pain	Critical Care Pain Observation Tool (CPOT) NRS Numeric Rating Scale BPS Behavioral Pain Scale	**A:** Assess, prevent and manage pain	☐
Agitation	Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS)	**B:** Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT) **C:** Choice of analgesia and sedation	☐ ☐
Delirium	Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Intensive Care Delirium Screening Checklist (ICDSC)	**D:** Delirium: Assess, prevent and manage **E:** Early mobility and exercise **F:** Family engagement and empowerment	☐ ☐ ☐

• **Fig. 69.5** ICU Liberation bundle chart. Intensive care unit (ICU) liberation is a quality improvement program geared toward reducing symptoms of pain, agitation, and delirium that threaten patients' sense of self-worth and dignity. These symptoms are monitored using valid and reliable tools, and the culture is shaped using the evidence-based ABCDEF (Awakening and Breathing Coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family engagement) bundle as a rounding checklist.



• **Fig. 69.6** The figure shows the data demonstrating the effect of the ABCDEF bundle on survival (*A*) and delirium and coma-free days (*DFCFDs*) (*B*)—that is, a day during which the patient was alive and both not delirious (CAM-ICU negative) and not in a coma (Richmond Agitation-Sedation Scale [RASS] score of –3 or higher), analyzed by partial compliance (dose response). *A,* Hospital survival plotted in relationship to partial compliance with the ABCDEF bundle after adjusting for patient age, Acute Physiology and Chronic Health Evaluation III (APACHE III), and the proportion of days a patient was mechanically ventilated. With each 10% increase in partial bundle compliance, the odds of hospital survival increase to 15% (odd ratio 1.15; 95% confidence interval 1.09–1.22; $P < 0.001$). *B,* DFCFDs plotted in relationship to partial compliance with the ABCDEF (Awakening and Breathing Coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family) ABCDEF bundle after adjusting for patient age, APACHE III, and the proportion of days a patient was mechanically ventilated. For every 10% increase in partial bundle compliance, there was a 15% increase in DFCFDs. (Adapted from Barnes-Daly MA, Phillips G, Ely WE. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med.* 2017;45:171–178.)

It is important to remember that delirium could be a manifestation of an acute, life-threatening problem that requires immediate attention (such as hypoxia, hypercarbia, hypoglycemia, metabolic derangement, or shock). After such concerns have been addressed, pharmacologic management should be considered. It should be recognized that although agents used to treat delirium are intended to improve cognition, they all have psychoactive effects that may further cloud the sensorium and promote a longer overall duration of cognitive impairment. Therefore until we have outcomes data that confirm beneficial effects of treatment, these drugs should be used judiciously in the smallest possible dose and for the shortest time necessary, a practice infrequently adhered to in most ICUs. Indeed, some cases prove refractory to all "cocktail" approaches to sedation and delirium therapy, and in these cases, a trial of complete cessation of all psychoactive drugs should be considered. Some reports have described the utility of dexmedetomidine (an α_2-agonist) as an adjunct to assist with weaning patients from all psychoactive medications.[129] Preliminary results from a prospective, randomized, yet unblinded trial in postoperative patients who had undergone cardiac surgery showed that sedation with dexmedetomidine at sternal closure was associated with an 8% incidence of postoperative delirium compared with 50% for either propofol or benzodiazepines.[130]

Benzodiazepines are not recommended for the management of delirium because of the likelihood of oversedation, exacerbation of confusion, and respiratory suppression. However, they remain the drugs of choice for the treatment of delirium tremens (and other withdrawal syndromes) and seizures. Current evidence suggests a possible role of dexmedetomidine as adjunctive therapy for management of withdrawal syndromes for its effects in reducing hypertension, tachycardia, and benzodiazepine requirements.[131–135]

The amnestic qualities of benzodiazepines make these agents especially useful when noxious or unpleasant procedures are required. It is likely, however, that residual accumulation of these drugs may lead to prolonged delirium long after they have been discontinued. In certain populations, particularly elderly patients with underlying dementia, benzodiazepines may increase confusion and agitation. In such cases, one may try to take advantage of the sedative effects of haloperidol in lieu of continuing the benzodiazepine therapy.

Currently no drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of delirium. Antipsychotics, especially haloperidol, are commonly administered for the treatment of delirium in critically ill patients.[136] However, evidence for the safety and efficacy of antipsychotics in this patient population is lacking.[105] The 2013 PAD Guidelines include no specific recommendations for using any particular medication to treat delirium.[106] Haloperidol is a "typical" butyrophenone antipsychotic,[137] which does not suppress the respiratory drive and works as a dopamine receptor antagonist by blocking the δ_2-opioid receptor, resulting in treatment of positive symptoms (hallucinations, unstructured thought patterns, and so on) and producing a variable sedative effect. There are data to suggest that haloperidol may have some

antiinflammatory properties,[138,139] although this is theoretical in terms of a helpful pharmacologic effect on disease (such as septic delirium) at this point and requires further study.

In the non-ICU setting, the recommended starting dose of haloperidol is 0.5 to 1.0 mg orally or parenterally, with repeated doses every 20 to 30 minutes until the desired effect is achieved. In the ICU, a recommended starting dose would be 2 to 5 mg every 6 to 12 hours (intravenous, intramuscular, or oral), with maximal effective doses usually in the neighborhood of 20 mg/day. This dose range will usually be adequate to achieve the "theoretically optimal" 60% δ_2-receptor blockage[140] while avoiding complete δ_2-receptor saturation associated with the adverse effects cited later. Because of the urgency of the situation in many ICU patients—owing to the potential for inadvertent removal of central lines, endotracheal tubes, or even aortic balloon pumps—much higher doses of haloperidol or a sedative are often used. Unfortunately, there are few data from formal pharmacologic investigations to guide dosage recommendations in the ICU. Once calm, the patient can usually be managed with much lower maintenance doses of haloperidol.

Newer "atypical" antipsychotic agents (e.g., risperidone, ziprasidone, quetiapine, and olanzapine) may also prove helpful for delirium.[141] The rationale behind use of the atypical antipsychotics rather than haloperidol (especially in hypoactive/mixed subtypes of delirium) is theoretical and centers on the fact that they affect not only dopamine but also other potentially key neurotransmitters, such as serotonin, acetylcholine, and norepinephrine.[141–143] There are prospective studies that examined the safety and efficacy of antipsychotics such as amisulpride,[144] quetiapine,[144–146] and risperidone.[147,148] These are generally small and quite heterogeneous in design, population studied, dosing regimens, and the use of delirium assessment tools. The use of haloperidol has been reported to have a mortality benefit in a retrospective analysis of critically ill, mechanically ventilated patients.[138] Skrobik and colleagues[141] reported that olanzapine and haloperidol were equally efficacious in treating ICU delirium in both medical and surgical patients but that olanzapine had fewer side effects (again, findings from a moderately ill group that must be confirmed and tested against placebo).The Modifying the Incidence of Delirium (MIND) study showed no difference in the duration of delirium between haloperidol, ziprasidone, or placebo when used for prophylaxis and treatment.[149] A small, prospective, randomized, double-blind, multicenter, placebo-controlled study randomly assigned 18 patients to receive scheduled quetiapine and 18 patients to receive placebo.[146] The quetiapine group had a faster resolution of delirium compared with the placebo group (1 day vs. 4.5 days, $P = 0.001$) and a shorter duration of delirium (36 days vs. 120 days, $P = 0.006$). The quetiapine group required fewer days of as-needed haloperidol (3 vs. 4 days). Kato and coworkers[150] reported a case study that suggests that genotyping may affect the choice of antipsychotic drugs. They showed that a patient with the cytochrome P450 (CYP) 2D6 genotype had persistent delirium and demonstrated severe extrapyramidal symptoms when treated with risperidone. When quetiapine (metabolized by CYP 3A4) was used instead, the patient's delirium cleared within 2 days without side effects. This case report is not proof of a positive effect of antipsychotics, yet it is interesting and suggests that pharmacogenetics may play an important role in medication choices in the near future. Ely et al. are conducting the MIND-USA (Modifying the Impact of ICU-Induced Neurological Dysfunction-USA) Study to define the role of antipsychotics in the management of delirium in vulnerable critically ill patients.[150a,151–153]

Adverse effects of typical and atypical antipsychotics include hypotension, acute dystonias, extrapyramidal effects, laryngeal spasm, malignant hyperthermia, glucose and lipid dysregulation, and anticholinergic effects, such as dry mouth, constipation, and urinary retention. Perhaps the most immediately life-threatening adverse effect of antipsychotics is torsades de pointes, and these agents should not be given to patients with prolonged QT intervals unless absolutely necessary. Patients who receive substantial quantities of typical or atypical antipsychotics or are coadministered arrhythmogenic drugs should be monitored closely with electrocardiography. In 2005, the FDA issued an alert that atypical antipsychotic medications are associated with a mortality risk among elderly patients. This warning was supported by a meta-analysis of a large volume of data from outpatient treatment of patients with dementia who were experiencing psychotic symptoms that resulted in their receiving antipsychotic medications.[154] Similar associations with higher stroke risk and fatality have been reported by other investigators.[155,156] Subsequently, other studies have suggested that this higher risk of death in non-ICU elderly patients treated with antipsychotics may not be limited to the atypical antipsychotic agents. Schneider and colleagues[155] found that the conventional antipsychotic haloperidol had an even higher mortality risk.

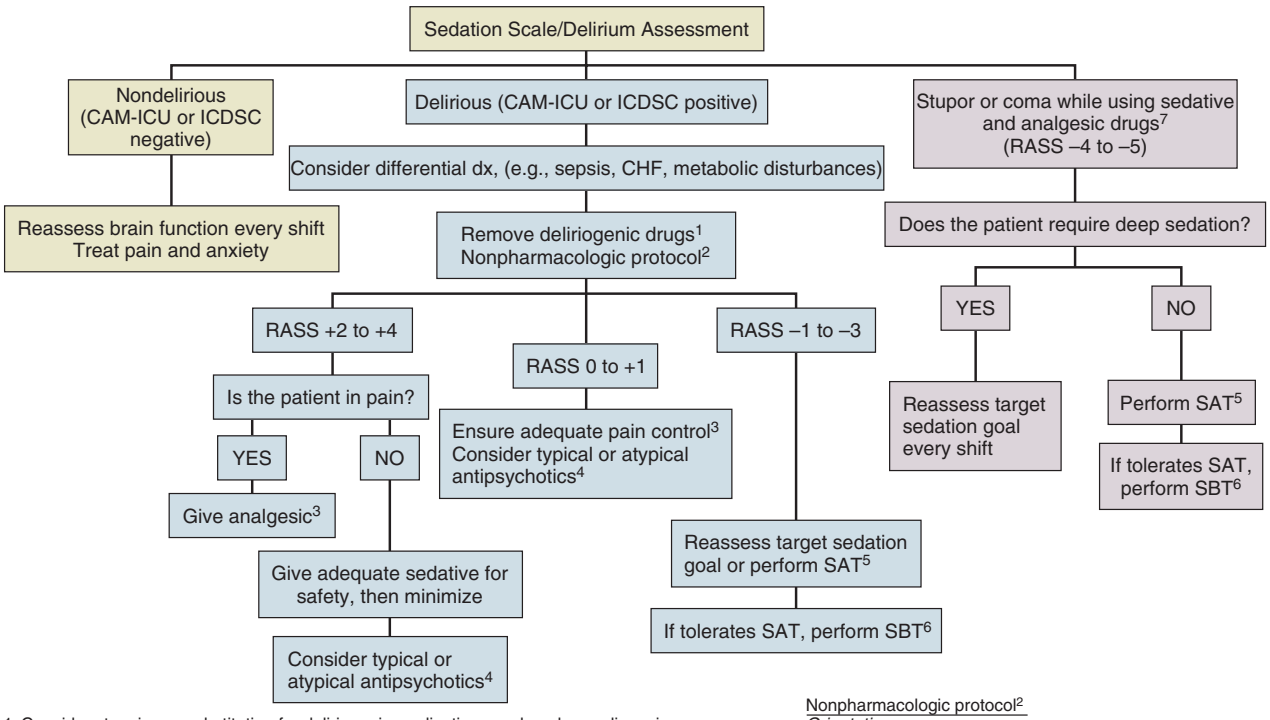
Along with haloperidol and the atypical antipsychotics for the treatment of acute brain dysfunction, a growing body of literature suggests a role for sedatives such as the α_2-agonist dexmedetomidine in the pharmacologic management of delirium. The MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction) trial[157] compared dexmedetomidine with lorazepam for targeted sedation greater than 24 hours in 106 mechanically ventilated patients. Sedation with dexmedetomidine resulted in more days alive without coma or delirium and lower prevalence of coma compared with sedation with lorazepam. Subgroup analysis also demonstrated that sedation with dexmedetomidine reduced the daily risk of delirium, particularly in patients with sepsis.[158] The SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) trial[159] compared dexmedetomidine to midazolam, another commonly used benzodiazepine in the ICU. This large prospective trial showed significantly lower prevalence of delirium in patients receiving dexmedetomidine compared with midazolam, an effect observed within 1 day of initiating sedation and sustained throughout the week of study drug administration.[159] In 2012, the MIDEX and PRODEX trials compared midazolam to dexmedetomidine (MIDEX) and propofol (preferred usual care) to dexmedetomidine (PRODEX) in mechanically ventilated patients requiring long-term sedation. These large trials, which together enrolled nearly 1000 patients, showed that dexmedetomidine was not inferior to midazolam or propofol for targeted light to moderate sedation and was found to be associated with improved communication between the patients and others involved in their care. Dexmedetomidine also reduced time to extubation and was associated with fewer neurocognitive disorders (including delirium) than propofol.[160] In each trial, the reproducible significant adverse effect associated with dexmedetomidine was bradycardia, which typically resolved without event and infrequently required adjunctive treatment beyond discontinuation of the drug.[160] Djaiani et al. recently showed that dexmedetomidine reduced delirium incidence in cardiac surgical patients in the ICU as compared to propofol,[161] while Su et al. showed a reduction in patients treated with dexmedetomidine in noncardiac surgical patients admitted to the ICU.[162] There is an ongoing trial (MENDS II study) to determine the best sedative medication to reduce delirium and improve

survival and long-term brain function in the ventilated septic patient.[162a]

Other agents such as the cholinesterase inhibitors have proved unsuccessful in the management of ICU delirium.[163–166] Given the hypothesis that delirium was associated with excess dopamine and a central cholinergic deficiency, it was logical to test the cholinesterase inhibitors such as rivastigmine, used in treating dementia, for the management of ICU delirium. However, in 2010, a large placebo-controlled trial evaluating rivastigmine as an adjunct to usual care with haloperidol was halted early owing to increased mortality risk and longer duration of delirium in patients receiving rivastigmine.[164] In 2011, another study tested the use of donepezil hydrochloride to reduce the prevalence and severity of delirium in older adults undergoing hip fracture repair without showing improvement in delirium presence or severity.[167] Other agents such as ondansetron[168,169] and melatonin[170–172] are being considered for the treatment of ICU delirium but thus far have little support in the literature.

Protocols and evidence-based strategies for prevention and treatment of delirium will no doubt emerge as more evidence becomes available from ongoing randomized clinical trials of both nonpharmacologic and pharmacologic strategies. To assist readers in developing a delirium management algorithm in their respective clinical arenas, we have provided an empiric protocol largely based on SCCM clinical practice guidelines (Fig. 69.7).

At this time, there are few data regarding which antipsychotic medications are most suitable for delirium. The nonpharmacologic interventions recommended in Fig. 69.7 have shown beneficial



1. Consider stopping or substituting for deliriogenic medications such as benzodiazepines, anticholinergic medications (metoclopramide, H_2-blockers, promethazine, diphenhydramine), steroids, etc.
2. See nonpharmacologic protocol—On the right
3. Analgesia—Adequate pain control may decrease delirium. Consider intermittent narcotics if feasible. Assess with objective tool.
4. Typical or atypical antipsychotics—While tapering or discontinuing sedatives, consider haloperidol 2 to 5 mg IV initially (0.5–2 mg in elderly) and then q6h. Guideline for max haloperidol dose is 20 mg/day due to ~60% D2-receptor saturation. May also consider using any of the atypicals (e.g., olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole). Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
5. Spontaneous Awakening Trial (SAT)—Stop sedation or decrease infusion (especially benzodiazepines) to awaken patient as tolerated.
6. Spontaneous Breathing Trial (SBT)—CPAP trial if on ≤50% and ≤8 PEEP and Sats 90%
7. Sedatives and analgesics may include benzodiazepines, propofol, dexmedetomidine, fentanyl, or morphine.

Nonpharmacologic protocol[2]

Orientation
- Provide visual and hearing aids
- Encourage communication and reorient patient repetitively
- Have familiar objects from patient's home in the room
- Attempt consistency in nursing staff
- Allow television during day with daily news
- Nonverbal music

Environment
- Sleep hygiene: Lights off at night, on during day. Sleep aids (zolpidem, mirtazapine)?
- Control excess noise (staff, equipment, visitors) at night
- Ambulate or mobilize patient early and often

Clinical parameters
- Maintain systolic blood pressure >90 mm Hg
- Maintain oxygen saturations >90%
- Treat underlying metabolic derangements and infections

• **Fig. 69.7** Delirium protocol. This empiric protocol, which is based largely on the current Society of Critical Care Medicine's clinical practice guidelines, is the algorithm we use to treat delirium in our intensive care units (ICUs). We wish to emphasize that such protocols need to be updated regularly with new data and also individualized at each medical center. Specific recommendations about the choice of antipsychotics to treat delirium have not been described, because limited data are available regarding the appropriate drug to use in ICU patients. The nonpharmacologic interventions recommended in this protocol have been shown to have beneficial results in non-ICU patients, but the extrapolation to ICU populations is speculative. *CAM-ICU,* Confusion Assessment Method for the ICU; *CHF,* congestive heart failure; *CPAP,* continuous positive airway pressure; *dx,* diagnosis; ICDSC, Intensive Care Delirium Screening Checklist; *PEEP,* positive end-expiratory pressure; *q,* every; *RASS,* Richmond Agitation-Sedation Scale; *Sats,* saturations.

results in non-ICU patients, but the extrapolation to ICU populations is speculative. Nevertheless, such data emphasize the need for more research in this area and underscore the importance of exercising caution in the treatment of delirium. We emphasize that protocols such as the ABCDEs of critical care[36,37] (Awakening, Breathing, Coordination, Delirium monitoring and management, and Early mobility) must be updated regularly with new data and individualized at each medical center to form an integrated approach to delirium monitoring, sedation targeting, and delirium management in critically ill ICU patients.

By way of summary regarding delirium management, the main thrust of our approach as health care professionals must begin with treatment of the underlying disease processes that are leading to brain dysfunction, then drug removal, and then modification of the environmental factors (hearing and vision aids, removal of restraints and early mobility, and sleep hygiene), which can be summarized via the mnemonic Dr. DRE (Diseases, Drug Removal, Environment). Only after all of these issues are addressed is it appropriate to add another medication such as an antipsychotic into the mix of the individual pharmacopeia for any patient.

Sleep Disruption in the Critically Ill

The sleep cycle is divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep.[173] NREM sleep is further divided into four stages according to an increasing depth of sleep.[130] A normal sleep cycle lasts approximately 90 minutes, cycling continuously between REM and NREM sleep. Stages 3 and 4 of the NREM sleep represent slow-wave or more restful sleep.[173]

Among critically ill patients, 61% report sleep deprivation, placing it among the most common stressors experienced during critical illness.[174–176] The typical sleep pattern of a critically ill patient is characterized predominantly by wakefulness and light sleep (sleep stages 1 and 2), a relative lack of REM sleep, and deep sleep (non-REM sleep stages 3/4).[177] The average amount of sleep in the ICU has been measured to be about 2 hours out of 24 hours, with less than 6% of it spent in REM sleep. In a study by Cooper and associates,[177] the causes of sleep deprivation in the ICU have been extensively reported. They consist of excessive noise and lighting, patient care activities such as procedures and baths, metabolic consequences of critical illness, mechanical ventilation, and the sedative and analgesic medications administered to these patients.[178] This disturbance in duration and quality of sleep has detrimental effects on protein synthesis, cellular and humoral immunity, and energy expenditure, resulting in respiratory and hemodynamic effects as well as cognitive function.[178,179] Studies of sleep disturbances related to noise, patient activities, and light have found that only about 30% of the sleep arousals were a result of these environmental factors, suggesting that other patient factors or management issues play an important role.[180] Of these, it is interesting that the psychoactive medications are common risk factors for both delirium and sleep disturbances, whereas sleep deprivation can itself lead to delirium.

Neurotransmission in Sleep

The ventrolateral preoptic (VLPO) nucleus in the anterior hypothalamus plays a critical role in sleep regulation.[181] Its major neurotransmitter is GABA, and during the awake state, the GABA release from the VLPO nucleus is inhibited by norepinephrine from the locus coeruleus.[181] With the inhibition of the release of GABA, neurotransmitters such as orexin, serotonin, histamine, and acetylcholine are released, resulting in a state of wakefulness (Fig. 69.8). During NREM sleep, norepinephrine release diminishes, thus removing the inhibitory effect on release of GABA from the VLPO nucleus. The firing of GABA neurons inhibits the neurotransmitters of wakefulness (orexin, serotonin, histamine, and acetylcholine), resulting in NREM sleep (Fig. 69.8). REM sleep, on the other hand, is facilitated by neurons in the pons that release acetylcholine. Studies show that serotonin and norepinephrine inhibit these neurons, suppressing REM sleep.

Sedative and analgesic medications are routinely administered to critically ill patients to promote sleep. However, although patients appear sedated, their sleep architecture is often adversely affected.[173] Benzodiazepines and propofol prolong stage 2 NREM sleep while decreasing slow-wave sleep and REM sleep. Opioids, on the other hand, increase stage 1 NREM sleep while decreasing slow-wave and REM sleep. An investigation of the use of dexmedetomidine (an α_2-agonist) in rats shows that it mimics and increases NREM sleep[181] but decreases REM sleep. By acting on the locus coeruleus, dexmedetomidine inhibits the release of norepinephrine, thus causing GABA output from the VLPO nucleus and inhibition of the neurotransmitters of wakefulness to produce an NREM sleep pattern. In contrast, benzodiazepines and propofol exert their sedative action on the VLPO nucleus to increase GABA and decrease the neurotransmitters, such as orexin, histamine, and serotonin, but without affecting norepinephrine release from the locus coeruleus. Further clinical trials are required to ascertain the role of these medications in improving the quality and quantity of sleep in critically ill patients and to determine whether such improvement may better the cognitive outcomes in ICU patients.

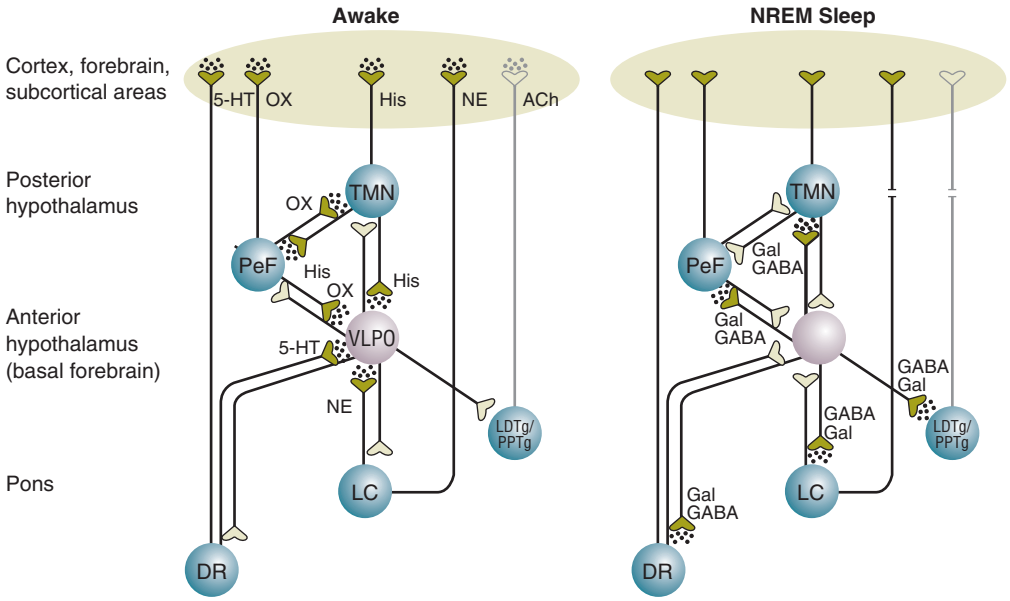
Although they lack anxiolytic properties, ω_1-receptor agonists, such as zolpidem, may preserve REM as well as slow-wave sleep.[182] Similarly, mirtazapine, a noradrenergic and specific serotonergic antidepressant, has been studied in healthy volunteers and has been shown to improve sleep efficiency, reducing the number and duration of awakenings.[183] The slow-wave sleep time was also increased, whereas stage 1 sleep time was reduced significantly. This agent had no significant effect on REM sleep variables.[184]

Numerous other medications routinely administered to critically ill patients affect sleep architecture. These include antiarrhythmic agents, inotropes and vasopressors, antibiotics, antidepressants, steroids, anticonvulsants, and bronchodilators.[173] The effects of some of these compounds on sleep patterns are summarized in Table 69.2.

Posttraumatic Stress Disorder

Definition and Diagnostic Criteria

The DSM-V[13] defines PTSD as a potentially debilitating psychiatric condition that develops as the result of exposure to a traumatic occurrence, in which the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others and that generates intense feelings of fear, helplessness, or horror in the person exposed to the trauma. Symptoms of PTSD fall into four categories: intrusive thoughts (such as repeated, involuntary memories; distressing dreams; or flashbacks of the traumatic event); avoiding reminders of the traumatic event (avoiding people, places, activities, objects, and situations that bring on distressing memories); negative thoughts and feelings (ongoing and distorted beliefs about oneself or others, fear, horror, anger,



• **Fig. 69.8** Neurotransmitter mechanism for wakefulness and non–rapid eye movement *(NREM)* sleep. The ventrolateral preoptic *(VLPO)* nucleus in the anterior hypothalamus is the major area of the brain that controls sleep induction and maintenance. Its major neurotransmitter is gamma-aminobutyric acid *(GABA),* and during the awake state, GABA release from the VLPO nucleus is inhibited by norepinephrine *(NE)* from the locus coeruleus *(LC).* With the inhibition of GABA, neurotransmitters such as orexin *(OX),* serotonin *(5-HT),* histamine *(His),* and acetylcholine *(ACh)* are released, resulting in a state of wakefulness. During NREM sleep, there is a hierarchical sequence of changes in which inhibition of the LC disinhibits the VLPO nucleus to release GABA and galanin *(Gal)* at the projections that terminate at the tuberomamillary nucleus *(TMN).* These inhibitory neurotransmitters inhibit firing of the TMN projections to the cortical and subcortical regions. *5-HT,* 5-Hydroxytryptamine (serotonin); *DR,* dorsal raphe; *LDTg*, laterodorsal tegmental nucleus; *PPTg,* pedunculopontine tegmental nucleus. (From Analgesics: receptor ligands: alpha 2 adrenergic receptor agonists. In Evers AS, Maze M [eds]. *Anesthetic Pharmacology: Physiologic Principles and Clinical Practice.* St. Louis: Churchill Livingstone; 2004. Used with permission from Dr. Mervyn Maze and Elsevier, Inc.)

guilt, or shame); arousal and reactive symptoms (being irritable and having angry outbursts; behaving recklessly or in a self-destructive way; being easily startled; or having problems concentrating or sleeping).

These symptoms must meet the following two criteria to be diagnosed as PTSD:

1. Symptoms must cause significant impairment in social, occupational, or other important functional domains.
2. Symptoms must be present for at least 1 month after exposure to the traumatic event or events.

Prevalence of ICU-Related Posttraumatic Stress Disorder

The incidence of PTSD anchored to the ICU experience and unrelated to past stressful experiences has been consistently around 10% in the first year after hospital discharge[185–188] in the most rigorous studies, despite historically reported higher rates in many other studies.[189,190] It is critically important to recognize that despite these reports of higher epidemiologic occurrences of PTSD after critical illness,[190] many studies have not distinguished pre-existing PTSD from ICU-related PTSD, nor have they used DSM criteria, or accounted for the ICU course. Using a multicenter ICU population of U.S. civilians and veterans, the most recent study to clearly identify ICU-related PTSD demonstrated an occurrence in 1 of 10 ICU survivors.[186]

Risk Factors for Posttraumatic Stress Disorder

A number of subject characteristics appear to raise the risk of PTSD symptoms or an actual diagnosis of PTSD, although consensus among the studies reviewed is limited. Reported risk factors include delusional memories of the ICU, a greater number of traumatic memories of the ICU, longer ICU length of stay, duration of mechanical ventilation, younger age, preexisting psychiatric history, female gender, and higher levels of sedation and neuromuscular blockade and delirium.[187,191–195]

Conceptual Explanations for Posttraumatic Stress Disorder After Critical Illness

Although the stresses associated with ICU hospitalization may differ from events typically described as "traumatic experiences," there are a variety of conceptual explanations for the development of PTSD after critical illness. They include (1) profound feelings of helplessness associated with the experience of critical illness, (2) high rates of preexisting psychiatric morbidity that may characterize ICU patients,[196] (3) cognitive impairment, including decreased working memory, which may limit individual abilities to suppress intrusive thoughts,[196] and (4) multiple traumatic episodes associated with anxiety, panic, or pain that occur during ICU hospitalization, such as intubations, extubations, nightmares, and respiratory distress.[197,198]

TABLE 69.2 Drugs Commonly Used in the Intensive Care Unit and Their Effects on Sleep Patterns

Drug Class/Individual Drug	Sleep Disorder Induced/Reported	Possible Mechanism
Benzodiazepines	↓ REM, ↓ SWS	γ-Aminobutyric acid type A ($GABA_A$) receptor stimulation
Opioids	↓ REM, ↓ SWS	μ-Opioid receptor stimulation
Clonidine	↓ REM	α_2-Adrenergic receptor stimulation
Nonsteroidal antiinflammatory drugs	↓ TST, ↓ SE	Prostaglandin synthesis inhibition
Norepinephrine/epinephrine	Insomnia, ↓ REM, ↓ SWS	α_1-Adrenergic receptor stimulation
Dopamine	Insomnia, ↓REM, ↓ SWS	δ_2-Opioid receptor stimulation/α_1-adrenergic receptor stimulation
β-Blockers	Insomnia, ↓ REM, nightmares	Central nervous system β-blockade by lipophilic agents
Amiodarone	Nightmares	Unknown mechanism
Corticosteroids	Insomnia, ↓ REM, ↓ SWS	Reduced melatonin secretion
Aminophylline	Insomnia, ↓ REM, ↓ SWS, ↓ TST, ↓ SE	Adenosine receptor antagonism
Quinolones	Insomnia	$GABA_A$ receptor inhibition
Tricyclic antidepressants	↓ REM	Antimuscarinic activity and α_1-adrenergic receptor stimulation
Selective serotonin reuptake inhibitors	↓ REM, ↓ TST, ↓ SE	Increased serotonergic activity
Phenytoin	↑ Sleep fragmentation	Inhibition of neuronal calcium influx
Phenobarbital	↓ REM	Increased $GABA_A$ activity
Carbamazepine	↓ REM	Adenosine receptor stimulation and/or serotonergic activity

REM, Rapid eye movement (sleep); *SE*, sleep efficiency; *SWS*, slow-wave sleep; *TST*, total sleep time.
From Bourne RS, Mills GH. Sleep disruption in critically ill patients—pharmacological considerations. *Anaesthesia.* 2004;59:374–384.

Attention has been focused on the quality and duration of sedation provided to ICU patients in relation to the risk of post-ICU PTSD. Particular interest has been placed on the role of benzodiazepines.[110,193] Both receipt of midazolam[199] and total dose of lorazepam[193] administered in the ICU have been found to be associated with greater risk of post-ICU PTSD. Also, higher doses of opiates have been associated with an increased risk of experiencing PTSD symptoms.[194] Conversely, from another study, Patel and coworkers did not find any association between PTSD risk and duration of delirium, benzodiazepine dose, or opiate dose.[186]

For many patients, extreme agitation is a significant component of the ICU experience and higher levels of agitation in the ICU have been identified as a predictor of PTSD-related symptoms.[199] Brewin and Holmes[200] suggest that immobilization with incomplete sedation promotes a dissociative experience that may be a PTSD risk factor.

A significant percentage of patients treated in the ICU have chronic medical illnesses,[201,202] which may increase anxiety or susceptibility to anxiety reactions. The presence of such stressors may have a cumulative effect on an individual's coping resources, leading to a greater vulnerability to PTSD. This concept is bolstered by evidence from numerous studies as well as the theoretical work of Turner and Lloyd,[203] which supports the notion that healthy coping responses are impeded by the "accumulated burden of adversity" associated with illness or disease.[204–206] Although the contribution of cumulative illness to the development of PTSD has not been assessed in ICU populations, investigations support an association between accumulated medical burden and higher risk of PTSD. For example, accident victims (without chronic medical illnesses) who are admitted to the trauma ICU have a lower prevalence of PTSD than their medical ICU counterparts (with multiple chronic diseases).[207] Alternatively, patients with chronic cardiovascular disease who have undergone cardiac surgery have relatively high rates of PTSD, which correlate positively with preoperative disease severity.[197]

The relationship between cognitive function and PTSD is a subject of ongoing debate, particularly as it relates to the role of memory in mediating the development of PTSD.[208] The importance of specific, explicit memories (memories pertaining to facts and events that are accessible to consciousness)[209,210] in the generation and maintenance of PTSD is difficult to estimate because they are the basis for nightmares, flashbacks, and intrusive thoughts and contribute to symptoms of avoidance and reexperiencing. Although a detailed treatment of these issues is beyond the scope of this chapter, we briefly discuss several key findings from the literature as they relate to ICU populations.

The preponderance of evidence suggests that the absence of episodic memory for a traumatic event is protective against the development of PTSD and that the risk of PTSD is markedly lower in individuals unable to recall a traumatic event than in those with explicit memory of it.[211–215] The literature is not unanimous and is narrow in scope, with virtually all relevant studies having been conducted on victims of motor vehicle accidents or other traumas with concomitant traumatic brain injury.[216] Theories of information processing suggest that traumatic memories can be encoded implicitly during periods of impaired consciousness and may provide the basis for the generation of PTSD symptoms, even if patients are not consciously aware of the memories.[217–220]

Additionally, during periods of impaired consciousness, the encoding of emotional experiences such as panic and severe pain appears to be sufficient for the generation of PTSD symptoms.[221]

Many ICU patients report little if any conscious awareness of their critical illness, although as Jones and associates[222] have reported, delusional memories, often with violent and paranoid themes, are pervasive among such patients. Distorted and fragmentary memories may be vestiges of the nightmares, hallucinations, or delusions induced by critical illness, a variety of medications, or other causes, and may be particularly likely to occur during delirium, which is ubiquitous in critically ill, mechanically ventilated patients.[208,223] Sedative medications may constitute one factor that mediates the development of delusional memories.[224] Delusional memories may exist in the absence of factual memories, which provide markers of reality and may serve to orient the patient. For example, daily sedative interruption has been found to be associated with fewer symptoms of PTSD,[225] suggesting that even limited factual memories from brief awakening may reduce PTSD. In addition, delusional memories tend to be stable over time and are significantly more persistent than factual memories.[226] Delusional memories may be more refractory to the normal cognitive processes of habituation and reappraisal because they are not well integrated into the long-term memory. Although research is limited, the presence of delusional memories of the ICU is associated with higher levels of anxiety and PTSD.[227,228]

Jones et al. evaluated the influence of ICU diaries on symptoms of post-ICU posttraumatic stress, among both patients and their family members, after 3 months from ICU discharge. Patients in the intervention arm received their ICU diary at 1 month after critical care discharge and the final assessment of the development of acute PTSD was made at 3 months. The incidence of new cases of PTSD was reduced in the intervention group compared with the control patients (5% vs. 13%, $P = 0.02$).[188] Diaries can probably help patients to change how they think about their illness as they reread the story and build an autobiographic memory. Families may also be helped because the diaries help to facilitate communication with the patient about their treatment and writing in the diary may allow them to express some of their feelings. A strong relation has been found between high levels of PTSD-related symptoms in family members and those in patients. So a therapy, such as a diary, that is shared between the patient and the family may be more effective than one that concentrates just on the patient.[188]

Similarly, Garrouste-Orgeas et al. assessed the influence of ICU diaries written by family members, nurses, and physicians on ICU survivors.[229] At the time of ICU discharge the diaries were provided to survivors and to relatives. For both patients and relatives, levels of posttraumatic symptoms measured by the Impact of Scale Event-Revised score were lower at 12-month follow-up compared with prediary and postdiary controls.[229] ICU diaries have also been associated with a reduction in related post-ICU psychiatric morbidities, including depressive and anxiety symptoms.[230] As with diaries/journals, a single counseling session has been shown to increase both patient and family coping ability after an ICU stay.[227] Both may also prevent, reduce, or help treat PTSD.

Other studies suggest that music, nature sounds, and various forms of massage and reflexology could all be used to reduce acute stress among ICU patients, including mechanically ventilated patients.[231] As acute stress is an important precursor of long-term psychological morbidity such as PTSD, these short-term practices could also have an impact on long-term outcomes. The risk of harm from such therapies is not generally high, but protocols and training for staff are needed.[231]

Long-Term Cognitive Impairment After Critical Illness

Medical and surgical management of critical illnesses can, and frequently does, result in de novo neurocognitive impairments. Approximately one-third or more of ICU survivors have LTCI.[232] It is difficult to make comparisons among studies owing to differences in definitions of neurocognitive sequelae, administered neuropsychological tests, time to follow-up, patient population, study design (prospective vs. retrospective), and inclusion of a control group. Nevertheless, current data suggest that neurocognitive impairments are extremely common in survivors of critical illness. Post-ICU long-term cognitive impairment involves memory, attention, and executive function problems and leads to inability to return to work, impaired activities of daily living, increased risk of hospitalization, and decreased quality of life.

Over the past decade and a half, cohort studies have conducted assessments of the cognitive function among survivors of critical illness and reported significant notable impairments sustained by those who survive a critical illness.[12,232–242] These studies have given rise to the concept of the post–intensive care syndrome, defined as new or worsened symptoms of cognitive impairment, disabilities in activities of daily living, and mental health impairment that arise after critical illness and persist beyond acute care hospitalization.[243,244] The populations of the patient cohorts in studies of LTCI include patients with ARDS, acute lung injury, sepsis, and respiratory failure in the ICU,[12,232,233,236,238–242] as well as two studies in general ICU patients.[234,237] The time to neurocognitive assessments was variable, with the majority occurring during the first year after hospital discharge. Three studies assessed patients more than 1 year later. A prospective longitudinal study monitored patients at hospital discharge and then at 1 and 2 years after hospital discharge,[245] and two retrospective studies assessed the patients at approximately 6 years after hospital discharge.[236,240]

The evidence from the 10 cohorts suggests that 25% to 78% of ICU survivors experience neurocognitive impairments.[232–241] Among specific populations, such as patients with ARDS, the prevalence of LTCI is even greater; it may be as high as 78% at hospital discharge, 46% at 1 year,[233] and 25% at 6 years.[240] Hopkins and colleagues[233] assessed the premorbid estimated intelligence quotient (IQ) of ARDS patients and found it was significantly higher than their measured IQ at hospital discharge. However, the patients' measured IQ improved to their premorbid level by 1-year follow-up, with no additional improvement at 2 years. The finding that patients recovered over time with regard to intelligence does not necessarily suggest a comparable recovery in all cognitive domains, because data from traumatic and anoxic brain injury literature suggest that some neurocognitive abilities are more likely to improve than others.[246]

A 2004 study found that neurocognitive impairments occur in 70% of ARDS patients at hospital discharge, 45% at 1 year, and 47% at 2 years.[245] The neurocognitive test scores of the ARDS survivors with neurocognitive sequelae (≈50% of survivors) fell below the sixth percentile of the normal distribution of cognitive function. These ARDS survivors had marked difficulty with tasks that require executive function, memory, attention, or quick mental processing. The neurocognitive impairments in critically patients are similar to those reported in medical ICU survivors[233] after carbon monoxide poisoning[247] and several years after elective coronary artery bypass graft surgery.[248]

In addition to ARDS survivors, neurocognitive impairments have been reported in the general population of critically ill patients. Jackson and colleagues,[232] evaluating 34 medical ICU survivors at 6 months, found that 33% had LTCI (using a very conservative definition of impairment as two test scores 2 standard deviations below the mean or three test scores 1.5 standard deviations below the mean). The neurocognitive impairments were similar to those reported in ARDS survivors; they included mental processing speed, memory, language, and visuospatial abilities. Additional support for cognitive impairment in the general critically ill population comes from a prospective cohort of 32 critically ill patients who underwent long-term mechanical ventilation (>5 days). The patients were evaluated at hospital discharge and 6 months later.[235] Of the patients who received long-term mechanical ventilation, 91% at hospital discharge and 41% at 6 months had impairments in attention, memory, mental processing speed, and executive function.[235]

Girard and colleagues showed that the duration of delirium was an independent predictor of LTCI at 1-year follow-up even after adjusting for relevant covariates.[54] It is hoped that other ongoing investigations will provide information about the risk factors for the development of LTCI and help guide interventions for prevention of the rather debilitating sequelae of critical illness that affect a person's quality of life. In one of the largest multicenter prospective ICU cohorts to date, a longer duration of ICU delirium has been found to be the major independent risk factor for long-term cognitive impairment up to 12 months after surviving a critical illness. In this population one of four ICU patients had cognitive impairment after 12 months following critical illness that was similar in severity to that of patients with mild Alzheimer disease and moderate traumatic brain injury.[12] This association was found to be independent of severity of illness, sedative or analgesic medication use, age, preexisting cognitive impairment, and comorbid conditions.[12] In this landmark study, the impairment was persistent and no different among medical or surgical ICU populations.[249]

Although the mechanisms by which delirium may predispose patients to long-term cognitive impairment after critical illness have not yet been elucidated, delirium is associated with inflammation and neuronal apoptosis, which may lead to brain atrophy[83,250] and white-matter disruption that are associated with cognitive impairment.[251,252]

Depression

Many ICU survivors experience significant affective symptoms, such as depression and anxiety.[192,253,254] The prevalence and severity of affective disorders, including symptoms of depression and anxiety in ICU survivors, range from less than 10% to 58%.[184,232,233,239,255] Depression has been reported to occur in up to 30% of ICU survivors,[232] and it is estimated that 47% have clinically significant anxiety.[192] Indeed, the high rates of depression among ICU survivors may be related to the cognitive impairment they experience, although this issue has not been evaluated in ICU cohorts. Affective disorders such as depression, PTSD, and anxiety may adversely affect test performance, especially if severe.[256,257] Moderate to severe depression may result in decreased effort and low motivation, which may in turn lower neuropsychological test scores in cognitive domains such as psychomotor speed and attention.[258,259] Moderate to severe anxiety, however, may lead to increased distractibility and blocked thoughts or words.[260,261] In some cases, severe depression may mimic symptoms of cognitive impairment, although there are important differences between these conditions. In general, individuals with depression retain the ability to learn and do not forget as rapidly, do not display significant decrements in language, are inconsistent with regard to orientation to time and date, and are typically more self-aware than their cognitively impaired counterparts.[262–266] A recent study showed that depression was five times more common than is posttraumatic distress disorder after critical illness and is driven by somatic symptoms, suggesting therapeutic approaches targeting physical rather than cognitive causes could benefit patients leaving critical care.[185]

A variety of instruments are available for use in the assessment of affective function. Tools such as the Geriatric Depression Scale-Short Form (GDS-SF),[265] the Beck Depression Inventory (BDI),[266] the Center for Epidemiologic Studies Depression Scale (CES-D),[267] and the Hospital Anxiety-Depression Scale (HADS)[268] assess depression. Anxiety can be assessed with the HADS[268] or the Beck Anxiety Inventory (BAI).[269] Discussion of these tools is beyond the scope of this chapter.

Concluding Thoughts

How might we incorporate these issues into our life as a health care professional? It is important as you encounter patients being newly admitted to the ICU with diseases such as severe sepsis or an exacerbation of chronic obstructive pulmonary disease to remind yourself that during subsequent days under your care, these patients will acquire new "neck-up" and "neck-down" (brain plus neuromuscular) diseases. It is imperative that these two new elements of disease burden become a major focus of medical attention during and after these patients' ICU stays. It is also important to recognize that these two categories of disability are inextricably linked. As we work to identify methods of intervention to prevent and treat these disabilities, it may be helpful to focus on modifiable aspects of care, such as reducing total exposure to psychoactive medications, reducing duration of delirium, mitigating sleep deficits and derangements, and minimizing periods of immobilization.

Key Points

- Delirium is a disturbance in attention, accompanied by a change in cognition or perceptual disturbance that develops over a short period of time and has a fluctuating course with a prevalence in medical and surgical ICU studies between 60% and 80% in cohorts restricted to those receiving mechanical ventilation and around 40% to 60% in ICU cohorts of nonventilated patients.
- Delirium is an independent predictor of longer duration of mechanical ventilation, longer ICU stays, higher costs, and a threefold higher risk of dying within 6 months or an increase of 10% risk of death per day of delirium.
- The development of tools such as the ICDSC and the CAM-ICU has allowed for the rapid diagnosis of delirium in patients by nonpsychiatrists and health care personnel even during mechanical ventilation.
- Sedative and analgesic medications and sleep disturbances in the ICU may be modifiable risk factors of delirium.

- The main thrust of delirium management must begin with treatment of the underlying disease processes that are leading to brain dysfunction, then drug removal (not addition), and then modification of the environmental factors (hearing and vision aids, removal of restraints, early mobility, and sleep hygiene). Summarize these via the mnemonic Dr. DRE. These are nicely summarized and operationalized in the evidence-based ABCDEFs of ICU care.
- Only after these issues are addressed is it appropriate to add another medication such as an antipsychotic into the mix of the individual pharmacopeia for any patient. Which medication to add (e.g., antipsychotic) is a point of ongoing investigation.
- Critically ill patients often have severe sleep deprivation with disruption of sleep architecture that is worsened by most sedative medications. The average amount of sleep in ICU patients has been measured to be about 2 hours in a 24-hour period, less than 6% of which is REM sleep often because of REM suppression from medications such as benzodiazepines and propofol.
- PTSD is a potentially debilitating psychiatric condition that develops in around 10% of ICU survivors as the result of exposure to a traumatic occurrence that generates intense feelings of fear, helplessness, or horror. Using ICU diaries in routine clinical care may alter PTSD outcomes among both patients and families.
- Medical and surgical management of critical illnesses is associated with long-term neurocognitive impairments in approximately two-thirds of ICU survivors. This form of cognitive impairment mimics dementia in many patients as they have moderate to severe deficits in memory, executive dysfunction, and other domains with profound ecologic validity.
- Between one-third and two-thirds of ICU survivors experience significant affective symptoms, such as depression and anxiety, which serve as another ongoing condition that all too often remains undiagnosed and therefore unaddressed by the medical teams caring for ICU survivors.

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Review Questions

1. Which one of the following statements is most correct for the treatment of delirium?

a. Medications should be considered for delirium only after failure of restoration of sleep/wake cycles and frequent reorientation.

b. Antipsychotics are approved by the U.S. Food and Drug Administration (FDA) and recommended by the 2013 Pain Agitation Delirium (PAD) Guidelines for the treatment of delirium.

c. Delirium prophylaxis with medications is encouraged in the PAD guidelines.

d. Recent studies found no role in the pharmacologic management of delirium with the α2-agonist sedative, dexmedetomidine.

Answer: a. Delirium could be a manifestation of an acute, life-threatening problem that requires immediate attention (such as hypoxia, hypercarbia, hypoglycemia, metabolic derangement, or shock). After such concerns have been addressed, pharmacologic management may be considered. It should be recognized that although agents used to treat delirium are intended to improve cognition and safety, they all have psychoactive effects that may further cloud the sensorium and promote a longer overall duration of cognitive impairment. The main thrust of our approach as health care professionals must begin with treatment of the underlying disease processes that are leading to brain dysfunction, followed by drug removal, and then modification of the environmental factors (hearing and vision aids, removal of restraints, early mobility, and sleep hygiene), which can be summarized via the mnemonic Dr. DRE (Diseases, Drug Removal, Environment). Medications should be reserved for extremely distressing symptoms, behaviors that threaten the safety of patients or staff, or alcohol or benzodiazepine withdrawal.

2. Which of the following is most accurate for diagnosis of delirium in the ICU?

a. The Folstein Mini Mental State Examination.

b. For patients arousable to voice, Richmond Agitation-Sedation Scale [RASS] scores of −3 and higher), the Confusion Assessment Method for the Intensive Care Unit (ICU) (CAM-ICU).

c. For unarousable patients, (RASS score −4 or −5), the Intensive Care Delirium Screening Checklist (ICDSC).

d. No bedside tools have been validated to diagnose delirium in ICU patients.

Answer: b. The diagnosis of delirium is a two-step process. Level of arousal is first measured with the use of a standardized sedation scale, like the RASS. This is a 10-point scale with scores ranging from −5 to +4, with a score of 0 denoting a calm and alert patient. Positive RASS scores denote positive or aggressive symptomatology ranging from +1 (mild restlessness) to +4 (dangerous agitation). The negative RASS scores differentiate between response to verbal commands (scores −1 to −3) and physical stimulus (scores −4 and −5). If the patient's RASS score is −4 or −5 or the patient is not arousable by verbal commands, no further evaluation for delirium is performed, because the patient is comatose and is unable to be assessed for delirium. For patients who are arousable (RASS scores of −3 and higher), delirium can be assessed by the ICDSC or the CAM-ICU. The ICDSC assesses eight features of delirium: altered level of consciousness, inattention, disorientation, hallucinations, psychomotor agitation/retardation, inappropriate mood/speech, sleep/wake cycle disturbance, and symptom fluctuation. The sensitivity and specificity of this tool are 99% and 64%, respectively. The CAM-ICU, which can be performed in about 60 to 90 seconds, consists of four features that assess the following: acute change or fluctuation of mental status (feature 1), inattention (feature 2), disorganized thinking (feature 3), and an altered level of consciousness (feature 4).

To be diagnosed as delirious, a patient must have a RASS score of −3 or higher, with an acute change or fluctuation in mental status (CAM-ICU feature 1), accompanied by inattention (feature 2) and either disorganized thinking (feature 3), or an altered level of consciousness (feature 4).

3. Which one of the following statements about long-term cognitive impairment (LTCI) after critical illness is most correct?

a. Approximately one of four of ICU survivors has LTCI that persists 12 months after the ICU.

b. Neurocognitive impairments occur in less than 15% of survivors of critical illness without preexisting dementia.

c. Duration of ICU delirium is not a risk factor for LTCI in survivors of critical illness.

d. Neurocognitive impairments have been reported only in survivors of acute respiratory distress syndrome.

Answer: a. Over the last decade and a half, cohort studies have conducted assessments of the cognitive function among survivors of critical illness and reported significant impairments sustained by those who survive a critical illness. These studies have given rise to the concept of the post–intensive care syndrome (PICS), defined as new or worsened symptoms of cognitive impairment, disabilities in activities of daily living (ADLs), and mental health impairment that arise after critical illness and persist beyond acute care hospitalization. Post-ICU long-term cognitive impairment may involve memory and attention and/or executive function problems and leads to inability to return to work, impaired ADLs, increased risk of hospitalization, and decreased quality of life. In one of the largest multicenter prospective ICU cohorts to date, longer duration of ICU delirium was found to be the major independent risk factor for long-term cognitive impairment up to 12 months after surviving a critical illness. In this population, one of four ICU patients had cognitive impairment after 12 months following critical illness that was similar in severity to that of patients with mild Alzheimer disease and moderate traumatic brain injury.

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Intensive Care Unit Administration and Education

SARA R. GREGG AND TIMOTHY G. BUCHMAN

CHAPTER OUTLINE

ICU Administration
- Attributes of an Effective ICU
- Collaboration
- Coordination of Critical Care Within Health Care Systems
- The Finances of Critical Care
- Augmenting Value
- Standardization
- Task Reallocation
- Administrative Principles That Appear Reliable and Effective
- ICU Workforce Planning: Models, Strategies, and Retention
- The Challenge of Clinical Research

Education in Critical Care: An Administrator's Perspective
- Pathways to Degrees, Licensure, Certification, and Credentialing
- Specific Education Issues

Summary

The missions of critical care units typically include clinical care, discovery, education, and administration. All must be addressed. Moreover, that address must be coordinated to advance all missions. All too often, education is an assumed by-product of clinical work and discovery. All too often, administrative tasks are initially ignored and hastily performed. Without intentional development, education and administration involute. The consequences of such neglect can be devastating, often leaving the critical care unit itself on life support. In this chapter, we emphasize the importance of all four missions, offering guidance to intensive care unit (ICU) leaders with an emphasis on administration and education. Much of this comes from experience. Appropriate references are cited where available.

ICU Administration

Attributes of an Effective ICU

What are the attributes of a high-performing unit? Integrity and vision. Although integrity and vision alone do not guarantee success (resources and leadership are necessary), we have never seen a high-performing unit absent either or both of those attributes.

By integrity, we mean that the unit functions as a cohesive whole toward mutually embraced principles. On our teams, we aim for quality, value (meaning that the quality must be affordable by patients, payers, and the health care system), and access (meaning that every patient in need must be accommodated). These constitute a classic business triad, meaning that any pair can be readily improved, but at the expense of the third. This requires a constant rebalancing of priorities, all within the human, physical, and financial resources available. This is achieved in part by "doing things right"—including hewing to standards and promoting all of the professions that bear on care of the critically ill. This is also achieved by "doing the right things"—hewing to ethical principles, embracing service as a form of leadership, blending toughness with mercy.

By vision, we mean that the practice of critical care and those who practice critical care coevolve. Administrators and educators must work together to craft a vision, lead toward that vision, and engage others toward that vision. Our discipline is scarcely a century old, yet many tools we bring to bear (capnography, bedside ultrasound, magnetic resonance imaging, and assessment of lactate and of troponin are just a few that come to mind) were unavailable, unknown, or unimaginable 3 decades ago. Health care is transforming rapidly in the face of new technology, health care consumerism, and heightened attention to costs. Hospital operating margins are continually shrinking while inefficient or unsafe care is increasingly being denied payment in the United States. This pattern will continue to grow as new pay-for-performance, pay-for-value, and pay-for-quality programs emerge. It is a truism that what we learned as students, what we practice as clinicians, and what we teach the next generation as instructors must all be different if the field is to progress. Those who administer and those who educate must not only anticipate change, they must also catalyze those changes. Further, they must adapt to change. Transformation always comes with costs, and it is the responsibility of leaders to manage both. The introduction or conversion of an electronic health record system is a familiar example of coevolution and the need for leadership to manage people, technology, and the processes of care to ensure that patients are made safer.

We emphasize that the most important word in the phrase "intensive care unit" is "unit." Care of the most vulnerable patients requires not only the colocation of caregivers, technology, patients, and families, but also a strategy that promotes consistency even in the face of forces that lead to disorder. The physical space that

encloses the ICU serves the same purposes as a cell membrane: containing the activity while selectively permitting the influx and efflux of resources and products. Energy is consumed not only in the tasks but also in the constant struggle to create order in the face of chaos. Stocking the clean utility room or the electronic medication dispenser serves as a convenient example: items that are outmoded, expired, or have fallen into disuse must be identified, evaluated and, where appropriate, superseded. Decisions about "what stays" and "what goes" are clinical decisions. Ensuring that those decisions are made regularly is an administrative responsibility.

Collaboration

The administration (and administrators) of larger health care organizations face challenges homologous to those faced by every ICU—for example, "do more with less." Ongoing dialogue with system leaders requires ICU administrative leaders to not only find a way to "have their voices heard" but also to "listen to what is being spoken" and adapt. Hostility manifested as silence, pejorative remarks, backbiting, and so on are profoundly destructive. It is worth the investment of time to develop and assert a code of conduct equally applicable to those inside and outside the ICU. This does not mean that the priorities of hospital leaders and the ICU will perfectly align, but it provides some guarantees that misalignments will be exposed, negotiated, and resolved insofar as possible. Conflict is inevitable in the chief administrative suite and at the bedside; promoting expeditious, honorable, and reasonable resolutions through collective adherence to a code of conduct is, in our view, essential to maintaining integrity.

The importance of collaborative coinvestment cannot be overstated. This is not strictly a matter of money, although budgets often need to be merged. Rather, it is a commitment that there should be a plan and an accounting of financial, physical, and human investment to achieve a desired goal. For example, requests to fund additional positions within the ICU should clearly state why those personnel are necessary and how their presence will measurably and favorably affect patient-centered outcomes for the unit and the health care system as a whole. If the new personnel are assigned tasks currently absorbed by others, what new activities and what improved outcomes can be expected of those shedding tasks? These are tough but realistic questions that illuminate shared expectations.

Health care system administrators demand strategy, and strategy nearly always involves sacrifice. This is true in business, in games, and in the allocation of health care resources. Sacrifice is not the same as "saying no." It most often involves using marginal time and dollars to achieve a desired end. For example, delaying replacement of a piece of equipment may free up funds to perform a study to show that there is a reason to make a different investment that results in better equipment. The sacrifice here will likely be investment of time and effort to conduct the study, write the report, and make the presentation.

We hasten to add that whereas strategy is important, logistics and execution are more important. Nearly every decision in ICU administration and education will be regarded as strategic owing to limitations on resources: "we have chosen to do this, not that; allocate here, not there; retain this, relinquish that." The effectiveness and impact of those decisions are utterly dependent on how the leadership team executes a decision. That execution nearly always requires engagement of and communication with key stakeholders.

Coordination of Critical Care Within Health Care Systems

Larger hospitals often have several ICUs that are specialized into service lines (e.g., general surgery, transplant, cardiothoracic, neurocritical care). Critical care fellowship training is aligned in a similar manner. Surgical critical care fellows were traditionally trained in surgical ICUs, anesthesia critical care fellows were assigned to cardiothoracic units, pulmonary/critical care fellows to medical ICUs, and so on. These specializations often lead to "siloed" ICUs run by different medical disciplines—either under medical school departments or private practice groups. In many cases, these ICUs function independent of other ICUs in their staffing (nurse practitioners, physician assistants, residents, fellows), budgets, and performance. This variation makes it difficult for hospital leaders to measure the value of any unit and attempts at comparing units often create tension among unit leaders, compounding and concealing inefficiencies.

What, then, are the coordinating characteristics that predict system-level success of critical care? The Academic Leaders of Critical Care Medicine (an ad hoc task force of the Society of Critical Care Medicine), studied existing critical care organizations (CCOs) and recently disseminated the results. Generally, CCOs collect two or more ICUs into a group and appoint CCO leaders who are held responsible for the success of the collective. The benefits and challenges of creating and sustaining CCOs are discussed in two recent reports. (For transparency, the authors of this chapter are leaders of a CCO composed of 14 ICUs with a total of 251 beds across 4 hospitals, 48 physician intensivists [only 25 full-time equivalents], 120 advanced practice providers, and tele-ICU monitoring center.)

Key findings of the Academic Leaders of Critical Care Medicine task force included the following. As of 2015, there are 27 identified CCOs across Canada and North America.[1] Two-thirds of the CCOs are in large urban health systems (>500 beds). Hospital administration initiated the transition to a CCO in 46% of the organizations; 50% are still gradually transitioning and 25% are completely established. Ideally, CCOs should be tasked with aligning all ICUs horizontally across the system to optimize performance, improve quality, reduce waste, and standardize policies and protocols. Horizontal integration is challenging in and of itself, and commonly there are units reluctant to integrate into the CCO, choosing to remain completely aligned with a parent department such as medicine or surgery. Stepwise component integration (e.g., initially pooling advanced practice provider training or clinician scheduling tasks) is a strategy to demonstrate both usefulness as well as good faith.

CCOs can also benefit from vertical integration of care.[2] Payors continue to implement value-based payment models. In these models, health systems and their partners will be required to take responsibility for a patient's entire care continuum and reimbursement will be bundled into episodes of care. The financial stability of health care organizations will hinge on how well they can manage population health. A CCO that is vertically integrated would coordinate downstream providers and organizations to ensure patients do not "fall through the cracks" on their way to recovery.

Slonim and Mariccini have pointed out weaknesses in the assertions that CCOs—and more specifically patients cared for in CCOs—benefit from such horizontal and vertical integration.[3,3a] Regarding horizontal integration, it is true that no prospective studies have been reported comparing horizontal integration with

the conventional isolated (siloed) approach. It is difficult to imagine a controlled trial because the process of horizontal integration takes time and before-and-after studies are subject to legitimate critique about the confounding effect of that time. Nevertheless, there are abundant data to suggest that horizontal integration provides for meaningful interunit comparative data as well as mechanisms to drive improvement (such as competitive incentive plans).

Regarding the weakness of vertical integration, the challenge is that vertical integration can never be complete unless there is a parent accountable care organization. A more limited vertical integration (perhaps from the emergency department through palliative care, but excluding preventative health and primary care) could be duplicative and wasteful in the setting of an accountable care organization. This is true, but ignores the reality that accountable care organizations are rarely complete. Indeed, vertical integration of a CCO could just as easily catalyze extension into a fully integrated accountable care organization. Given the widely recognized and reported costs of communication and handoff errors across services, the delays commonly encountered in transfers into and out of the ICU, and the financial consequences of inappropriate care being delivered in inefficient locations, we believe that even in the absence of direct comparative evidence a bias toward vertical collaboration and integration is justified and justifiable.

The Finances of Critical Care

Leaders of CCOs commonly remark that they have three tasks: (1) keep the peace; (2) "unload the trucks" (meaning keep the patient care going and keep the patients flowing); and (3) don't break the bank. The first task requires diplomacy and equanimity. The second requires the application of clinical acumen and logistical skills, all of which is commonly learned and practiced during training and participation in the ICU. The third imperative—fiscal responsibility—requires skills that are typically neither taught nor learned until ascent to a leadership position.

Nonclinical administrators typically introduce that third imperative into the conversation with allusions of "building value" and "improving performance." The central problem is cost: in the United States, it is estimated that critical care costs more than $100 billion annually. Payors are consistently reducing reimbursements. Thus the expectation is that the CCO leader will "do more" and likely have to do more "with less." Viewed through the lens of the hospital finance officer, the aggregate costs assigned to critical care outweigh the aggregate revenues that are accrued, with the result that CCO leaders are asked to become "more efficient." The initial response to such conversations can safely begin with the observations that acute care hospitals require ICUs to care for the most physiologically vulnerable patients, and further that many other parts of the hospital enjoy utilization benefits that are driven by critically ill patients. (Laboratory and imaging studies are revenue generators.)

Such initial responses only serve to remind administrators and others outside the ICU that critical care is an essential hospital-based service, and that the creation of value is different than unit-based profitability. (A thought experiment may serve to clarify the difference: spending a little extra money in the ICU [reducing profits] may make sense if more patients are sent home in better health and with reduced use of long-term care facilities and reduced unit and hospital readmissions [creating value].)

Fiscal negotiation therefore depends on being able to calculate attributable costs, attributable revenues, and attributable benefit to patients, families, and the health care institution. Understanding the financial model of the hospital (and, if applicable, the parent health care organization) usually rests with the CCO administrator.

Augmenting Value

CCO leaders have at least three core strategies by which they can augment value: economies of scale, standardization, and task reallocation.

Scale offers economies in at least three ways: with the total number of ICU beds, with the size distribution of the ICUs within the organization, and with the purchase of equipment and supplies.

With regard to the total number of ICU beds, there are administrative infrastructure and clinical staffing costs that are incurred when the first patient occupies the first bed: staff, unit equipment (such as a dedicated defibrillator), supplies (central line kits, for example), and other resources must be available to that initial patient. Each succeeding bed offers additional operational efficiency. For example, one ICU nurse can typically care for two patients, so addition of the second bed adds only minimal nursing cost. An ICU physician can care for dozens of patients. A bronchoscopy cart might serve adjacent units. The number of beds and volume of patients served generally leads to economies of scale, with the understanding that the economies are punctuated with the need to increment resources when thresholds are reached (step fixed costs).

The size distribution of ICUs yields both efficiencies and inefficiencies. Whereas traditional recommendations held that the ideal size of a physical ICU was 12 beds, contemporary models that feature new teams of professionals (advanced practice providers, respiratory therapists, pharmacists, dietitians, and so on) suggest that 18 to 24 beds can be efficiently managed by a single primary team. Professional "coverage" can often be aggregated during off-hours to provide essential services. The efficiency here relates to labor cost. Many health care organizations report around 54% of their budget to labor; in the ICU, labor costs are higher owing to staffing ratios and often approach 70% of total costs. Unfortunately, CCOs often inherit legacy units and their physical sizes. CCO leaders therefore must demand design efficiencies when new ICUs are proposed. It should be remembered that size can also create inefficiencies; the usual problem relates to communication barriers as the unit increases in size.

Regarding economies of scale, most health care organizations have supply chains that operate on the principles of bulk purchasing, local warehousing, and just-in-time delivery. The cost models are complex, including not just the purchase prices but the logistical cost of maintaining local and warehouse inventory. Thus the decision (for example) to use a particular brand of mattress pad different from the health system standard can result in many thousands of dollars of hidden costs. This problem expands quickly with complex equipment. Imagine having a single type of ventilator; it means one type of spare parts, one type of accessories, one reservoir of clean machines on standby for use, and one type of training cost. These savings quickly add up. This should not suggest slavish dependence on a single source for essentials, but it does suggest that purchasing in bulk consistently provides unique leverage at many points in the care continuum, which is only partially reflected in the purchase contract price.

Standardization

Standardization—better thought of as removing unnecessary variation—can apply to people, processes, equipment, and supplies. Standardization has benefits and risks. Regardless, standardization

is rarely embraced owing to beliefs about what is best for a particular patient. We consider the issues in turn.

Critical care professionals are trained more to competencies and less to standards. A history and physical examination, for example, can be completed in many ways. There are neither expectations nor restrictions on specific sequences provided that the key findings are gleaned and reported. Although most practitioners develop a consistent routine, there is no agreed-upon "one best way." This general attitude is not only pervasive but is in fact reinforced by the appointment of preceptors and teachers who view themselves as guides more than "instructors." (In contrast, flight instructors are expected to teach from a common syllabus, instruct the performance of specific maneuvers, and grade the learner's performance against written completion standards.) Although licensure, board certification, and hospital credentials are often asserted to verify standards, only observation and audits can evaluate the translation of professional standards to clinical practice.

Processes are easier to observe, audit, evaluate, and change. The range of processes available to standardize is vast and far exceeds the time and effort available. Prioritization is necessary. The assignment of priority rests on two types of questions. The first type relates to difficulty. Is standardization feasible? How difficult will it be to standardize this or that process? How much training, monitoring, and evaluation will be required? The second type relates to impact. Is the standardization essential to patient safety or critical outcomes? If the outcome is not critical, will standardization reduce costs or improve satisfaction? None of this is easy—witness the difficulty in standardizing a process that should be easy and has great impact on safety—namely, handwashing. Although cash incentives are effective, even small tokens like coffee cards and candy bars are powerful tools to change behaviors.

ICUs develop equipment and supply preferences that become enshrined as necessities. With rare exception, "different" represents a cost. If there are several types of ventilators, spares and repairs and skills must be maintained for all types. Similar to all durable equipment, from beds, to defibrillators, to monitors, to ultrasound machines, the consumables add up as well. A tour through the "clean utility room" often reveals near-identical kits and, worse, items that expire through lack of regular use. Equipment and supplies often represent the first and easiest targets for standardization.

Task Reallocation

Critical care can be viewed as a series of decisions and actions. Each depends on completion of a set of tasks. The tasks can be further divided into those that must be performed at the bedside (e.g., inserting a bladder catheter) and those that could be performed remotely. An alternate division of tasks relates to the profession(s) qualified to complete the task. The aforementioned bladder catheter could be inserted by a physician, an advanced practice provider, a nurse, or a specialized catheter insertion "team."

Although a class of professionals is typically recognized as having the best expertise and qualifications to perform a task, it often emerges that some tasks are better performed by different professionals or different groupings. Insertion of peripherally inserted central venous catheter line teams is one example of a task where constant repetition seems to improve outcomes. Yet there are many tasks that are often inefficiently performed. The process of charting, for example, can be accelerated with voice recognition transcription or use of a scribe.

Monitoring of vital signs, laboratory data, and medication interactions can be performed remotely. The expansion of tele-ICU services suggests that many cognitive aspects of patient care can be distributed to members of the care team quite distant from the bedside, including the evaluation of patients and the prescription of diagnostics and therapeutics.

Some tasks have "sunsetted" owing to technological advancements, such as the filing of laboratory data and imaging reports into physical charts. Others are candidates for simplification and automation, such as the recording of intravenous fluid administration that can be automated via device integration. We do not mean to suggest a wholesale revision of workflows, but rather a critical examination of the value stream and the assignment of each team member to the specific tasks.

Administrative Principles That Appear Reliable and Effective

1. Within the ICU, keep the hierarchies flat. This does not mean there should not be leaders. Quite the opposite—there should be a leadership team that visibly embodies the behaviors expected of the workforce. At a minimum, this demands a partnership between the nurse unit director and the physician unit director. In our practice, we include the lead advanced practice provider (APP) and the designated unit educator. Together, they set the tone and the expectations for the unit. Together, they guide conversation and deliberation about unit practice. Together, they evaluate outcomes and address opportunities. Extending this concept to CCOs, leadership should feature the professions that define critical care.
2. Set standards high and goals higher; demand the former and incentivize the latter. The standards should be as general and as widely applicable as possible. For example, there should be standards of family visitation, hand hygiene, use of universal precautions, and timely administration of antibiotics when sepsis is suspected. Such general standards do not preclude local additions that are necessarily focused in particular units—for example, adherence to practices regarding extraventricular drains in neurology units and intraaortic balloon pumps in cardiac units. Rather, the mechanisms by which those general standards are communicated, compliance evaluated, and corrected provide a foundation for unit-specific behaviors.
3. Reward performance. We believe that incentives are important to bring groups together toward common achievements; it is important that the challenge as well as the incentive engage more than one profession in the ICU. Anything that can be measured can potentially be used to drive behaviors. One of our early initiatives was to create an incentive plan for providers. By deploying incentives, Murphy et al. significantly reduced red blood cell transfusions, chest x-ray, and arterial blood gas utilization, resulting in an estimated cost savings of $1.5 million.[3] Mortality also decreased during their study period. Albumin utilization was also decreased over a 2-year intervention with an estimated savings of $2.5 million.[4]

   Carpenter et al. incentivized providers to merely account for their patient care time—both billable time and nonbillable services. Over the 6-month period, billable time increased from 53% to 63% of APP shifts. Interestingly, although the physicians were ineligible for this incentive, their billable time increased from 4.7 hours per day to 6.3 hours per day.[5] Although improvement can be achieved in simply reporting data without setting expectations or using incentives, in our opinion, incentives are more effective.

   We annually examine existing processes and engage all ICU leadership teams in identifying and selecting two to four metrics

TABLE 70.1 Incentive Domains and Metrics

Domain	Sample Metrics
Patient-/family-centered care	• Family satisfaction survey (FS-ICU 24) • Pain/agitation/delirium management • Advance directives
Finance	• Chest x-ray utilization • Arterial blood gas utilization • Red blood cell transfusions • Pharmacy or laboratory costs • Meeting or exceeding budget
Productivity	• Patient care time accounting • Documentation lag
Quality	• Hemoglobin A1c Testing • Nutrition implementation • Central line insertion protocols and timely removal • Vancomycin utilization • Early mobility • Ultrasound training • Low tidal volumes

FS-ICU 24, Family Satisfaction in the Intensive Care Unit questionnaire, revised, shortened form.

for which improvement is feasible (quality, value, and/or access) and improvement would have meaningful impact. A list of domains that have formed the bases for recent incentives is included in Table 70.1. Note that many of the metrics cross several domains.

4. Administration must care for staff if staff members are to care for patients. We will neither review nor dwell on "burnout," a construct that is increasingly applied to critical care among the many medical professions. We simply remark that critical care is hard work. Although most critical care professionals find their work deeply satisfying, they are no different than the general population in being susceptible to depression, fatigue, isolation, and other common threats to mental health. One area in which critical care professionals may differ from the general population is their chronic and repeated professional exposure to emotionally stressful situations.

We hasten to add that critical care professionals knowingly choose such exposures when they join the professions, yet only a fraction experience burnout syndrome. Others are energized by the continuing challenges. The challenge for CCO leaders is thus to ensure that the ICU remains an attractive and rewarding place to work for all. Although compensation is important, a sense of teamness and of a "work family" sharing the joys and burdens may play heavily into decisions by an employee to remain or depart. Those who report burnout emphasize isolation, depersonalization, and emotional exhaustion. Thus attention to well-being cannot be a response to crises but rather must be engineered into the fabric of daily work.

ICU Workforce Planning: Models, Strategies, and Retention

This chapter would be lacking if we did not mention the shrinking critical care workforce. The second imperative for CCO leaders—namely, to sustain the clinical processes of care—is threatened by the lack of qualified personnel.

By 2030, nursing shortage ratios will be largest in the Western portion of the United States, followed by the South, Midwest, and Northeast regions. The total national deficit could range from 725,000 to 1.1 million nurses.[6] In 2004 nurses were surveyed about the shortage. Ninety-eight percent of nurses believed that the shortage would increase stress on nurses, 93% indicated it would lower quality of care, 93% reported it would cause nurses to leave the profession, and only one-fifth believed that their working conditions would improve or that respect for nurses would increase.[7]

Physician intensivists are also becoming scarce. The COMPACCS (Committee on Manpower for Pulmonary and Critical Care Societies) study predicted an intensivist shortfall of 35% by 2030.[8] Rather than focusing on increasing the number of intensivists, Kahn and Rubenfeld suggest several alternatives: staffing ICUs with nurse practitioners and physician assistants, using telemedicine to monitor several units, and regionalization of care, transferring only the highest-acuity patients to tertiary or quaternary hospitals.[8a]

Complementary to the physician and nurse shortages is a relative abundance of nurse practitioners and physician assistants: APPs.[9] APPs are trained to provide medical care under the supervision of attending physicians and have been used in ICUs since the late 1970s.[10] In the ICU, APPs round on patients, conduct histories and physicals, admit and discharge patients, and perform procedures such as central venous line insertions, arterial lines, and intubations. APP-to-patient ratios vary greatly across the United States and Canada from 1 APP to 3 patients to 1:8 patients.[11] Our own data suggest that day shift APPs are most efficient with 6 patients, whereas nighttime APPs can care for 10 to 12 patients. Specific ratios aside, a method for providing counsel for these APPs when physicians are not physically present should be considered. We have deployed tele-critical care to leverage our scarce experienced physicians and critical care nurses, thereby enabling guidance on demand. The conversation is not about independent practice of APPs, but rather how to support their more complex decision making.

The Challenge of Clinical Research

Clinical research comes to the ICU in two ways. The patient may be enrolled in a protocol related to the primary illness for which critical care is incidental. An example would be a patient with cancer receiving experimental therapy in whom sepsis develops with the patient requiring ICU management. Alternatively, the ICU may have its own experimental protocols. For example, patients with sepsis might be randomly assigned to receive a placebo or a study drug in addition to standard care. In either case, professional staff members in the ICU providing care to a patient participating in a research protocol are expected to know (1) their general responsibilities to a patient participating in a research protocol and (2) sufficient specifics about the study, device, and/or drug to promote subject safety while ensuring protocol adherence. Although the medical unit director, nurse unit director, educator, study coordinator, and study investigator are jointly responsible for ensuring that training sufficient for safe conduct of the study in the ICU has occurred, the administrator is expected to know which studies are ongoing and, moreover, to verify that staff educational needs are met. Failure to do so may result in protocol violation, patient injury, and study interruption.

Education in Critical Care: An Administrator's Perspective

Care of the critically ill patient demands synchronized application of knowledge, technical skills, and attitudes from multiple professions. The need for specialized training is self-evident. This section briefly reviews the convergent training pathways and the role of the administrator in facilitating effective learning toward practice. This section omits consideration of formal training in critical care research, except where such training is needed to prepare bedside professionals to participate in clinical research trials.

Pathways to Degrees, Licensure, Certification, and Credentialing

Although the professions of critical care are diverse, there are homologies among the paths to competency. Nurses, APPs, physicians, pharmacists, and other allied health personnel generally must complete undergraduate medical education toward a degree in the health professions. (As used here, undergraduate education denotes training that includes classroom and patient-facing experiences that serve as a foundation for the profession before focus in critical care medicine and lead to initial degrees in the profession: BSN, MS [for PAs and NPs], MD or DO, PharmD, and so on.)

Such undergraduate programs typically require some limited exposure to acute and critical care medicine. For this largest cohort of learners, administrators must ensure that learners are constantly accompanied by teacher/supervisors; that appropriate confidentiality agreements are in place; and that the role of the learner is appropriately restricted (often to observation and unofficial "student" entries into the medical record). As the demand for ICU exposure is high, the central challenge faced by administrators is titrating the flow.

Completion of the foundational degree fulfills a key component toward licensure. In general, licensure is sufficient to qualify for some care privileges, although there are nuances. For example, a newly graduated physician may qualify for limited licensure as a trainee provided he or she is supervised in an accredited postgraduate training program. A newly graduated physician assistant will have one or more supervising physicians.

In the critical care environment, licensure is tantamount to obtaining a "learner's permit," and newly licensed professionals typically require some form of mentorship. Such mentorship may be complex and structured as in postgraduate training programs (residencies) for physicians and APPs. It may consist of mentored on-the-job-training, which is the norm for new nurses coming to the ICU. The administrator has three typical tasks associated with mentorship of the newly licensed professional: (1) verifying the existence of a training plan; (2) verifying the assignment of one or more supervising mentors, including clarification of the roles and responsibilities of trainee and mentor; and (3) monitoring completion, including an objective determination from the responsible individuals that training is satisfactory and complete and further an attestation that the trainee can practice independently.

Certification (typically board certification) complements licensure. Whereas licensing is a regulatory and legal matter, certification by a board representing that profession validates not only that the individual has completed a prescribed course of training but also that certain advanced competencies have been evaluated and found satisfactory, typically by an examination that may be written, oral, simulated, or a combination thereof. The administrator's primary role in certification is often as custodian of records verifying that the necessary training has been completed, qualifying the trainee to enter the certification pipeline and complete the evaluation process. Of note, certification by a board occurs not only at different stages across professions but also can occur at different experience levels within a profession. For example, board-certified internal medicine physicians require 2 to 3 years of postgraduate training to complete critical care medicine training and enter the examination process, whereas board-certified surgeons and anesthesiologists require a single additional year of critical care medicine training. Progress to completion is typically profession and discipline specific. The administrator must understand the pipeline, including how trainees in all the professions are actually funded for their training. This is crucial to annual budgeting.

Credentialing to one or more hospitals is required before independent practice of critical care medicine within a profession. Privileges are granted to the professional permitting services within a scope of practice. For example, a pharmacist can dispense drugs and consult on selection and dosing; a nurse can administer drugs; and a provider (physician or APP) must prescribe a drug but typically cannot dispense and only in some cases may administer the drug. Although each profession is associated with a set of core competencies (e.g., airway management), the granting of privileges is individual, based not only on training, licensure, certification, and self-reported experience but also on contemporary peer evaluation. The administrator's role in credentialing is generally to ensure that staff in all professions maintain the credentials necessary for critical care practice, which typically includes scheduled recurring professional practice evaluations and completion of required continuing professional education.

Specific Education Issues

The previous section outlined educational processes and milestones with homologies among the critical care professions. The administrator is often called on to offer solutions to three related challenges.

1. The number of learners exceeds the capacity of the trainers and/or training sites. Although this may be perceived as a challenge confined to academic health science centers, it affects every hospital and critical care site because critical care staffs predictably have turnover. There is a need, even with the most experienced professional joining a new hospital or ICU, to ensure that the new hire knows the scope of practice, is familiar with the local emergency procedures, and achieves minimal competency with the electronic medical record. All of this takes professional time and it is rarely (if ever) accounted for in the budget. The administrator is therefore required to verify training assignments while ensuring that patient care needs are met. This invariably requires prioritization of needs, balancing most requests, and declining requests when they would cause hardship to the unit or danger to the patients.
2. Initial learning typically occurs within professional silos, yet care invariably requires rapid communication and collegial interaction among the different professions. The challenge can emerge in several forms, most often surfacing after an adverse outcome or a complaint about professional behavior. More often than not, the root of the problem can be traced to failure to transition from a "parallel play" to a "team effort" mindset. The challenge, then, is to create educational experiences that catalyze the transition. One approach involves shared educational experiences, such

as setting requirements that all staff must train toward certain certificates (e.g., Fundamental Critical Care Support, Advanced Cardiac Life Support). Another approach involves simulation of common emergencies at a simulation center or within the ICU. Yet another approach involves multiprofessional educational conferences, including morbidity and mortality.

3. Continuing education is required of all professions and professionals who practice in the ICU to maintain licensure and credentialing. Although this requirement might seem a challenge for the professional more than the administrator, failure to plan for continuing education incurs substantial cost. Some requirements are intramural, such as completion of annual infection prevention education. Staff members who fail to complete the intramural education are summarily suspended. Other requirements are extramural, including a set number of hours of continuing education to maintain licensure. In the absence of planning to meet the licensing requirements, there is typically a hurried effort to gain credits. There may even be a temporary lapse of privileges (and the need for expensive replacement staff) while necessary continuing education credits are acquired. Such problems are best prevented by planned intramural continuing education appropriate to many of the critical care professions complemented by planned attendance at regional and national professional meetings.

Summary

This chapter has covered some of the broader aspects of critical care administration and education. Performance improvement strategies, burnout, and workforce shortages were also briefly discussed.

To be effective, critical care leaders must develop a vision and a practical plan to achieve it. Regardless of vision, an operational plan needs to be able to quickly demonstrate value to an organization. This could come in the form of lowering costs, improving quality, patient satisfaction, and so on. This value proposition is particularly important to the successful formation of CCOs. CCOs can integrate both horizontally and vertically, which provides opportunities for economies of scale, standardization, and task reallocation. In an accountable care organization, vertical integration could also improve care coordination for critically ill patients.

Health care in the United States is rapidly evolving and leaders must embrace change to survive. Reimbursement models are shifting toward episodes of care rather than paying for each patient visit as a separate transaction. These "value-based" care models represent significant financial risks for health care organizations. Critical care leaders will need to adapt to these changes and find ways to thrive in increasingly difficult landscapes.

Education is threaded through training pathways, ICU operations, and research protocols. Although the administrator is neither expected to design nor approve content, nor to determine whether a professional has met training completion standards, the administrator must be sufficiently familiar with the activities to ensure that education meets the needs of patients and professionals alike. The need for close collaboration with clinical leaders is self-evident.

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Review Questions

1. Which of the following is most true about conflict in critical care?
   - **a.** Conflict should be confined to the administrative suite ("C-suite")
   - **b.** Conflict is inherently destructive
   - **c.** Conflict resolution is an essential skill for providers and administrators
   - **d.** Conflict is the underlying cause of burnout in the ICU

   Answer: c. Conflict, which is defined as the existence of alternate perspectives on a situation or alternate approaches to solving a problem, is inherent to all aspects of critical care. Conflict resolution is therefore an essential skill for providers at the bedside and administrators at all levels. There is no evidence that conflict is the underlying cause for ICU burnout
2. The priorities of critical care leaders universally include each of the following EXCEPT:
   - **a.** Balancing revenue and expense
   - **b.** Managing interpersonal conflicts
   - **c.** Ensuring reliable and qualified staffing
   - **d.** Enhancing discovery and innovation

   Answer: d. While research (discovery and innovation) is a common good, it is not an essential priority. Leaders must ensure continuous patient care, manage schedules, and ensure that interpersonal conflicts do not interfere with safety and effectiveness as their top priorities.
3. Which of the following is most correct concerning the comparison of integrated critical care organizations (CCO) with historically isolated ("silo'ed") ICUs?
   - **a.** No direct comparison between the performance of the two models has been presented in the peer-reviewed literature as of mid-2018
   - **b.** CCO offer a more flexible and reliable staffing model
   - **c.** CCO offer a more cost-efficient approach to critical care
   - **d.** CCO enhance discovery and innovation

   Answer: a. Despite conventional wisdom, the hypothesis that CCO outperform traditional models has never been directly and prospectively tested.
4. Regarding the use of incentives to change performance in ICUs
   - **a.** Pay-for-performance incentives are inherently inimical to team performance
   - **b.** Incentives are inherently bad because they encourage slavish adherence to a protocol
   - **c.** Incentives have been shown to change behaviors and improve outcomes in critical care
   - **d.** Incentives are best directed at managers and supervisors in ICUs

   Answer: c. Incentives have been shown to change behaviors and improve outcomes. Incentives are typically directed at outcomes and not method; teams are invited to be creative in their approach. For optimal effect, group incentives that include all team members are preferred to those that simply reward managers and supervisors.

71

Diagnosis and Management of Liver Failure in the Adult

CONSTANTINE J. KARVELLAS AND NICHOLAS MURPHY

CHAPTER OUTLINE

Decompensation of Chronic Liver Disease
- Precipitating Factors of ACLF
- Supportive Management of ACLF in the ICU

Acute (Fulminant) Liver Failure
- Etiology
- Clinical Course
- Management
- Artificial Liver Support
- Liver Transplantation

Liver failure is most often encountered as result of decompensation of chronic liver disease but can also occur de novo in patients with normal hepatic function. These patients are often described as having fulminant or acute liver failure, depending on the definition used.

Liver failure is characterized by a constellation of physical signs and symptoms including jaundice, coagulopathy, and encephalopathy. Not all of these need be present for a diagnosis to be made, but as the syndrome progresses they are usually present to varying degrees. Liver failure progresses to multiple-organ failure and ultimately death in a large proportion of patients, and supportive care plus removal of the primary cause is the mainstay of treatment. Liver transplantation may be indicated in a small group. Liver support systems are being actively investigated and may, in the future, have the ability to bridge a patient to recovery or transplantation.

Decompensation of Chronic Liver Disease

"Decompensation" in cirrhosis of the liver is a term used to describe the onset of visible signs of portal hypertension such as the development of ascites and variceal bleeding. These signs and symptoms can also be described as "symptomatic" cirrhosis, with the onset of liver failure in symptomatic cirrhosis described as "decompensation." One often leads to the other, but for the purposes of this chapter decompensation refers to the onset of liver failure.

The pathologic basis of acute decompensation in chronic liver disease or acute on chronic liver failure (ACLF) is incompletely understood but is thought to be precipitated by systemic inflammation, and if looked for hard enough, some signs or symptoms of infection will be seen in most patients.[1,2] Patients with well-compensated cirrhosis often decompensate following a defined event. The precipitants can be split into two types: (1) those related to direct liver insult, such as ischemia, a toxic insult such as alcohol, or a superimposed viral infection; and (2) those in which the liver is affected as a bystander in a systemic inflammatory process, such as after an episode of sepsis or a gastrointestinal bleed. This can be contrasted to the progressive liver failure of end-stage cirrhosis. Both present with similar clinical pictures, but in ACLF there remains the possibility of improvement and reversibility, and if these patients do recover, they return again to the previous mortality trajectory.[1,2]

Differentiating between the two is difficult but the presence of a precipitating factor and history can be useful. In patients with end-stage liver cirrhosis, there is often a history of gradual deterioration in biochemical parameters, clinical status, and other organ function, whereas in ACLF there is often an acute deterioration. Organ support in the former setting is of dubious utility as it is almost always futile (Fig. 71.1).

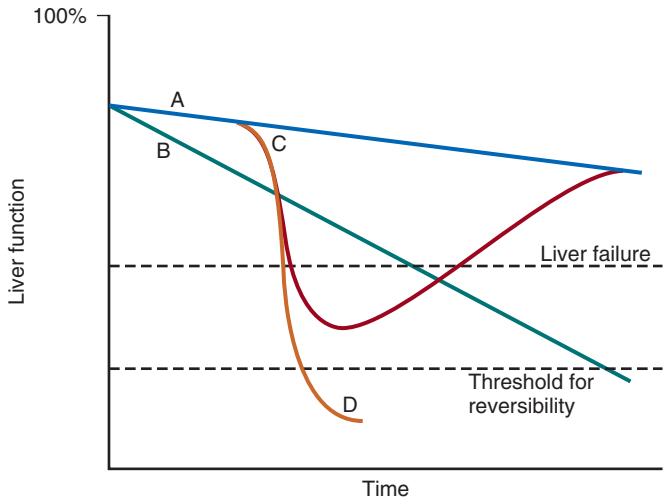
The European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium proposed a working definition for ACLF as "acute deterioration in liver function over a period of 2–4 weeks, usually associated with a precipitating event, leading to severe deterioration in clinical status with a high risk of short term mortality."[1]

ACLF often occurs with multiple-organ dysfunction. This may be because of the underlying precipitating event, such as pneumonia or bacterial peritonitis, or as a result of the severe deterioration in liver function. Often it is difficult to distinguish which came first. Renal failure is the most common organ failure associated with ACLF, and it is the severity of organ dysfunction that dictates the outcome.[3]

Precipitating Factors of ACLF

Alcoholic Hepatitis

Alcoholic hepatitis is a common manifestation of alcohol abuse. Between 20% and 30% of heavy drinkers present with it at some time. The clinical picture is variable and ranges from a relatively mild syndrome associated with loss of appetite, nausea, and vomiting with right upper quadrant pain to severe life-threatening liver



• **Fig. 71.1** Graphs A and B represent the trajectory of liver function in cirrhosis. B is indicative of a patient with progressive end-stage disease. A has a more shallow trajectory until there is a precipitating event, at which time either graphs C or D can be followed. C recovers with intervention back to the previous trajectory, but D does not.

decompensation, but the most obvious sign is the sudden onset of jaundice, which this can be the first indication of liver disease in a heavy drinker. Overall, after first presentation, 35% to 50% of patients will die within the first month of diagnosis.[4] It usually presents after a bout of heavy drinking and often occurs on a background of cirrhosis. Patients' conditions frequently deteriorate after stopping alcohol. This may be due to the immunosuppressive effects of alcohol. In patients without cirrhosis, abstinence and nutritional support can lead to a marked improvement in liver function over time.

See the online supplement for additional text on alcoholic hepatitis.

Portal Hypertensive Bleeding

Portal hypertension is a significant complication of chronic liver disease, leading to the formation of portosystemic collateral vessels. Of these vessels, the most significant clinically are those that occur in the wall of the stomach and esophagus. In patients with portal hypertension as a result of cirrhosis, the development of gastrointestinal varices occurs in approximately 60% at the time of diagnosis.[11] The incidence of the first acute bleed in an unselected patient is relatively low at about 5% per year, but it can be catastrophic when it occurs.[12] The mortality rate associated with the event has fallen over the past 20 years from approximately 30% to 50% to about 20%, and control of the initial bleeding episode is achieved in about 90% of patients.[13] Half of all fatalities occur in the first 5 days after an acute bleed; about half of them are due to uncontrolled bleeding and the rest are due to multiple-organ failure. This pattern remains the same when mortality rate in the first 6 weeks after the first bleed is examined.[13]

See the online supplement for additional text on portal hypertension.

The use of antibiotic prophylaxis has been shown to reduce the incidence of infection in this group of patients and to improve the short-term mortality rate.[20,21] It has been proposed that infection is the precipitant to an acute increase in portal pressure that may trigger bleeding.[22]

Bacterial Peritonitis

Patients with chronic liver disease are at increased risk of infection. The immunosuppression associated with chronic liver disease is incompletely understood but relates to a range of factors, including an impaired innate and adaptive immune response.[23,24]

In cirrhotic patients with ascites, decompensation to liver failure is often precipitated by infection. Bacterial peritonitis is a common and severe complication. It can be completely asymptomatic but can present with a range of symptoms and signs, including local signs of peritonitis, abdominal pain, diarrhea, and signs of systemic inflammation, such as fever, rigors, elevated white blood cell count, hypotension, and tachycardia.[25]

Bacterial peritonitis is often spontaneous, without any obvious source, although it can be secondary to other intraabdominal disease. It is generally caused by aerobic gram-negative bacteria, although gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA) should be suspected if there is treatment failure, especially if the patient has been taking prophylactic antibiotics.[26] In any patient with ascites and decompensation of liver disease, spontaneous bacterial peritonitis (SBP) should be suspected. Diagnosis is demonstrated by sampling of the ascitic fluid. An absolute leukocyte count in ascitic fluid of greater than 250/μL is diagnostic. Antibiotics should be started as soon as SBP is suspected, following blood culture and a diagnostic ascitic tap. Empiric broad-spectrum antibiotic coverage for gram-negative and MRSA organisms (depending on local prevalence) should be started until culture results are available.

Renal failure is a significant complication of SBP in patients with cirrhosis and is discussed later. The use of human albumin solution in SBP has been shown to reduce the incidence of progression to renal failure and should be considered in this setting.[25]

Supportive Management of ACLF in the ICU

The presentation of ACLF depends on the precipitating event or events but the clinical picture and pattern of organ failure overall look very similar. Hyperbilirubinemia and the resulting jaundice are almost universal, as are other biochemical manifestations of poor liver function. Plasma protein production is deranged, leading to a prolongation of prothrombin time and hypoalbuminemia. Thrombocytopenia resulting from hypersplenism and sepsis is also characteristic. The effects on the coagulation system are complex, however, as there is a concurrent reduction in the production of endogenous anticoagulant proteins in the liver, resulting in a relative rebalancing. Infection leads to consumption of factors and platelets and so the use of thromboelastography is recommended in bleeding patients. Lower levels of factors can result in difficulties maintaining coagulation during times of stress, particularly during infections, and evidence of a heparin-like effect has been shown.[27] It is also interesting to note that the incidence of thromboembolism is not lower in patients with cirrhosis even in the setting of a prolonged international normalization ratio (INR), suggesting that standard measures of coagulation are unreliable.[28]

The pattern of circulatory changes associated with cirrhosis is distinctive. Hypotension and an increase in cardiac output are typical, resulting in a hyperdynamic circulation. Peripheral vasodilatation, however, is not distributed evenly and occurs mainly in the splanchnic circulation as a result of sinusoidal portal hypertension. Splanchnic vasodilatation results in effective arterial

Features suggestive of malnutrition, such as muscle wasting and vitamin deficiency, are seen commonly. In severe decompensation, other intercurrent illnesses such as pneumonia or urinary tract infection or a gastrointestinal bleed are often present. Systemic inflammation may be the precipitant of decompensation in these patients.[5]

In alcoholic hepatitis, liver enzymes are moderately raised with an aspartate aminotransferase (AST) level rarely greater than 300 IU. The ratio of AST to alanine aminotransferase (ALT) is usually raised to greater than 2.[6] A high white blood cell count and bilirubin are also typical. The liver is usually enlarged and fatty on ultrasound. Portal hypertension often complicates the clinical picture, presenting as worsening of ascites. Assessment of filling pressures can be difficult if ascites is tense. Further hemodynamic monitoring is recommended if there is any doubt regarding filling status or if cardiac output is thought to be compromised.

Strictly speaking, liver biopsy is required to make the diagnosis of alcoholic hepatitis and is often performed to assess the extent of fibrosis, although it is not required for acute management. Demonstrated under light microscopy, the Mallory hyaline and a neutrophil infiltration (the amount of which is a marker of severity and prognosis), necrosis of hepatocytes, collagen deposition, and fatty change establish the diagnosis.

The prognosis of patients with alcoholic hepatitis depends on the severity of the disease. Risk stratification is important, both in defining the indications for the use of specific pharmacologic agents aimed at the interruption of progression and in clinical research. Serum markers and liver histologic findings provide the best means for risk stratification, with the presence of cirrhosis a poor marker.[7] In many cases, however, biopsy is precluded because of the risks of bleeding. Serum bilirubin, coagulation parameters, and creatinine levels have been shown to predict outcome and have been combined into several scoring systems: the discriminative function; Child, Turcotte, Pugh; the Mayo end-stage liver disease (MELD) score; and the Glasgow Alcoholic Hepatitis score have been used to evaluate outcome. Of these, the MELD score appears to offer the best prediction of mortality risk because of the inclusion of renal function (creatinine) as well as liver function; renal deterioration in this setting has a particularly poor prognosis.[8] Standard critical care prognostic scores have also been used to assess the prognosis of patients with decompensated chronic liver disease of any cause. The Sequential Organ Failure Assessment (SOFA) score has been shown to provide useful prognostic information.[1,9]

In early disease, abstinence and good nutrition, including supplementation with B vitamins, is the mainstay of management. In severe disease, progression to hepatic encephalopathy and organ failure can be rapid. In addition to general supportive care, specific therapies have been used in an attempt to halt and reverse the hepatic inflammation, but none other than corticosteroids have been demonstrated to prevent the fall into multiple-organ failure and ultimately death.[10]

Control of bleeding episodes is via direct endoscopic therapy, usually in the form of band ligation in the case of esophageal varices.[14] Terlipressin, a synthetic analog of vasopressin, can be used as an adjunct to band ligation. Terlipressin induces splanchnic vasoconstriction and reduces portal pressure and has been shown to reduce mortality rate.[15] There is some evidence that somatostatin may reduce the amount of blood transfused but the evidence is weak.[16] Uncontrolled bleeding owing to either failed endoscopic or pharmacologic therapy or when resources do not allow immediate endoscopic therapy may be managed with balloon tamponade of the stomach or esophageal varices. Primary control of esophageal varices is usually successful, but balloons should not be inflated for more than 12 hours because of the risks of mucosal necrosis. Care should be exercised when inserting and inflating a Sengstaken-Blakemore or Minnesota tube because perforation of the esophagus is usually fatal in this setting. After control with the insertion of a balloon tamponade device, further endoscopic therapy, surgical shunting, or transjugular intrahepatic portosystemic stent shunts (TIPS) may be attempted. Of the shunt procedures used TIPS is the most commonly attempted where personnel with technical skills are available. The procedure involves decompressing the portal circulation into the hepatic vein via a stent inserted percutaneously through the liver via the internal jugular vein. The procedure is a very successful salvage therapy for controlling bleeding but can induce certain complications, including (1) volume overload as a result of portal shunting into the right atrium, which can induce heart failure; (2) bypassing the portal circulation, resulting in ischemic liver injury and, rarely, liver failure; and (3) worsening of encephalopathy grade (the most common complication), resulting in failure to awaken from the procedure, the need for extended ventilation, and the risk of hospital-acquired infection. There have not yet been any controlled trials of TIPS as salvage therapy in this setting, and it is unclear what role TIPS has in the management of acute bleeding varices as it may result in just prolonging the dying process. Despite better prevention of rebleeding when compared with endoscopic therapy in patients with bleeding varices, a mortality benefit cannot be shown with TIPS.[17] Garcia-Pagan and colleagues have shown that TIPS, performed not as salvage therapy but used as a primary form of therapy once the initial bleed has been controlled, results in a dramatic reduction in rebleeding rates and mortality rates.[18] Coagulation abnormalities are commonly present in patients with acutely bleeding varices, and abnormalities in clotting factors have been shown to be independent prognostic factors in patients with esophageal varices. Attempts to treat coagulation abnormalities with clotting components should be undertaken during an acute bleed to include fresh frozen plasma and platelets targeted to correct abnormal partial thromboplastin time and platelet count. Activated factor VII has not demonstrated significant benefit in this setting.[19]

Bleeding from varices is associated with infection. Between 35% and 60% of cirrhotic patients with bleeding varices have documented infection over the following 2 weeks.[20]

underfilling with the resulting activation of compensatory mechanisms.[29] During decompensation circulatory changes become more pronounced with an increase in portal pressure; systemic vasodilatation worsens and blood pressure drops further and becomes less responsive to vasopressor support. Recent work shows that cardiac output may fall in those who develop acute kidney injury (AKI)/hepatorenal syndrome, as do cardiac filling pressures and pulmonary artery pressure. These changes point toward some form of cardiac depressant factor associated with decompensation.[29] There is a reduction in intrarenal blood flow owing to the activation of compensatory mechanisms designed to maintain arterial volume, such as the renin-angiotensin system and sympathetic nervous system. This results in a further reduction in glomerular filtration rate and urine output. Cardiac function may be further compromised by liver failure–associated cardiomyopathy, which is manifested by a low or normal cardiac output in the setting of reduced afterload.[30] There may also be a relative hypovolemia in the setting of a normal or raised central venous pressure because of raised intraabdominal pressure caused by ascites. Echocardiography is very helpful in the delineation of any cardiac dysfunction and can help assess pulmonary artery pressure to assess if the patient has portopulmonary hypertension.[31] A pulmonary artery catheter should be used if there is any doubt.

AKI is the most common form of organ dysfunction seen in patients with ACLF and has significant attributable mortality risk.[32] There are four main causes; those associated with bacterial infection are the most common, followed by hypovolemia and parenchymal disease, with hepatorenal failure the least common.[3] However, hepatorenal failure has a particularly poor outcome. The diagnosis of AKI in the setting of liver disease is problematic, as conventional measures of renal function are less indicative of renal function.

Hepatorenal syndrome (HRS) is a severe complication of advanced cirrhosis. Its clinical manifestations are related to changes in renal, hepatic, and the systemic circulation. HRS is a consequence of intense renal vasoconstriction, leading to a reduction in renal perfusion and glomerular filtration. The ability of the kidney to excrete sodium and free water is also severely impaired without histologic changes accounting for this renal impairment. Traditionally, HRS has been described in two different clinical patterns, according to intensity and onset of renal failure: Type 1 HRS increasingly represents the severe end of the spectrum of renal failure in cirrhosis. It is characterized by rapidly progressive renal failure with oliguria. It is defined as a doubling of the serum creatinine level to more than 2.5 mg/dL or a 50% reduction in 24-hour creatinine clearance to a level less than 20 mL/min in less than 2 weeks. Type 2 HRS progresses slowly and represents a less severe deterioration in renal function that may remain stable for extended periods of time. The dominant clinical feature of a patient with type 2 HRS is refractory ascites. This is the result of intense sodium retention, reduced glomerular filtration, and marked stimulation of the renin-angiotensin system. More recently, the International Club of Ascites (ICA) in 2011 revised traditional criteria to define HRS-type AKI (HRS-AKI) as including diagnosis of cirrhosis with ascites, increase in serum creatine (SCr) by 50% with final SCr value greater than 133 µmol/L (1.5 mg/dl), no response to diuretic withdrawal/plasma expansion with albumin 1 g/kg per body weight, absence of shock, absence of nephrotoxins (nonsteroidal antiinflammatory drugs, iodinated contrast) and an absence of macroscopic signs of structural kidney disease.[33]

Until recently there was no effective treatment for patients with HRS other than liver transplantation, but over the past 15 years observational and interventional studies have shown that countering the compensatory circulatory changes that promote intrarenal vasoconstriction with use of systemic and selective vasoconstrictors plus plasma volume expansion with albumin can lead to significant improvement in renal function.[34] The aim of therapy is to focus vasoconstriction on the dilated splanchnic vessels, resulting in a redistribution of the blood volume back into the systemic arterial circulation. Over time this results in suppression of the compensatory mechanisms; a reduction in plasma renin activity, sympathetic activity, and circulating catecholamines; and an associated increase in glomerular filtration rate, sodium excretion, and urine output.[35] Many different vasoconstrictors have been tried in this setting. The drug most commonly studied is terlipressin, and it is often given with 20% human albumin solution. This approach has been subjected to a randomized controlled clinical trial in which the addition of albumin was associated with an improvement in renal function.[36] Evidence suggests that vasoconstrictor therapy, with or without plasma volume expansion, results in an improvement in renal function in about a third of patients with type 1 HRS. The best predictor of response to therapy is the baseline serum creatinine level, and those who do respond have a significant rise in their arterial pressure.[34,37]

Hepatic encephalopathy (HE) is almost universal during decompensation cirrhosis and is characterized by loss of normal day/night differentiation, confusion, somnolence, asterixis, hyperreflexia, and progression to coma. It is reversible in the event of recovery of liver function or removal of the precipitating event. The etiology of hepatic encephalopathy is incompletely understood but relates to the inability of the failing liver to clear circulating toxins, most notably ammonia. There are other important factors, including minor degrees of cerebral edema and systemic inflammation. Interaction of these components leads to the profound levels of encephalopathy seen in ACLF.

Ammonia production in the gut is important in the pathogenesis. Ammonia is usually cleared from the portal circulation in the liver. The mainstays of treatment are colonic cleansing with enemas and enteral disaccharides such as lactulose. Both of these procedures have been shown to improve encephalopathy grades. The restriction of protein, once fashionable in patients with liver disease, is contraindicated. The majority of these patients are malnourished/sarcopenic, and adequate enteral nutrition is essential.[38]

Patients with ACLF and high grades of HE require intubation and ventilation, if not because of hypoxia, then to allow airway protection. Airway protection is most frequently needed in patients with bleeding esophageal or gastric varices requiring endoscopic therapy for large-volume hematemesis in the presence of HE and a difficult or prolonged endoscopic procedure. Patients with ACLF are usually exquisitely sensitive to sedative and anesthetic agents, particularly benzodiazepines, which can prolong coma. Care should be exercised in their use and shorter-acting agents such as propofol are preferred.

Large-volume paracentesis should be considered in any patient with tense ascites. There is evidence that large-volume paracentesis improves lung mechanics and oxygenation in nonventilated patients but data in ventilated patients are lacking.[39–41] Hepatic hydrothorax is a persistent pleural effusion, almost always associated with ascites, usually on the right side of the chest. It can be massive in size, containing many liters of fluid, and is thought to be caused by communication from the peritoneum. Management can be difficult. Direct drainage with thoracocentesis is usually inadvisable, as the fluid accumulation is persistent, leading to continued need for chest tube placement, which carries the risk of infection. Management should be directed at the ascites and includes diuretics, salt

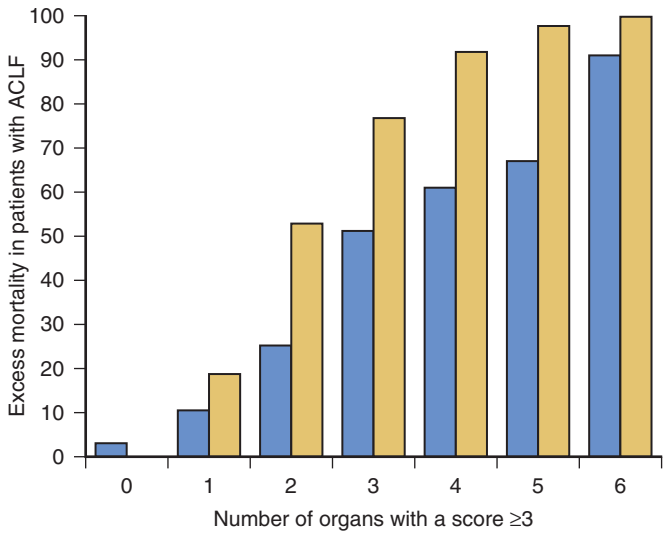
restriction, and paracentesis. TIPS can be used to control both ascites and hydrothorax, but is associated with worsening encephalopathy grade in some patients.[42]

Adrenal dysfunction in patients with critical illness, particularly patients with septic shock, has been documented extensively.[43] Studies have suggested an improvement in outcome with steroid use but subsequent investigations have been less clear. Current recommendations suggest steroid treatment should not be based on adrenal stimulation and should be reserved for those with vasopressor-resistant septic shock or early acute respiratory distress syndrome within 14 days of onset.[43] Patients with ACLF have also been shown to have a high incidence of adrenal suppression, although it is not clear if this has a different etiology from other critically ill patients. Patients with adrenal suppression have worse hepatic and renal function, more organ failure, and a higher intensive care unit (ICU) and hospital mortality rate.[44] There remains, however, a lack of consensus regarding definitions of adrenal dysfunction and appropriate testing in patients with liver disease and in which patients require treatment.[45] However, in patients with cirrhosis and septic shock admitted to the ICU with adrenal insufficiency, as defined by a suboptimal response to adrenocorticotropic hormone stimulation, replacement of hydrocortisone (50 mg every 6 hours) results in a higher incidence of shock resolution and hospital survival when compared with historical control subjects.[46]

Outcome and Data on ICU Use in Decompensated Cirrhosis

Despite ICU care, the outcome in patients with decompensated cirrhosis is poor. In one study overall cumulative mortality rates were 36% in the critical care unit, 46% in the hospital, and 56% at 6-month follow-up.[47]

In patients who require organ support within the critical care environment a number of observations can be made. Derangement of acute physiology at admission is a predictor of outcome, as it is for unselected patients admitted to the ICU.[48] In addition, the number of organs requiring support also is predictive of outcome, as it is in unselected patients.[47,49] If you compare the number of organs failing (defined as an organ-specific SOFA score >3), there is an excess mortality rate associated with cirrhosis when compared with an unselected group (Fig. 71.2).[50] The CLIF consortium has developed the CLIF-ACLF score (based on SOFA but evaluated in patients with ACLF), which demonstrates a mortality of more than 80% with failure of more than three organs.[51]



• **Fig. 71.2** This graph shows the relative mortality rates associated with the number of failing organs as defined by a SOFA (sequential organ failure) score of greater than 3. In patients with cirrhosis *(yellow bars)* there is an excess mortality rate at each position. *Blue bars*, Unselected group.

Acute (Fulminant) Liver Failure

Acute liver failure (ALF) is a syndrome manifested by the rapid cessation of normal function in individuals with previously normal hepatic function. The rate of decline in function dictates the manner in which the syndrome manifests and influences the outcome. The cause is the main influence on the rate of progression and the likelihood of spontaneous recovery.[52]

The pathologic basis of the massive hepatic necrosis was described in detail by Lucké and Mallory after the Second World War in 1946.[53] The presence of the American army in East Asia and Africa resulted in exposure to both epidemic and serum hepatitis, and data regarding the clinical course of the syndrome and its pathologic features were collated via the army medical services.

In 1970 Trey and Davidson introduced the term fulminant hepatic failure to encompass the current clinicopathologic understanding of the syndrome.[54] This definition was an attempt to encapsulate the clinical course and to differentiate it from decompensation of chronic liver disease. They described a syndrome of rapidly progressing liver failure (within 8 weeks) in which the defining point was the onset of hepatic encephalopathy following the onset of symptoms in someone without previous liver disease. They make the point that the syndrome is potentially reversible in some patients. This definition is still used today; however, it has become clear that this definition is too narrow and that subgroups exist. This point is important as these subgroups predict the likely prognosis and potential for survival without a liver transplant.[52]

The rate of progression from the onset of jaundice or other initial symptoms (such as fatigue or acute viral illness) to development of encephalopathy is used to define subgroups. This in part relates to the cause of liver failure and to the way the pathologic expression of the pattern of organ failure presents. For example, patients with significant acetaminophen-induced hepatotoxicity generally present with liver failure within 7 days of ingestion, unless ingestion was staggered over a period of time when the timing of liver insult is difficult to define. In contrast, patients presenting with seronegative hepatitis (unknown cause) can have a very variable presentation, some with a prolonged illness over a period of months, resulting in a patient who is deeply jaundiced with evidence of portal hypertension, such as ascites, at the onset of encephalopathy, and others with a relatively short presentation period. These two extreme ends of the syndrome split the group into hyperacute and subacute, with ALF in the middle. Interestingly, it is the hyperacute group that has the best chance for spontaneous recovery, although this group has the highest risk of cerebral edema. The subacute group has the worse prognosis with medical management alone.[52]

ALF is rare, with about 1 to 6 cases per 1 million of the population in the developed world.[55] The incidence in the rest of the world is less clear because of the paucity of data (Box 71.1).

Etiology

Worldwide, and in the developing world in particular, approximately 95% to 100% of patients presenting with ALF have viral hepatitis.[56]

Within the United Kingdom and as recently reported in the United States, paracetamol (acetaminophen) hepatotoxicity is the leading cause of ALF. This is followed by liver failure of unknown cause or seronegative hepatitis.[57,58]

The pattern of ALF within the United Kingdom and United States has been changing over the past 30 years.[57,58] Up until the late 1990s, the rate of hospital admission owing to acetaminophen ingestion had risen year by year. In the United Kingdom acetaminophen overdose is usually due to deliberate self-harm. In contrast, the U.S. data suggest that over half of all patients with ALF owing to acetaminophen were due to therapeutic misadventure. Some doubts have been expressed regarding this interpretation as misadventure in some cases that appear to be occult suicide attempts.[58,59]

In 1998 legislation was introduced in the United Kingdom to restrict the over-the-counter sale of paracetamol to 16 tablets from most retail outlets and 32 from pharmacies in the form of blister packs. Interpretation of the effects of the legislation has proved to be complex, in large part because there were no prospective audits initiated at the time to study it. Early interpretation suggested that admissions to hospital, severe liver toxicity, and transplantation for acetaminophen fell.[60] The picture is more complex, though. Death rates have fallen; however, much of this reduction can be related to the withdrawal of co-proxamol during the mid-2000s. Co-proxamol, a combination of paracetamol and dextropropoxyphene (a mild opioid), was a prescription-only medication associated with a high degree of fatality if taken in overdose; most of these cases occurred out of hospital and were attributed to the effects of dextropropoxyphene on respiratory depression.[61] Admission to the hospital because of acetaminophen has continued to rise year by year, but the number of pills taken on average has fallen and so the case fatality rate is lower. The numbers of patients referred to transplant centers is also lower than before the legislation, but the number of patients who received transplants has remained about the same, indicating the small number of determined overdoses and misadventure cases has remained relatively stable.

In the United Kingdom and the United States, the incidence of acute hepatitis A virus and hepatitis B virus (HBV) infection has fallen dramatically since the 1980s[57,58] (Figs. 71.3 and 71.4).

Less than 1% of acute hepatitis A or B progress to ALF. In the United States and United Kingdom, as a proportion of the total, the number of admissions with ALF owing to viral hepatitis has fallen steadily and is currently responsible for less than 5% of all admissions in the United Kingdom and 11% in the United States.[57,58]

Indeterminate hepatitis (non-A to -E hepatitis, seronegative ALF, indeterminate) is often presumed to be viral in origin and is the most common presentation, excluding acetaminophen in the United Kingdom and United States along with viral hepatitis in the developing world. It is a diagnosis of exclusion and, as diagnostic capabilities improve, is falling in incidence in some centers.[57]

• BOX 71.1 Hyperacute, Acute, and Subacute Liver Failure

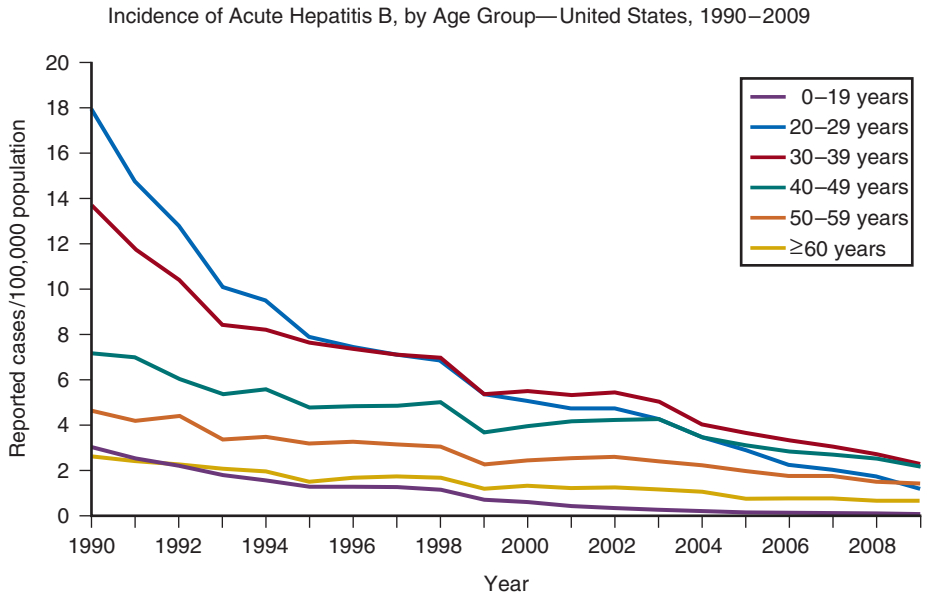
Hyperacute liver failure
- Jaundice to encephalopathy within 7 days—usually secondary to acetaminophen hepatotoxicity

Acute liver failure
- Jaundice to encephalopathy in 8–28 days

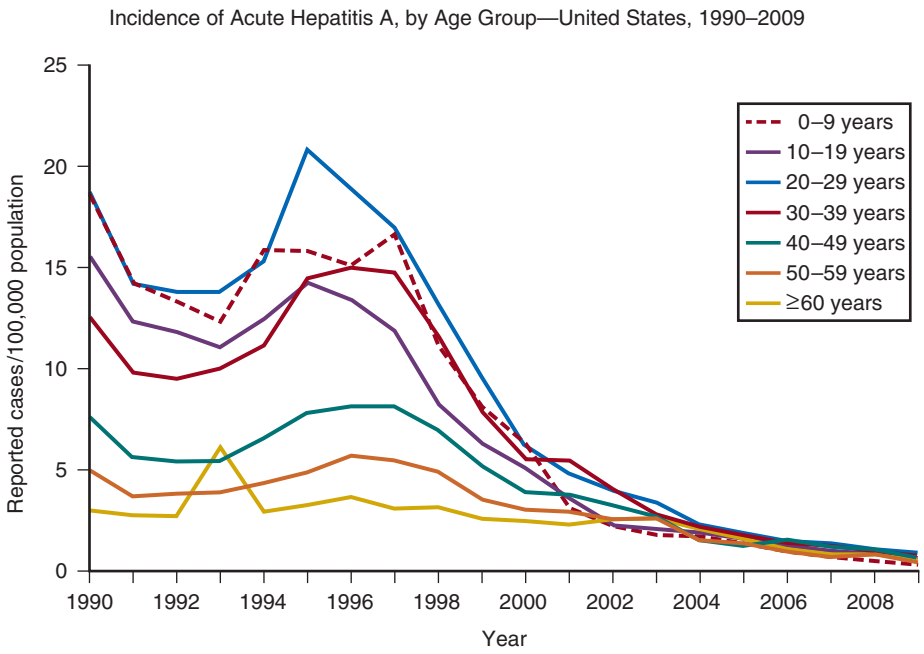
Subacute liver failure
- Jaundice to encephalopathy in 29 days to 6 months

Acetaminophen (Paracetamol)

Acetaminophen-induced liver failure is the cause of the majority of hyperacute liver failure. Acetaminophen poisoning is a common cause of presentation to acute and emergency departments in the United Kingdom and United States; however, the case progression to ALF after acetaminophen ingestion is rare, at just 0.6% of all presentations in the United Kingdom.[62]



• Fig. 71.3 The incidence of acute hepatitis B in the United States by age group 1990–2009. The incidence has fallen in all age groups over this time. (From National Notifiable Diseases Surveillance System.)



• **Fig. 71.4** The incidence of acute hepatitis A in the United States by age group, 1990–2009. The incidence has fallen in all age groups in recent years. (From National Notifiable Diseases Surveillance System.)

It was in the mid-1960s that the main mechanisms of acetaminophen-induced liver injury were elucidated. The scheme outline by various groups revealed the production of electrophilic quinone imine (N-acetyl-p-benzoquinone imine [NAPQI]), which covalently binds to hepatic proteins, was central to the resultant centrilobular necrosis seen after poisoning. The two major pathways for metabolism are the glucuronidation and sulfation of the phenolic group, with the metabolites produced excreted in the urine. In therapeutic doses approximately 80% of the drug is metabolized via these two pathways and 5% to 10% is excreted unchanged in the urine. The remainder is metabolized via the hepatic mixed function oxidase, cytochrome P450, to produce NAPQI.

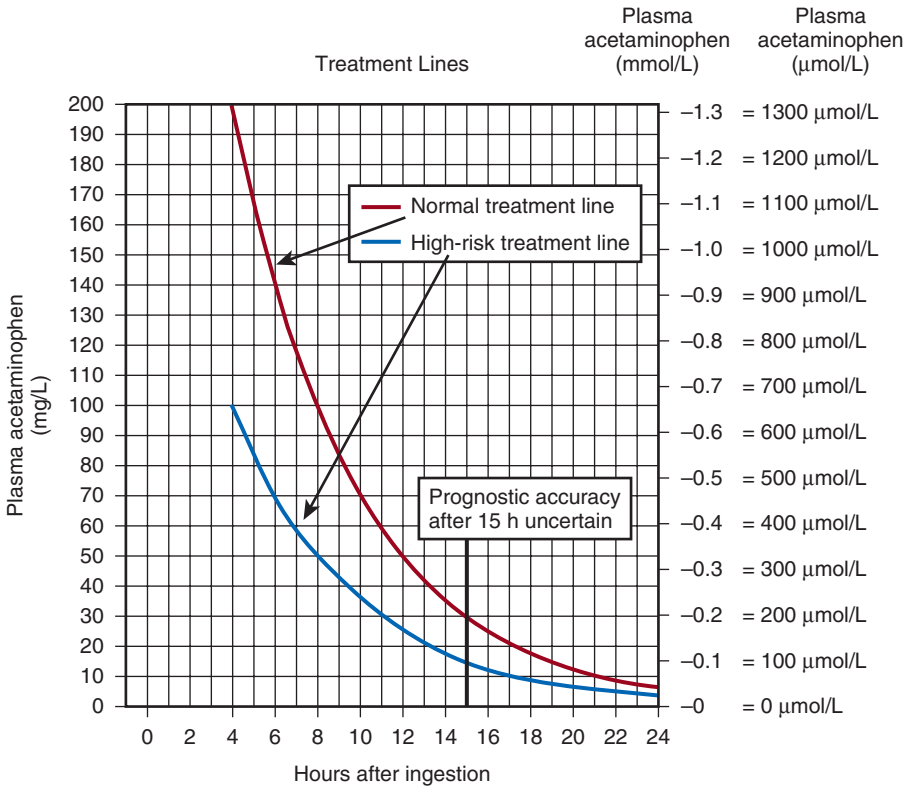
After poisoning the half-life of acetaminophen is greatly prolonged because of the saturation of glucuronidation and sulfate conjugation. As a result, there is an increase in the quantity of NAPQI produced. NAPQI is extremely reactive in biologic systems and has a short half-life. After poisoning, reaction of NAPQI occurs within the centrilobular portions of the liver and leads to necrosis in experimental models. It reacts with cellular constituents in a covalent and noncovalent manner. The exact mechanisms by which NAPQI induces cell death are incompletely understood but include the deactivation of critical cellular proteins, the induction of reactive oxygen species, and the activation of Kupffer cells.[63] The loss of regulatory protein function results in abnormal calcium homeostasis and resultant energy failure within the cell and mitochondria.[63] Other events such as noncovalent interaction with intracellular signaling and lipid peroxidation also contribute to the toxicity of this molecule. After this primary toxic phase there is a secondary or extrinsic phase. This extrinsic phase is equated with the recruitment of immune cells to the liver. The liver is one of the major immune organs of the body. Up to 35% of the liver is made up of nonparenchymal cells, including endothelium, Kupffer cells, and resident lymphocytes. These cells, together with macrophages within the liver, perform a major role in immune regulation and in the filtering of antigens from the gut contents via the portal circulation. They are also implicated in the pathologic processes that occur after liver insult. Massive activation of immune cells in response to the intrinsic cellular damage induces the release of cytokines and chemokines both locally and into the systemic circulation.[64,65]

The pathophysiologic consequences of severe liver injury result from a combination of factors, including the release of cytokines and other inflammatory molecules resulting from the necrosis of hepatocytes and activation of local and systemic immune cells, and from the loss of metabolic activity related to a critical reduction in liver cell mass. The relative contribution of these factors is not completely clear but is debated and has led to attempts at therapy, including temporizing hepatectomy and nonbiologic liver assist devices.

The minimum dose that can induce hepatic damage appears to be about 125 mg/kg. This represents 15 × 500-mg tablets in a 60-kg individual, although hepatic necrosis has been recorded at much lower doses, especially if associated with hepatic enzyme induction. Doses above 250 mg/kg (30 × 500-mg tablets in a 60-kg individual) will often produce damage, and doses in excess of 350 mg/kg invariably produce significant damage.[66]

The symptoms over the first 24 hours after a significant intake of acetaminophen, irrespective of amount ingested, are usually nausea and vomiting. During the next 4 to 5 days, if liver failure ensues, there is a gradual worsening of the patient's general condition. Those with significant overdose should be admitted to the hospital and monitored closely.

The antidote for acetaminophen poisoning is N-acetylcysteine (NAC). It provides complete protection against hepatotoxicity if given within 12 hours of nonstaggered ingestion.[67] Within 12 hours, if the time from ingestion is known with certainty and a plasma acetaminophen level is obtained, reference can be made to the nomogram to determine if the potential for hepatotoxicity



• **Fig. 71.5** Normal treatment line and high-risk treatment line for the initiation of N-acetylcysteine (NAC) treatment based on serum acetaminophen levels and hours after ingestion. The high-risk line has been adopted as the standard and only treatment line in the United Kingdom. This is done to avoid confusion and to reduce the risk of undertreatment in patients with chronically induced hepatic enzymes, such as those receiving antiepileptic medication, chronic ethanol abusers, or smokers. If there is any doubt about the number of hours since ingestion, or if there is any suggestion of a staggered overdose or chronic overingestion, NAC should be administered. (From Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine. *Drug Safety Update*. September 2012;6[2]: A1.)

is present. The nomograms are unreliable if the time from ingestion is uncertain or if there was staggered ingestion over a period of time, as often occurs with therapeutic misadventure or repeated overdose. The use of alcohol often accompanies ingestion, making timing unreliable. Situations that alter normal cytochrome P450 function such as drug induction, (chronic ethanol use, phenytoin, and isoniazid) again render the information unreliable.[68] The use of the nomogram as the only basis for the decision to withhold NAC therapy is to be discouraged because of the uncertainty associated with this timing and the catastrophic potential if NAC is erroneously withheld (Fig. 71.5).

The main effect of NAC is to increase hepatic glutathione production. This promotes the conjugation of NAPQI and its subsequent excretion. In addition, NAC may act as an antioxidant within and outside the liver. It is most effective if given within the first 8 hours after overdose but is still effective after this time, although less so. There is some evidence that NAC is effective when administered to the patient up to 72 hours after poisoning, although the mechanism of action is unclear and probably relates to antioxidant effects rather than to any effect on acetaminophen metabolism.[69] The role of NAC in established ALF from any cause is more controversial despite widespread use, but data have lent support to its use certainly at lower coma grades. However, the mechanism of action is unclear.[70,71]

Viral Hepatitis

Both epidemic and serum hepatitis were recognized well before the viral form was discovered. In the seminal work of Lucké and Mallory in 1946, they describe 196 patients who died of ALF after both epidemic hepatitis and serum hepatitis, related to the administration of blood products during World War II.[53]

ALF after acute viral hepatitis is uncommon, with a reported incidence of 0.2% to 4% depending on the underlying cause.[72] Liver failure after viral hepatitis tends to run an acute or hyperacute course with the onset of encephalopathy occurring within days or weeks of the first symptoms.[73]

Hepatitis A is now rare in the United States and Western Europe but is still a common form of acute enterally transmitted hepatitis in the underdeveloped world where it is mainly a mild and self-limiting illness of children.[73,74] Infection with hepatitis A carries the lowest risk of conversion to acute hepatic failure of all the hepatotropic viruses. In the West the incidence of ALF after hepatitis A appears to be higher than in the endemic areas. It occurs more commonly in adults and is more severe. Persistent infection with hepatitis A has also been reported[75] and even recurring after liver transplantation.[76] Diagnosis is made on the basis of immunoglobulin (Ig) M antibodies at the time of hospitalization, although false-negative results can occur.[77]

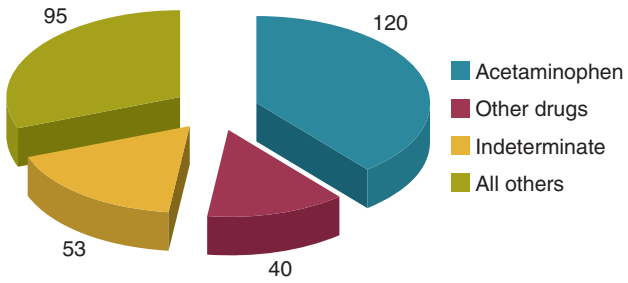
Hepatitis B may lead to ALF is several settings. It occurs most commonly after acute infection but can occur after an acute increase in viral replication following immunosuppressive therapy such as cancer chemotherapy or steroids, as well as with coinfection with other viral agents such as hepatitis delta virus. The host immune response is thought to be responsible for the severity of reaction to the virus, subsequent clearance, and the induction of ALF. This can be seen after the withdrawal of immunosuppressive therapy when there is a very active immune response to the increased viral load. In acute infection the surface antigen of hepatitis B (HBsAg) is often negative but IgM antibodies to the viral core (HBcAb) are usually positive. Mutations to the precore stop codon or the core promoter region of the viral genome may be associated with a higher incidence of ALF.[78] These particular genes code for hepatitis B e antigen (HBeAg), and lack of this antigen is associated with a more profound immune response. There have been reports of a very high incidence of ALF associated with outbreaks of acute hepatitis B in the setting of intravenous drug use and chronic hepatitis C infection.[79] Lamivudine antiviral therapy for acute HBV-induced hepatitis has been tried, but because of the lack of controlled trials, it is difficult to know if it or other drugs like it help.[80]

Hepatitis C, as a cause of ALF, is rare in northern Europe and the United States but has been described.[81] There is a wide spectrum of clinical presentation associated with acute infection with the more florid presentation associated with a more rapid clearance rate, suggesting that the magnitude of the initial immune response is important.[82] Liver failure associated with acute infection appears to be more common in India and the Far East.[83] Acute infection may contribute to decompensation in patients with preexisting liver disease, and hepatitis C seropositivity may predispose to liver failure when coinfection with another hepatotropic virus is present.[83]

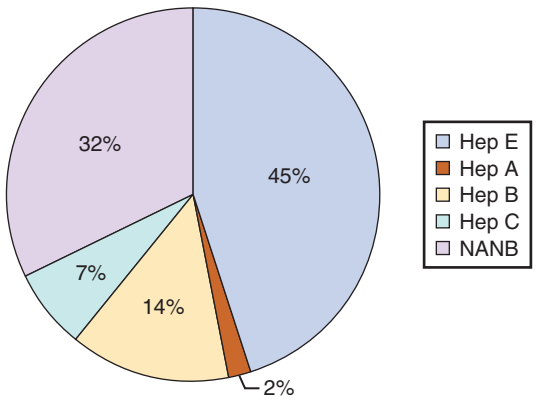
Hepatitis E is likely the most common cause of ALF worldwide and certainly for the Indian subcontinent.[83] In the Far East acute HBV infection is the most common cause of ALF owing to the high levels of endemicity.[84]

The existence of hepatitis E was inferred before serologic evidence was available by a process of exclusion. It was long assumed that most if not all epidemic enteric hepatitis was due to the A virus. When serologic markers for hepatitis A became available in the early 1980s, it was apparent that the majority of waterborne epidemic hepatitis were due to other agents, producing a syndrome similar clinically to hepatitis A.[85] Hepatitis E does not produce a chronic infection and in the vast majority is a self-limiting infection that occurs most commonly in young adults, in contrast to hepatitis A, which is primarily an infection of children. The incidence of hepatitis E associated with ALF is low, with a case-related mortality rate reported at about 0.5% to 4% in the general population but with a much higher mortality rate in pregnancy, as high as 20% in the third trimester. Pregnancy itself appears to be a risk factor for ALF, with a quarter of all infected female patients reported as pregnant in one series. However, this may not be particular to hepatitis E but rather due to the high incidence of epidemic hepatitis E in a relatively immunosuppressed state and pregnant patients do not have a worse prognosis compared to nonpregnant patients with ALF owing to hepatitis E.[83,86]

Five genotypes have been described, with genotypes 1 to 4 infecting humans and genotype 5 infecting only birds. Genotype 1 is the most common in Asia, with genotype 2 more common in Africa and South America. Genotype 3 can infect both human and animals, whereas genotype 1 and 2 have been described only in humans.[87] In the West, travel to endemic areas is a risk factor, but sporadic cases are now being seen more commonly in the developed world. Some of these cases have been associated with contact with animals.[87]



• **Fig. 71.6** Etiology of acute liver failure in the United States 1998–2001 based on 17 centers (n = 308). (From Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137:947–954.)



• **Fig. 71.7** Causes of acute liver failure in an Indian center 1989–1996. (From Khuroo MS, Kamili S. Aetiology and prognostic factors in acute liver failure in India. *J Viral Hepat*. 2003;10:224–231.)

Seronegative hepatitis is the second most common cause of ALF worldwide in most published series. In northern Europe and the United States it ranks behind acetaminophen toxicity, and in the developing world it is second to acute viral hepatitis (Figs. 71.6 and 71.7).

Seronegative hepatitis can be conveniently thought of as a single entity. In reality it is probably an amalgam of various causes that have defied definition or characterization, including acute presentations of autoimmune hepatitis, idiosyncratic drug reactions, and viruses.[88,89] Seronegative hepatitis has a variable clinical presentation, including a slow insidious onset of general malaise, jaundice, and ascites, followed by progressive signs and symptoms of liver failure. At presentation the patient may be deeply jaundiced and may already have ascites and splenomegaly. It can also present with a hyperacute picture. The pattern of signs, symptoms, and organ failure is dictated by the rate of progression. In subacute seronegative hepatitis, the presenting clinical picture can be similar to that of decompensated chronic liver disease, causing occasional diagnostic difficulty. A liver biopsy is sometimes needed to differentiate between the two.

Acute Presentation of Autoimmune Hepatitis

Autoimmune hepatitis can occur at any time of life from childhood until old age. It is more common in women with a male/female ratio of 1:3. Presentation can be asymptomatic, discovered after

routine laboratory testing, or more commonly, the infection may present with jaundice and general malaise. In rare cases autoimmune hepatitis can present as ALF.[90] Unfortunately, there are no serologic tests with sufficient sensitivity or specificity to make the diagnosis certain. Patterns of markers in the right clinical setting and in the absence of other causes may be useful.[91] The diagnosis of autoimmune hepatitis in the setting of ALF is difficult and a degree of uncertainty often lasts. Classically there is a combination of elevated immunoglobulin levels, autoantibodies, and confirmatory histologic evidence of hepatitis in the absence of active viral markers. Elevation of autoantibodies is often seen in patients with ALF owing to other causes such as drug-induced liver disease.[90] Liver failure should be assessed in the same way as for other causes, and once signs of encephalopathy become apparent, standard prognostic criteria apply. The role of steroids is unproved but should be considered in patients before the onset of encephalopathy. Once the patient is listed for transplantation, steroid use is controversial because of increased risk of infection.

Drug-Induced Liver Disease

The liver is a major site for drug metabolism in the body. Metabolism of xenobiotics (a chemical found in an organism but which is not normally produced or expected to be present in it) takes place in a series of specialized enzyme reactions that increase the water solubility of lipophilic molecules by the incorporation of polar groups. Drug metabolism often involves a number of processes. Intermediates produced during the process are sometimes more toxic than the parent drug and can cause liver damage by a number of mechanisms.

Drug-induced liver disease may be due to a known dose-dependent toxicity, as with acetaminophen. Alternatively, unpredictable, rare, idiosyncratic reactions can occur with any drug with a frequency of about 1 in 1000 to 1 in 100,000 patient prescriptions.[68] Drug-induced liver failure can mimic all forms of acute and chronic liver disease. However, the predominant clinical presentation consists of either acute hepatitis or cholestatic liver disease. The former has a reported mortality rate of 10% irrespective of the drug.

The patterns of injury associated with these idiosyncratic reactions relate to the mechanism of damage and the cells involved.[92] Many patterns have been described but it is massive hepatic necrosis that most often presents as ALF. Liver failure associated with severe cholestasis and veno-occlusive disease is also seen.[92]

Liver injury usually is seen within 6 months after the initiation of therapy. Even if the diagnosis of drug-induced liver failure is considered, a search for other possible causes should be performed. Although any drug is capable of inducing liver injury, more common causes include herbal remedies and recreationally used drugs such as "ecstasy" and cocaine. If suspected, a comprehensive history with a timetable of drug initiation should be constructed. Management includes stopping the offending drug and supportive care. Transplantation should be considered once liver failure occurs as the outcome from drug-induced liver failure, other than that induced by acetaminophen, can be poor.[93] Presentation profiles for various drugs causing ALF are shown in Table 71.1.[68]

Pregnancy-Induced Liver Disease

In general, pregnancy-associated liver failure has the best prognosis when compared to all other causes of ALF, and prompt recovery can be expected with delivery of the fetus in most cases, if recognized early enough. Pregnancy-associated liver failure can present in several ways, including the syndromes of preeclampsia and the HELLP syndrome (hemolysis, elevated liver function tests, and

TABLE 71.1 Idiosyncratic Drug Reactions and Effects on Cells

Type of Reaction	Effect on Cells	Examples of Drugs
Hepatocellular	Direct effect or production by enzyme-drug adduct leads to cell dysfunction, membrane dysfunction, cytotoxic T-cell response	Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin
Cholestasis	Injury to canalicular membrane and transporters	Chlorpromazine, estrogen, erythromycin and its derivatives
Immunoallergic	Enzyme-drug adducts on cell surface induce IgE response	Halothane, phenytoin, sulfamethoxazole
Granulomatous	Macrophages, lymphocytes infiltrate hepatic lobule	Diltiazem, sulfa drugs, quinidine
Microvesicular fat	Altered mitochondrial respiration, β-oxidation leads to lactic acidosis and triglyceride accumulation	Didanosine, tetracycline, acetylsalicylic acid, valproic acid
Steatohepatitis	Multifactorial	Amiodarone, tamoxifen
Autoimmune	Cytotoxic lymphocyte response directed at hepatocyte membrane components	Nitrofurantoin, methyldopa, lovastatin, minocycline
Fibrosis	Activation of stellate cells	Methotrexate, excess vitamin A
Vascular collapse	Causes ischemic or hypoxic injury	Nicotinic acid, cocaine, methylenedioxymethamphetamine
Oncogenesis	Encourages tumor formation	Oral contraceptives, androgens
Mixed	*Cytoplasmic and canalicular injury, direct damage to bile ducts*	*Amoxicillin-clavulanate, carbamazepine, herbs, cyclosporine, methimazole, troglitazone*

IgE, Immunoglobulin E.
From Lee WM. Drug-induced hepatotoxicity. *N Engl J Med.* 2003;349:474–485.

low platelets), liver rupture, and acute fatty liver of pregnancy (AFLP).[94] Any cause of ALF can occur during pregnancy, and in particular viral hepatitis can be particularly fulminant in its course. This is especially true for hepatitis E and herpes simplex virus infection.

Although originally thought to be a variant of preeclampsia there is evidence that HELLP syndrome may be a separate entity and in fact more related to AFLP.[95] Both HELLP syndrome and preeclampsia appear to be related to an endothelial injury, possibly immunologically initiated with activation of the coagulation and complement cascades and an imbalance of prostaglandin and thromboxane, resulting in increased vascular tone, microangiopathic hemolytic anemia, and vascular thrombosis.[96] About 2% to 12% of severe preeclampsia is complicated by HELLP.[94] HELLP is thought to occur in approximately 1 in every 1000 live deliveries, and patients usually present in the third trimester with nonspecific signs often seen in preeclampsia such as weight gain as the result of edema and hypertension. In addition, right upper quadrant pain accompanied by nausea and vomiting is commonly seen. Laboratory abnormalities include hyperbilirubinemia owing to liver dysfunction and evidence of hemolysis. Transaminase levels are modestly raised and the platelet count is usually less than 100,000/μL. Liver biopsy, although commonly normal in preeclampsia, shows specific changes of periportal necrosis and fibrin microthrombi. Microvascular steatosis may also be present.[96] The liver failure associated with HELLP syndrome is manifest as a prolonged prothrombin time and ascites. Renal failure is common. Maternal mortality rate is low but fetal mortality rate has been reported to be between 20% and 60%, although some reports suggest this is lower at 7% and associated with twin pregnancies.[96–98] The treatment of choice is delivery of the infant. Conservative therapy is associated with an increase in both maternal and fetal complications.

Spontaneous rupture of the liver can occur in the setting of both preeclampsia and the HELLP syndrome, although it can occur de novo. It often presents with sudden onset of right upper quadrant pain accompanied by signs of hypovolemia or shock and is more common in multiparous women.[96] Spontaneous rupture of the liver has high maternal and fetal mortality rates. Its pathogenesis is unclear, but it appears that periportal hemorrhage associated with HELLP syndrome may occur close to the capsule, resulting in lifting and bleeding into the potential space. These areas of the capsule then coalesce and rupture. Management of this devastating complication includes prompt delivery of the fetus, local surgical control with packs, and aggressive management of the accompanying coagulopathy. Embolization of any feeding vessels in the liver may be of utility if such skills are available. Hepatectomy followed by liver transplantation can be lifesaving and has been performed.

AFLP occurs during the third trimester of pregnancy and should be considered in any patient exhibiting signs of liver dysfunction. It is uncommon with an incidence of approximately 1 in 6659 live births.[99] If left untreated, maternal and fetal mortality rates are high. The treatment of choice is delivery, and prompt recovery can then be expected. There is usually a prodromal illness over a couple of weeks with nonspecific symptoms progressing to jaundice and encephalopathy. Symptoms and signs of preeclampsia or HELLP syndrome are seen in a third of cases, and there is some evidence of a common origin owing to a fetal fatty acid metabolism disorder.[95] Diagnosis is critical and it should be differentiated from viral hepatitis or hepatic failure related to other causes. Liver biopsy can aid in the diagnosis and can be performed via the jugular route if coagulopathy precludes the conventional approach. Characteristic zone 3 microvesicular steatosis is seen. Delivery is the best treatment if diagnosed early. Characteristic features include normoblasts on blood smears and high serum urate levels. Bleeding can be a major problem during operative delivery. On occasion transplantation may be the only viable option. Triggers for transplantation in pregnancy-induced liver failure are not well defined and the King's College Criteria perform poorly. Arterial lactate in the setting of encephalopathy appears to be the best predictor.[98]

Wilson Disease

Wilson disease is a rare autosomal recessive disorder resulting from copper toxicity with primarily brain and liver manifestation. It usually presents in the second or third decade of life, although it can present from early childhood until late middle age.[100] The disease can present with predominantly liver or neurologic symptoms. Neurologic symptoms relate to the distribution of copper to the basal ganglia and result in movement disorders. Patients presenting with liver disease may presents with an active hepatitis, established cirrhosis, or ALF. Other signs such as Kayser-Fleischer rings are associated but not pathognomonic for Wilson disease. These green-brown rings in the cornea result from the deposition of copper.

ALF caused by Wilson disease can present at any age but more commonly presents in the early 20s. High urinary copper excretion is possibly the most predictable laboratory finding, although the patient may be anuric on presentation. A low serum ceruloplasmin is an additional indicator but again is unreliable in ALF. A high serum bilirubin level in combination with modest elevations of transaminases and alkaline phosphatase is often seen, as is intravascular hemolysis, contributing to the raised bilirubin level. Patients with severe liver failure caused by Wilson disease have an almost 100% mortality rate without liver transplantation, which should be considered as soon as the diagnosis is made.[100] There is debate as to whether liver failure secondary to Wilson disease is truly ALF, as cirrhosis is invariably present on liver biopsy at the time of presentation. Nevertheless, many patients present acutely and the presentation is often catastrophic. In this sense the timing of the onset and the lack of previous symptoms place fulminant Wilson disease in the ALF group. In an uncontrolled series the administration of D-penicillamine before the onset of encephalopathy was associated with survival.[101]

Neoplastic Infiltration

Poorly differentiated solid tumors such as breast and lung and hematologic malignancies can sometimes present with a syndrome of liver failure. There is often diagnostic delay and difficulty.

The syndrome can be considered part of the hypoxic hepatitis group as zone 3 necrosis is often seen. The metabolic demand of the neoplastic cells and congestion within the liver sinusoids results in infarction of hepatocytes. Hepatosplenomegaly and a raised alkaline phosphatase are often present. Other stigmata, including palpable lymphadenopathy and marrow or peripheral blood film changes, may be present. Imaging may be diagnostic, especially with massive hepatomegaly, but biopsy may be required.[102]

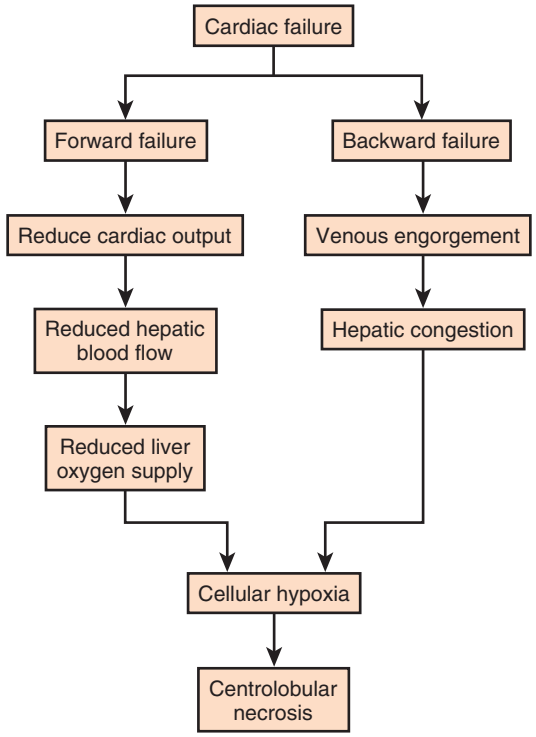
Budd-Chiari Syndrome

ALF secondary to Budd-Chiari syndrome is usually fatal without transplantation. The syndrome is defined as outflow obstruction to the hepatic veins and the underlying pathogenesis is thrombosis in the majority, but tumor invasion or vascular membrane obstruction may be the cause. This is a rare disorder that occurs

predominantly in young adults and affects more women than men. Overall, the 5-year survival rate varies from 50% to 80% in different series.[103] The vast majority of patients with the syndrome have at least one predisposing clotting abnormality, either congenital or acquired, such as a malignancy, myeloproliferative disorders, protein C or S deficiency, polycythemia rubra vera, lupus anticoagulant, antithrombin III deficiency, antiphospholipid syndrome, and so on.[104] The fulminant form of the syndrome in which the patient develops encephalopathy within 8 weeks of the onset of symptoms is rare, and it is much more common for Budd-Chiari syndrome to present in a subacute form over a 3- or 4-month period, characterized by ascites, abdominal pain and hepatomegaly, jaundice, coagulopathy, and raised AST and alkaline phosphatase levels. Others present with signs of portal hypertension, including refractory ascites and variceal bleeding, and relatively intact hepatocellular function. The diagnosis is made with the combination of clinical presentation and imaging, including Doppler ultrasound studies of the hepatic vessels, plus or minus liver histologic examination, usually via the jugular route because of coagulopathy. Management of the syndrome depends on the manner in which it presents and the underlying cause. Medical management of the syndrome involves the use of anticoagulants and diuretics in an attempt to control ascites. Thrombolysis can be attempted in selected patients with recent onset of disease.[105] In patients in whom there is progression to signs and symptoms of liver cell failure, some sort of portosystemic shunting procedure may reduce symptoms and prevent progression of the disease, allowing time for collateral vessels to develop. Transjugular intrahepatic portosystemic shunt (TIPSS) is most often attempted unless there is evidence of a hypertrophied caudate lobe and inferior vena cava compression, making mesoatrial shunting a better option. In patients with signs of liver failure care must be used when considering a TIPSS procedure, as this can precipitate decompensation and rapid progression to ALF.[106] Liver transplantation is ultimately the only option in many patients in whom there is a failure of medical and shunt therapy as well as in the fulminant presentation of the syndrome.[107] Anticoagulation is usually necessary in the immediate postoperative period.

Veno-Occlusive Disease of the Liver

Veno-occlusive disease (VOD) of the liver is a nonthrombotic obstruction of the sinusoids, which may extend to the central veins, in the absence of thrombosis or other underlying disorder of the hepatic veins.[108] As a result of a toxic challenge, there is acute damage to the endothelial cells, followed by their detachment and their embolization in the central area of the lobule, where they cause a postsinusoidal outflow block.[108] The most common cause is myeloablative chemotherapy induction regimens in preparation for bone marrow transplantation (BMT), being seen in up to 54% in some older series.[109] Other toxins are known to cause it and it was first described in children after the ingestion of herbal teas in South Africa; it represents a nonspecific response to certain noxious stimuli. Particular induction regimens such as high-dose cyclophosphamide and total body irradiation are implicated in the pathogenesis. The more aggressive induction regimens appear to result in a higher incidence of VOD. Recent reduction in incidence may be due to a reduction in the use of myeloablative regimens and better monitoring of plasma drug concentrations.[110] The symptoms of VOD usually occur within 2 weeks of BMT. The development of jaundice, hepatomegaly, abdominal pain, and encephalopathy in the setting of recent BMT strongly suggests the diagnosis. Severe cases are characterized by evidence of hepatocellular necrosis and a high AST concentration. In 25% of cases, which are characterized as severe, the syndrome is progressive, leading to ALF.[111] Treatment options in these patients are limited as the outcome is poor with medical management or liver transplantation, although there is hope that newer therapies such as defibrotide (a DNA derivative anticoagulant with multiple modes of action), if initiated early before the onset of multiple-organ failure, may improve the outlook. In addition, the prophylactic use has been tried in several uncontrolled reports.[108]



• **Fig. 71.8** The most common cause of hypoxic hepatitis results from a combination of liver congestion owing to chronic cardiac failure and an acute drop in cardiac output causing liver ischemia.

Hypoxic (Ischemic) Hepatitis

"Shock liver," "ischemic hepatitis," or more recently hypoxic hepatitis is the most common cause of significant rise in serum aminotransferase (S-AT) seen in hospitalized patients (Fig. 71.8).

There is often an underlying chronic reduction in oxygen delivery to the liver owing to comorbid disease states such as congestive cardiac failure or chronic respiratory failure. There is then a subsequent sudden acute drop in oxygen delivery resulting from a decrease in cardiac output or further hypoxia.

Diagnostically, there are three conditions that should be met: the appropriate clinical setting of circulatory, cardiac, or respiratory failure with a massive rise in S-AT and the exclusion of other causes of massive hepatic necrosis, such as viral or drug-induced liver failure.[102]

In patients with chronic congestive heart failure (CCHF), liver congestion is common. This is usually manifest as mild abnormalities of liver function test results, a prolonged prothrombin time, and mild ascites in some. Hepatic congestion is usually clinically unapparent unless jaundice is present, which can occur after multiple bouts of CCHF. Chronic congestion can lead to fibrosis and ultimately cirrhosis in some patients. Acute rises in serum transaminase levels and prolongation in prothrombin time, representing acute hepatic necrosis, most commonly develop in patients with

CCHF when there is a sudden drop in cardiac output resulting from an event such as an arrhythmia or myocardial infarction. It is relatively uncommon for the liver to become involved during shock states because of the huge redundancy in blood supply and the ability of the portal system to compensate for any reduction in hepatic arterial flow. If, however, portal flow is already compromised because of passive congestion, then an acute drop in hepatic blood flow can result in ischemia. It is uncommon for hypoxic hepatitis to occur without a recognizable precipitant, but it can occur as the result of a silent myocardial infarction or arrhythmia, for example. It can occur before the diagnosis of CCHF has been made or be the primary diagnostic event in a younger patient with a cardiomyopathy. Clinically, severe ischemic hepatitis becomes apparent between 24 and 48 hours after an event and is manifest as huge rises in S-AT (up to 10–20 times normal). There is prolongation of the prothrombin time, encephalopathy, hypoglycemia, jaundice, and renal failure. The syndrome is usually self-limiting once the hemodynamic disturbance has receded, and there is a rapid fall in serum transaminase levels (usually 50% in the first 72 hours).[112] Occasionally, progressive liver cellular failure leads rapidly to death. Management should be aimed at investigating and supporting the underlying cause.

Heat Stroke

Liver failure in the setting of heat stroke can be considered to be part of the hypoxic hepatitis group of causes. The argument for its inclusion here is the zone 3 necrosis seen in the liver after autopsy in patients who survive long enough for a reperfusion injury to occur.[102] The pathophysiology is complex but is probably related to dehydration and cardiovascular collapse plus increased oxygen demand and acute cardiac failure.[102] Exertional heat stroke may occur in new recruits to the army or police force engaging in physical initiation programs. It can also occur in unacclimatized athletes in hot conditions or with drug overdoses such as cocaine and hyperpyrexia syndrome such as those induced by MDMA (methylenedioxy-N-methylamphetamine). It is a potentially devastating syndrome that can lead to multiple-organ failure and death. It ranges from mild involvement to ALF and is seen to develop during the first few days after the event. Management is supportive and the majority improves over a period of days to weeks. Liver transplantation has been used in severe cases but the outcome is poor owing to coincident organ failure.[113]

Mushroom Poisoning

A number of fungi are associated with the induction of liver failure after ingestion. Of these, the most common and most deadly are of the genus Amanita. Amanita-associated hepatotoxicity follows a triphasic response after ingestion. The first is a self-limiting, nonspecific gastrointestinal upset that occurs within the first 6 to 24 hours. Nausea and vomiting, abdominal cramps, and diarrhea are often seen and it can mimic food poisoning. This is followed by a period of recovery and a few days later by progressive liver failure.

Management is essentially supportive, although many specific therapies have been tried in the treatment of Amanita toxicity such as high-dose penicillin, silibinin, cimetidine, and NAC, but none has been shown to improve outcome.[114]

Clinical Course

History and Physical Examination

The presentation and clinical course of ALF depends on its cause and the rate of progression of the syndrome. This varies widely from admission via an emergency department after an acetaminophen overdose or acute viral hepatitis versus admission from a hepatology outpatient department in a patient with progressive jaundice and ascites. Owing to its relative rarity, the diagnosis can often be missed during initial contact and this delay may detrimentally influence the outcome.

The history initially focuses on the rate of progression of the illness and any clues to the cause. The first symptoms are often the onset of jaundice (typically noticed by a relative). Any history of foreign travel or high-risk behavioral activity (intravenous drug use or unprotected sex) associated with the contraction of viral hepatitis should be investigated. A thorough drug history should be taken for prescribed and recreational drug use for the preceding 6 to 10 weeks. Drug therapy or recreational use that can induce or inhibit hepatic enzymes should be noted. If the patient is unable to provide this information, the relatives and the patient's primary care physician should be contacted for help.

The history may be self-evident in the case of acetaminophen hepatotoxicity, especially if the patient self-presents after deliberate self-harm. However, therapeutic misadventure, which is a relatively common cause of hepatotoxicity, especially in the United States, may not be obvious unless considered by the physician.[115] Any patient presenting with coma should have a drug screen (including acetaminophen).

Subacute liver failure has, by definition, a more insidious onset. Jaundice is often preceded by nonspecific symptoms of fatigue and general malaise. Abnormal liver enzyme levels are often revealed during the initial workup. Subsequent investigations include viral, iron, copper and genetic studies, in addition to attempting to rule out decompensation of chronic liver disease as a cause the current symptoms and signs. Liver biopsy may be considered in subacute liver failure (Fig. 71.9).

Initial Resuscitation and Emergency Care

Patients presenting with acute or hyperacute liver failure tend to follow a similar course irrespective of cause. Initial therapy and emergency care are dictated by the condition of the patient at presentation. Liver failure is a multisystem disease and can progress very rapidly to multiple-organ failure.

Patients presenting with rapidly progressive hepatic encephalopathy via the emergency care system often are intubated and ventilated at the time of or shortly after admission. Emergency physicians often perform a head computed tomography (CT) scan because of diagnostic uncertainty.

The symptoms and signs of hepatic encephalopathy in ALF are subjectively different from those seen in decompensated chronic liver disease or in patients with stable chronic encephalopathy. Agitation and aggressive behavior are more common in ALF. This may be based on an increased turnover of the excitatory neurotransmitter glutamate in ALF associated with an acute increase in cerebral ammonia uptake.[116]

The West Haven criteria, designed to assess coma grade in patients with cirrhosis, are often applied to patients with ALF and are useful because of familiarity.[117] However, once the patient becomes unconscious at grade IV encephalopathy, the scale does not provide any further information and is too crude to provide a clinically useful description of the level of consciousness. The Glasgow Coma Scale (GCS) score, although not assessed specifically in this setting, is useful in relating clinical information to others.[118] Encephalopathy grade can progress very quickly, especially with hyperacute presentation. Intubation and sedation are recommended once grade III encephalopathy (GCS < 10) is achieved because of

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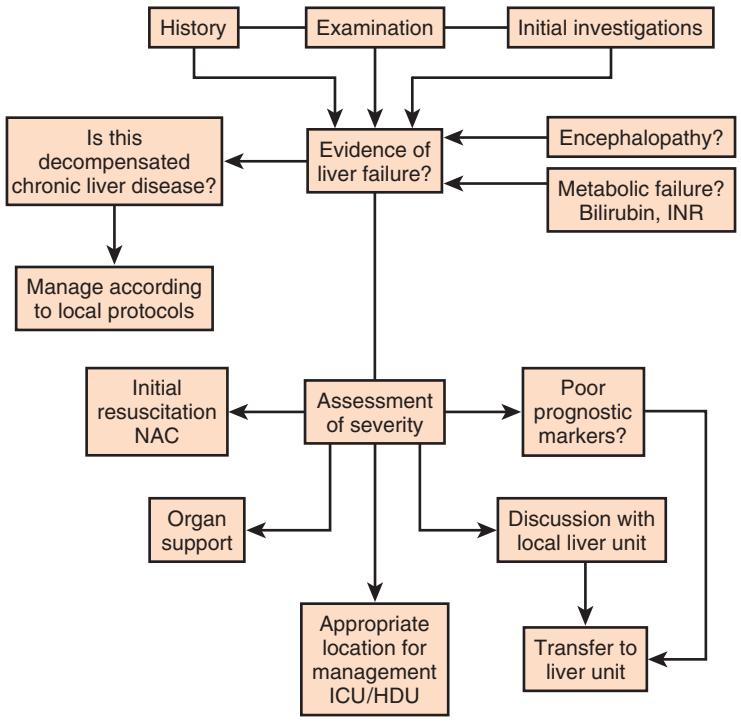
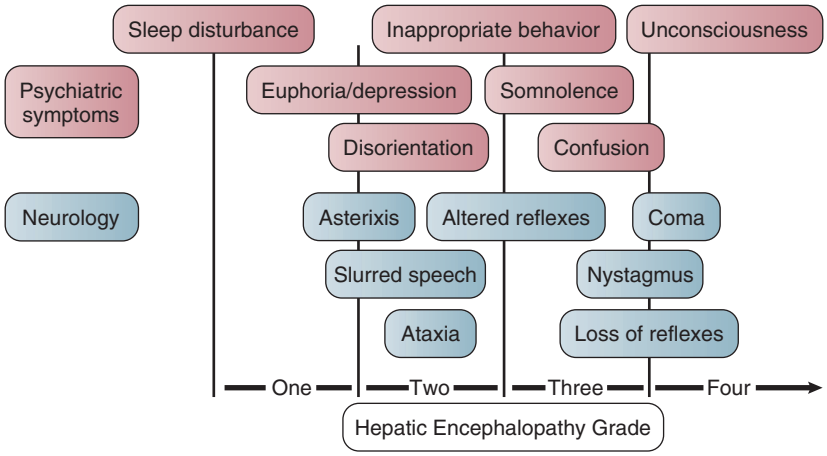


• **Fig. 71.9** Initial management of a patient presenting with liver failure. *HDU,* High-dependency unit; *ICU,* intensive care unit; *INR,* international normalized ratio; *NAC,* N-acetylcysteine.



• **Fig. 71.10** Hepatic encephalopathy grade in acute liver failure.

the attendant risks to airway and possibilities of raised intracranial pressure, discussed later. Fig. 71.10 describes encephalopathy grade and GCS score.

Early contact with a regional liver center should be made in any patient with signs of acute severe liver dysfunction as serial blood results and clinical signs can be relayed to the center by phone. Patients who have taken acetaminophen can often be managed by phone but plans for transfer can be made well in advance, if necessary. As liver failure progresses over the next several days, a number of organ systems may become affected.

After the safe and appropriate management of airway and breathing, focus can be directed to the correction of any circulatory dysfunction. Patients with ALF can progress rapidly to circulatory shock. The circulatory changes associated with ALF are predictable, usually associated with systemic vasodilatation and relative hypovolemia. This can be profound and require significant volume resuscitation. Monitoring at this stage should include a central venous catheter and direct arterial access for both blood pressure monitoring and repeated blood tests. Care must be given to monitoring of serum electrolyte levels because they often become deranged during this initial period. In particular, hyponatremia and hypophosphatemia are common.[119–121] This may be due to excess quantities of hypotonic fluid administration. A typical flowsheet of investigations of a patient presenting with acetaminophen poisoning from a referring hospital is shown in Table 71.2.

Regardless of cause, patients with significant liver damage or signs of secondary organ dysfunction should be managed within the ICU. The speed at which patients' conditions deteriorate can

TABLE 71.2 Acetaminophen Overdose Case Example: Laboratory Data

A 20-year-old woman, an intravenous drug user, took a 250-tablet overdose (500 mg of acetaminophen) the day before presentation at the hospital emergency department. She received N-acetylcysteine alanine transaminase 25 h after the ingestion. The patient was then transferred and listed for transplantation. The table shows the results of laboratory testing.

Laboratory Tests				
Dates	7/10/2003	8/10/2003 AM	8/10/2003 PM	9/10/2003 AM
INR	2.08	3.17	3.79	6.2
Bilirubin (mmol/L)	12	37		35
AST/ALT (U/L)	273/223	8,535/4,254		15,734/10,060
Alkaline phosphate (U/L)				100
Albumin (g/L)	52	45		30
Glucose (mmol/L)	4.1		7.5	5.2
Urea (mmol/L)		5.5		3.0
Creatinine (μmol/L)		86	83	128
pH		7.38	7.41	7.39
Lactate (mmol/L)			5.4	

AST/ALT, Aspartate transaminase/alanine transaminase; *INR*, international normalized ratio.

be very rapid and it is not uncommon for hepatic encephalopathy to progress from grade 0 to grade IV over several hours.

For prognostic reasons it is important not to avoid correcting any biochemical coagulopathy at this stage if possible. Despite quite significant prolongation of prothrombin time, bleeding from line sites is uncommon in the initial stages of ALF. In fact, there is evidence that the patients are prothrombotic in vivo.[122]

Investigation in a Patient With Suspected Acute Liver Failure

Initial investigations provide a baseline from which important diagnostic and prognostic information is taken. Serial blood test measurements should be performed as severity and prognosis are assessed over time from initial presentation (Table 71.3). Depending on the manner and speed of presentation, a complete blood cell count, clotting tests, liver function tests, arterial blood gas measurements, and ammonia level testing should be performed twice daily, if not more often, in the early stages to assess progression of the illness. A liver ultrasound scan to assess liver size and blood supply should be performed.

Transfer Criteria Guide

ALF is a sporadic syndrome with a case incidence of about 2000 per year in the United States.[123] Management is complex and liver transplantation is the only effective therapy in severe cases. Transfer to a unit with experience in the management of these patients, preferably one with a liver transplant program, provides optimal care. It is often difficult to decide when or whether to transfer a patient with acute liver dysfunction and this decision varies according to cause and presentation. The best described clinical course is that after severe acetaminophen poisoning after a deliberate overdose.[52] Staggered overdose and therapeutic misadventure are less predictable in their clinical course but often have a poor outcome and can be considered a poor prognostic risk factor.[124]

The following criteria for transfer are based on expert opinion and have not been subjected to rigorous study and err on the side of caution[72] (Fig. 71.11):

- In patients with a subacute presentation it is better to transfer patients before they have progressed to grade II encephalopathy because of the additional complications associated with transferring ventilated patients.
- Patients with acute or hyperacute liver failure showing signs of early encephalopathy should be intubated and ventilated before transfer. This can occasionally result in disagreement between referring hospitals and receiving liver units on how the transfer should be managed. There are many anecdotal stories from liver units around the world describing patients who become unmanageable during transfer in planes, helicopters, and road ambulances, resulting in injury to patients and staff.
- Heroic transfers are almost always inappropriate. Patients should not be considered for transfer if they require rapidly accelerating inotropic support, have severe hypoxemia, or already have fixed dilated pupils. There is little point in a patient dying in an ambulance.

Management

Supportive Care

Airway and Ventilation

Patients with ALF who reach grade II or higher encephalopathy require intubation and ventilation to provide safe management in the setting of increasing agitation, protection of the airway from stomach contents, or transfer from peripheral hospitals. In patients with severe liver failure, it can be expected that encephalopathy grade will progress; therefore waiting until some predefined stage before intubation often delays adequate resuscitation and monitoring.

Controlled ventilation to a normal partial pressure of arterial carbon dioxide ($PaCO_2$) is recommended at this stage. The use of

TABLE 71.3 Initial Investigation and Common Findings

Laboratory Test	Finding(s)
Complete blood cell count	Platelets often low
Urea and electrolytes	Serum sodium often low, especially in acetaminophen hepatotoxicity Urea often low because of reduced production Serum creatinine is useful prognostic marker
Liver enzymes	Serum AST/ALT variable, very high in acetaminophen toxicity Bilirubin is prognostic marker in nonacetaminophen liver failure Also can be high in Wilson disease from hemolysis
Phosphate	Often low, especially in acetaminophen toxicity High level indicative of poor prognosis; suggests lack of regeneration
Magnesium	Often low
Prothrombin time, international normalized ratio (INR)	Very sensitive indicator of liver function Has prognostic significance in all forms of acute liver failure May improve with vitamin K in deficiency states
Viral serology for all known hepatotropic viruses	
Urinary copper, plasma ceruloplasmin if Wilson disease is suspected	Ceruloplasmin level often very low but can be normal Urine copper usually high
Arterial ammonia	Has some prognostic value and may be an indicator of cerebral edema in patients at risk
Arterial whole blood lactate	Very sensitive marker for liver function, particularly in acetaminophen toxicity High level indicative of poor prognosis
Serum glucose	Hypoglycemia common
β-Human chorionic gonadotropin in women	Unwanted pregnancy can be a precipitant of deliberate self-harm

AST/ALT, Aspartate transaminase/alanine transaminase.

Referral to specialist unit after acetaminophen ingestion. Any of these criteria should prompt referral.

Day 2	Day 3	Day 4
Arterial pH < 7.30 INR > 3.0 or PT > 50 s Oliguria Creatinine > 300 μmol/L Hypoglycemia	Arterial pH < 7.30 INR > 3.0 or PT > 50 s Oliguria Creatinine > 300 μmol/L Encephalopathy Severe thrombocytopenia	INR > 6 or PT > 100 s Progressive rise in PT to any level Oliguria Creatinine > 300 μmol/L Encephalopathy Severe thrombocytopenia

INR, International normalized ratio; *PT,* prothrombin time.

Referral to specialist unit in non-acetaminophen ingestion etiologies. The presence of any of these criteria should prompt referral.

Hyperacute	Acute	Subacute
Encephalopathy Hypoglycemia Prothrombin time > 20 s INR > 2.0 Renal failure Hyperpyrexia	Encephalopathy Hypoglycemia Prothrombin time > 20 s INR > 2.0 Renal failure	Encephalopathy Hypoglycemia (less common) Prothrombin time > 20 s INR > 1.5 Renal failure Serum sodium < 130 μmol/L Shrinking liver volume

INR, International normalized ratio.

• **Fig. 71.11** Transfer criteria to a specialist unit. (From O'Grady JG. Acute liver failure. *Postgrad Med J.* 2005;81:148–154.)

hyperventilation is not indicated unless in a salvage setting with further monitoring.[125,126]

Circulation

The circulatory changes associated with ALF can be profound.[127] The pathologic bases for these changes are incompletely understood but similar in many ways to changes observed in patients with a systemic inflammatory response owing to sepsis or trauma. The pattern observed depends on the cause and the rate of onset of the syndrome. In hyperacute liver failure as the result of acetaminophen overdose, patients can develop fulminant peripheral cardiovascular collapse that can be an early mode of death.[128] Others with a more subacute onset can develop peripheral vascular changes similar to those with decompensated chronic liver disease.

Fluid resuscitation should be commenced as soon as possible after presentation and should be directed by invasive monitoring. The type of fluid used for resuscitation has not been subjected to controlled trials in this setting, but large volumes of hypotonic fluids should be avoided as this may contribute to cerebral swelling seen in this group, and it has been shown that hypertonic saline solution infusion reduces the incidence of intracranial hypertension (ICH) in patients with ALF.[119]

If mean arterial pressure remains less than 65 mm Hg after adequate fluid resuscitation, a vasopressor should be commenced. Norepinephrine is the vasopressor of choice as it induces vasoconstriction without the induction of lactate production as often seen with the use of epinephrine, although epinephrine has been used in this setting successfully.

Vasopressin and its longer-acting analog terlipressin have been used as vasopressors in septic and cardiogenic shock.[129,130] Terlipressin results in profound systemic vasoconstriction and, if used inappropriately, has the potential to reduce cardiac output and hence oxygen delivery. It has been shown to increase ICH in ALF owing to an increase in cerebral blood volume because of the breakdown in cerebrovascular autoregulation.[131] However, the data are mixed and a more recent study suggests that vasopressin/terlipressin may be a useful adjunct to norepinephrine in ALF.[132]

The majority of patients presenting with ALF are young adults, and as a result, comorbid cardiac dysfunction is usually absent. Cardiac depression has been reported in association with acetaminophen.[128] On occasion cardiac disease can present as ALF in the case of ischemic hepatitis.

Relative adrenal insufficiency has been shown to occur in patients with septic shock and in patients with decompensated chronic liver disease and ALF.[44,133–135] The use of stress doses of corticosteroids in ALF has been shown to reduce norepinephrine requirements in patients with ALF.[136] The effect on survival is uncertain, though.

Renal Support

AKI is common in ALF with a reported incidence of up to 70%.[137] Acetaminophen causes direct renal tubular dysfunction, possibly by affecting membrane protein function, and occasionally renal failure is the predominant organ affected.[138,139] As a result, AKI can be expected in this setting. Although it is most commonly associated with acetaminophen, the incidence in other causes, such as Wilson disease as a result of the direct toxic effects of copper, is also high but it is less prominent in ALF owing to viral hepatitis or seronegative hepatitis.

The Acute Kidney Injury Network (AKIN), proposed a definition of AKI in ICU patients, defined as an absolute increase in serum creatinine of greater than 0.3 mg/dL or higher (26 µmol/L) within 48 hours. Once AKI is established, a staging system then defines the severity of the AKI. These criteria were then adopted by the international multidisciplinary Kidney Disease Improving Global Outcomes (KDIGO) in their 2012 clinical practice guideline.[140] The use of hepatorenal syndrome in ALF is also inappropriate because this term does not adequately describe the often rapid clinical deterioration. This is not to say that altered systemic and renal hemodynamics do not contribute to the pathophysiology of renal failure as they do in critical illness in general. In the subacute presentation of this syndrome, early renal dysfunction can be similar in presentation to that seen in end-stage chronic liver disease with sodium and water retention in the absence of intrinsic renal damage.[141]

Management of AKI is essentially the same as in ALF and other forms of critical illness and consists of maintenance of intravascular volume, cardiac output, and mean arterial pressure.[123,142]

Renal replacement therapy is necessary in most patients with ALF at some time. Continuous venovenous hemofiltration (CVVH) is the most efficient and safest method for renal support and should be started early.[143] Indications for the early use of renal support are not limited just to oliguria. CVVH has been shown to improve hemodynamic stability in patients with critical illness and has been used as salvage therapy in patients receiving high-dose vasopressors.[144] High-volume hemofiltration (4000 mL/h ultrafiltrate exchange) has been studied in ALF and has been shown to reduce serum lactate, base deficit, and norepinephrine requirements when compared with historical control subjects.[145] Evidence for survival benefit for high-dose renal replacement therapy in critical illness is lacking, however, and recent high-quality studies suggest that there is a ceiling of dose above which there is no additional survival benefit.[146,147] Patients with liver failure do not tolerate the lactate load associated with lactate-buffered replacement fluid during CVVH, which can induce a systemic acidosis.[148] Also, the infusion of large quantities of lactate-containing fluid reduce the utility of serum lactate as one of the most important prognostic indicators.[149] As a consequence, the use of bicarbonate hemofiltration is recommended.[150]

CVVH can often be performed successfully without anticoagulation in ALF. If required, a loading dose of 2000 units of heparin and thereafter 500 to 1000 units/h, depending on the activated clotting time, can be used if needed to allow CVVH. If bleeding is a problem or there is severe thrombocytopenia, epoprostenol should be instituted (2.5–5 ng/kg per minute) either alone or in association with low-dose heparin (100 units/h). Blood flow rates of 200 mL/min and above will help with filter life.

Intracranial Hypertension

Etiology

The hallmark of ALF is the development of hepatic encephalopathy, which with severe liver failure progresses to deep coma. In addition to the progressive coma, early reports of patients with signs of raised intracranial pressure (ICP) were noted in the literature.[151] What is less clear is whether they possess a common cause. Certainly patients with subacute liver failure can develop a deep coma without signs of cerebral edema, but patients with signs of ICH always develop high-grade encephalopathy before this.

Cerebral edema was noted and commented on in the seminal clinicopathologic review of servicemen presenting with fulminant epidemic hepatitis during the East Asian campaign of the Second World War.[53] However, the recognition that cerebral edema was a distinct clinical entity and cause of death associated with ALF did not become clear until much later.[151,152]

Management strategies place the risk of ICH at the forefront of care, and prophylactic therapy, monitoring, and treatment are widely debated in the literature.[153,154] The incidence of cerebral edema in ALF is not completely clear and is dependent on the cause of ALF, the severity, and the rate of onset. It is important to distinguish between ICH and cerebral edema. The former requires the measurement of pressure within the cranial vault and results in brain ischemia and signs of tentorial herniation. The latter is difficult to define clinically and depends on how earnestly it is sought. CT and postmortem studies have suggested an incidence between 50% and 80% of those with high-grade encephalopathy.[151,155] The pathologic changes of cerebral edema and ICH in ALF are not completely understood, but in recent years progress has been made in understanding the processes involved.[156]

Ammonia has long been implicated as important in hepatic encephalopathy and, as the evidence mounts, is increasingly recognized as an important factor in the cause of cerebral edema in ALF.[157] Recent work has shown that whole blood ammonia predicts outcome and the chances of cerebral herniation.[158,159] Electron microscopic analysis of postmortem brain biopsy and gravimetric analysis of brain water content, in animal models, have shown that swelling occurs in the gray matter and that astrocytes are the main target.[160,161] Ammonia may induce astrocyte swelling by a number of possible mechanisms. It is detoxified in astrocytes by combining with glutamate to produce glutamine. Astrocytes are the only cell type in the brain that contains glutamine synthetase, and this normal pathway maintains the ratio of glutamate to glutamine within astrocytes and neurons. The raised serum ammonia induces a buildup of glutamine within astrocytes, increasing the osmotic potential, absorption of water, and an increase in volume. Evidence of this effect can be inferred by the fact that inhibition of glutamine synthetase, which catalyzes the reaction, prevents brain swelling in experimental models.[162] An osmotic effect may not be the only mechanism by which glutamine induces cellular swelling, however, but there is circumstantial evidence that it occurs to some extent. In subacute and chronic liver disease there is time for adaptation to the increase in astrocyte osmotic potential by the excretion of intracellular osmolytes such as myoinositol.[163] In ALF there is less time for adaptation because of the rapid increase in intracellular glutamine.

Other possible mechanisms include a breakdown in cellular energy metabolism induced by an increase in intracellular glutamine and ammonia. Impairment of α-ketoglutarate dehydrogenase and pyruvate dehydrogenase induced by oxidative stress and ammonia results in a breakdown in astrocyte energy production and an increase in glycolysis. This is supported by an increase in extracellular lactate and brain lactate flux in clinical studies.[116,125] Mitochondrial dysfunction induced by ammonia may also play a role.[157]

In addition to the cytotoxic edema seen early in ALF, changes in cerebral blood volume may play an important role in the development of ICH. Cerebral blood flow varies widely in patients with ALF, and the normal close relationship between cerebral metabolism and flow appears to be lost.[164] In animal models of liver failure there is a gradual increase in cerebral blood flow but this situation is less clear in human studies.[156,165] Cerebral metabolism is generally reduced with high-grade encephalopathy in patients with ALF, and there is evidence that relative or absolute cerebral hyperemia can contribute to ICH.[131,166]

An increase in cerebral blood flow may induce ICH by a number of mechanisms and induce further cerebral swelling. This could occur owing to an increased flux of potentially toxic metabolites such as ammonia or by an increase in cerebral water content because of an increase in cerebrovascular hydrostatic pressure. The blood-brain barrier has been considered to remain intact in ALF, but recent evidence suggests that there is some impairment, although the degree to which this contributes to cerebral swelling is still being debated.[161,167]

Cerebrovascular autoregulation is lost in ALF.[165,168] The cause is unknown but a gradual cerebral vasoparesis concurs with clinical observation. Autoregulation can be restored by hyperventilation and mild hypothermia but not by the use of indomethacin.[169] It has been suggested that the increase in astrocyte glutamine plays a role in this gradual vasoparalysis and loss of autoregulation by the induction of local nitric oxide or carbon monoxide.[156] It is relatively common to find a patient with a high ICP and jugular venous oxygen saturation above 80%. This suggests a state of luxury perfusion (unregulated blood supply in excess of demand) in which an increase in cerebral blood volume in an already swollen brain accounts for the associated increase in ICP.[170]

Patients with ALF often develop a systemic inflammatory response. Depending on the cause and severity of hepatic necrosis, damage-associated molecular pattern molecules and pathogen-associated molecular pattern molecules are released from the liver. These, in turn, activate the innate and adaptive immune response, culminating in the pathophysiologic picture associated with ALF. The severity of the inflammatory response has been shown to correlate with the degree of encephalopathy and the severity of ICH, and there is evidence that neuroinflammation in response to circulating cytokines exacerbates ICH.[171]

Management

In the management of ICH in ALF it is important to target those at risk. The development of ICH sets the management of ALF apart from other forms of critical illness, and ALF remains a leading cause of death despite advances in the understanding of the etiology of ALF and management of patients with ALF.[172,173] Monitoring the pressure within the cranial vault is difficult and invasive. Despite investigation, a reliable noninvasive method for the evaluation of cerebral blood flow, cerebral oxygenation, and ICP remains elusive.[174]

There are important points that need to be considered when managing a patient with ALF and possible raised ICP:

- Prediction of patients at risk of ICH
- How to monitor the brain
- Prophylactic management
- Treatment of established ICH

Predicting Intracranial Hypertension

In ALF the development of cerebral edema is seen in patients with the shortest time between the development of jaundice and the onset of encephalopathy.[52] A fulminating presentation, lack of time for cerebral adaptation, and systemic burden of a necrotic liver appear to be the likely reasons. Patients with acetaminophen toxicity make up the largest number in this group. Other causes can fall into the hyperacute group, including patients with ALF owing to hepatotropic viruses, particularly HBV. In contrast, patients with subacute liver failure have a smaller risk.

It has been suggested that the incidence of ICH after acetaminophen toxicity has fallen since the mid-1980s.[175] However, it still represents a significant complication in this setting. Recent work from King's College Hospital in London suggests an incidence of 20% to 30% in all patients with ALF. Data from our own unit suggest that ICH is implicated in the death of 25% of all patients with ALF and 35% of those after acetaminophen-induced toxicity.[172,173]

• BOX 71.2 Risk Factors for Brain Swelling in Acute Liver Failure

Are There Risk Factors for Intracranial Hypertension?

- Less than 40 years of age
- Very low or high jugular venous oxygen saturation
- Significant organ dysfunction requiring support
- Severe hyponatremia <130 mmol/L
- Arterial ammonia >150 μmol/L
- Pupillary abnormalities or seizures
- High temperature, tachycardia, hypotension, signs of infection

Young age has consistently been found to be a risk factor.[151,173] Arterial ammonia concentration has been shown to correlate with death and cerebral herniation.[158,159,173,176] Recent commentary suggests that arterial ammonia should be measured serially in all patients with ALF and that ICP monitoring be instituted if the concentration is greater than or equal to 150 μmol/L.[170]

Hyponatremia in patients with ALF is common and is associated with a poor outcome in ALF,[177] and data have shown an inverse relationship between ICP and serum sodium in patients with ALF[178] (Box 71.2). The severity of the inflammatory response and organ failure are positively associated with the risk of developing ICH. Systemic inflammation may exacerbate ICH in a brain primed by ALF.[173]

Monitoring the Brain

A number of monitoring devices and methods can be used to screen for raised ICP or cerebral ischemia or both. Some of these devices are more invasive than others and the possible risks and benefits need to be understood.

CT is a standard investigation in any patient with suspected intracranial disease. Cerebral edema can be recognized in CT scans of patients with ALF and the severity correlates crudely to encephalopathy grade, but the correlation between imaging and severity of ICP measurement is poor.[155,179] As little additional information is gained, very careful consideration should be undertaken before transporting this very sick group of patients to the CT scanner. Occasionally there are diagnostic difficulties or a suspected complication of ICP bolt insertion and CT scanning might be considered.

Functional brain imaging with single positron emission tomography has been used to investigate the distribution of cerebral blood flow in ALF and magnetic resonance imaging scanning has been used to investigate the distribution of intracerebral water, but neither has found a place in clinical practice.[126,180,181]

In patients with suspected ICH the direct monitoring of cerebral oxygenation and blood flow are appealing but current methods have technical and clinical limitations. Tissue partial pressure of oxygen (P_{O_2}) and interstitial metabolites, using intraparenchymal probes, have been investigated in traumatic brain injury (TBI) and to a limited extent in ALF.[116,182] They have the advantage in traumatic injury of providing localized information around the area of injury. The use of cerebral microdialysis (sampling of the cerebral interstitial fluid using a microcoaxial catheter with a semipermeable membrane) remains a research tool in ALF at the present time.

Methods used for the estimation of global cerebral oxygenation include the sampling of jugular venous (JV) blood for oxygen saturation and products of metabolism such as lactate. A JV saturation of less than 55% suggests an ischemic brain. This can be due to a reduction in blood flow in excess of demand because of brain swelling or cerebral vasoconstriction as the result of hypocarbia if the patient is being hyperventilated. An increase in demand because of seizure activity can also manifest as a reduction in JV saturation.[183] High jugular saturation (>80%) may represent a hyperemic brain, and steps can be taken to reduce cerebral blood volume if ICP is raised. Very high JV saturation is often seen as a terminal event and may represent a complete loss of oxygen extraction by the brain (Fig. 71.12).

Near-infrared spectroscopy is a noninvasive technique used to assess the oxygen content of various organs. It can be used to determine cerebral oxygenation and changes in cerebral perfusion in ALF and warrants further investigation.

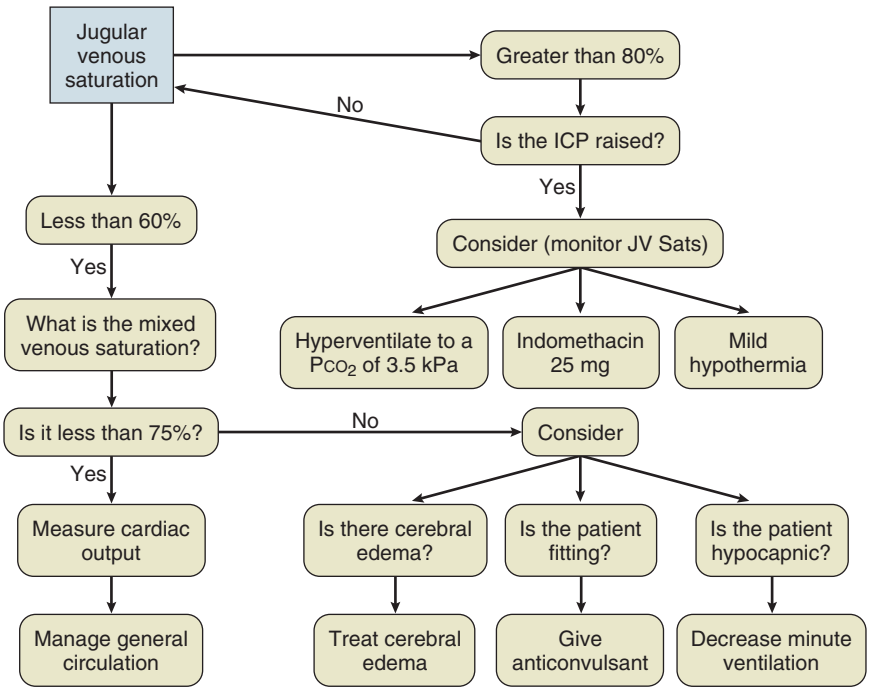
Noninvasive measurement of cerebral blood flow using transcranial Doppler has been investigated in ALF. In one study it was found to be predictive of changes in cerebral blood flow induced by hyperventilation.[184] More recent investigation has shown changes in transcranial Doppler waveform as ICP increases, but it is not clear how reproducible these results are.[185]

The recognition that ICP is raised in a significant proportion of patients with ALF and that this is implicated in significant rates of morbidity and mortality has led to the use of direct measurement of ICP with various forms of monitoring.[151,186] These techniques, although fully supported internationally in TBI, are controversial in the field of ALF, and there remains a dichotomy of opinion in most countries, with some units using them and others not.[153,154,187,188]

Controversy revolves around the lack of evidence of improved outcome with the monitoring of ICP and the risk of intracranial bleeding complicating insertion. The overall reported risk of bleeding is 5% to 20%, the majority of which is not clinically significant. Mortality rate has been reported at between 1% and 3%.[186,188] The risk of bleeding after placement is higher than that seen after TBI. There is no definitive evidence for the role of activated factor VII in this setting.[189]

It has not been possible to prove that ICP monitoring improves survival in ALF, as a randomized controlled clinical trial has not been performed to evaluate it. However, it is generally accepted that medical intervention can reduce ICP and prevent cerebral ischemia and brain herniation in patients with ALF.[170] Published data suggest that in patients with an ICP monitor the intervention rate increases compared with patients without a monitor and the length of survival in the critical care unit, if not overall survival, increases.[188,190] The majority of patients with ALF die of multiple-organ failure caused by sepsis. Intervention to reduce ICP may just prevent early cerebral death.

Although the risks of monitoring are documented, the risks of not monitoring are less clear. Without monitoring ICP, there is a tendency toward therapeutic paralysis because of uncertainty and a tendency to manage all patients as if they had raised ICP. The reassurance of a normal ICP enables a reduction in sedation and paralysis. It enables tracheal suctioning and other nursing care without the uncertainty of worsening an unknown ICP. With ICP monitoring, modest increases in ICP can be treated early before clinical signs suggest impending brain herniation. Monitoring ICP allows the calculation of cerebral perfusion pressure and, together with the monitoring of jugular oxygen saturation, affords a more complete picture of cerebral perfusion and oxygenation. The use of ICP monitoring has been advocated in the setting of liver transplantation for ALF and, of course, enables continued clinical research into the management of cerebral edema.



• **Fig. 71.12** Monitoring cerebral oxygenation with jugular bulb sampling. *ICP,* Intracranial pressure; *JV,* jugular venous; P_{CO_2}, partial pressure of carbon dioxide; *Sats,* saturation.

Prophylactic Measures

In patients at high risk of cerebral edema a number of prophylactic interventions have been shown to reduce the incidence of ICH. Based on retrospective data showing an inverse relationship between ICP and serum sodium in patients with ALF, moderate hypernatremia was investigated as a possible prophylactic intervention.[119,178] Maintaining serum sodium between 145 and 155 mmol/L using hypertonic saline solution was found to reduce ICP from baseline and reduce the incidence of surges in ICP.[119] Hypothermia improves outcome after out-of-hospital cardiac arrest and has been investigated in patients with TBI. Early reports suggest hypothermia can reduce ICP and ammonia production in patients with ALF. However, prophylactic hypothermia has not been shown to reduce the incidence or improve outcome in this setting.[191] Simple measures such as raising the head of the bed to a 30-degree angle and the avoidance of excessive stimulation are also prudent.

Cerebral Perfusion Pressure

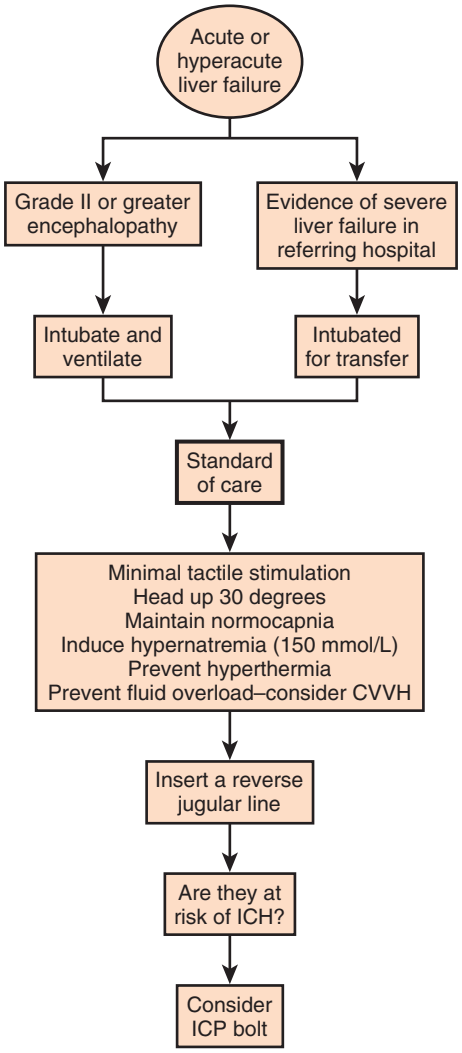
In TBI there is a consensus of opinion supporting the use of cerebral perfusion pressure (CPP) as a treatment goal.[187] In ALF the concept of CPP-directed therapy is less useful. To assume a correlation with cerebral blood flow requires a consistent cerebrovascular resistance, which is not the case in ALF.[170] This is due to the loss of cerebrovascular autoregulation, and attempts to increase cerebral perfusion are often unsuccessful as the use of a vasopressor results in an increase in ICP as brain blood volume increases.[131,192] However, this is not to say that CPP should be ignored entirely but the safe lower limit of CPP has yet to be defined, as there are many reports of patients surviving with normal cerebral function despite a low CCP.[193] The normal lower limit of cerebral autoregulation is reached at a mean arterial blood pressure of about 50 mm Hg, below which flow becomes pressure dependent. In patients with absent autoregulation, such as in ALF, CCP should probably be maintained above 40 mm Hg (the normal lower limit of autoregulation with an ICP ≤10 mm Hg), but no data exist to support this statement. Maintenance of CPP in ALF is best achieved by decreasing ICP and aiming for a mean arterial pressure with fluid and a vasopressor that does not increase ICP above 25 mm Hg. Attempting to improve cerebral oxygen balance is also attractive in this setting. This may be attempted with intravenous indomethacin (which has been shown to improve CPP without compromising cerebral oxygenation), hypothermia, increased sedation, and hyperventilation.[169,194–196] Monitoring cerebral oxygenation is very useful during such a maneuver.

General Management of Patients With Raised Intracranial Pressure

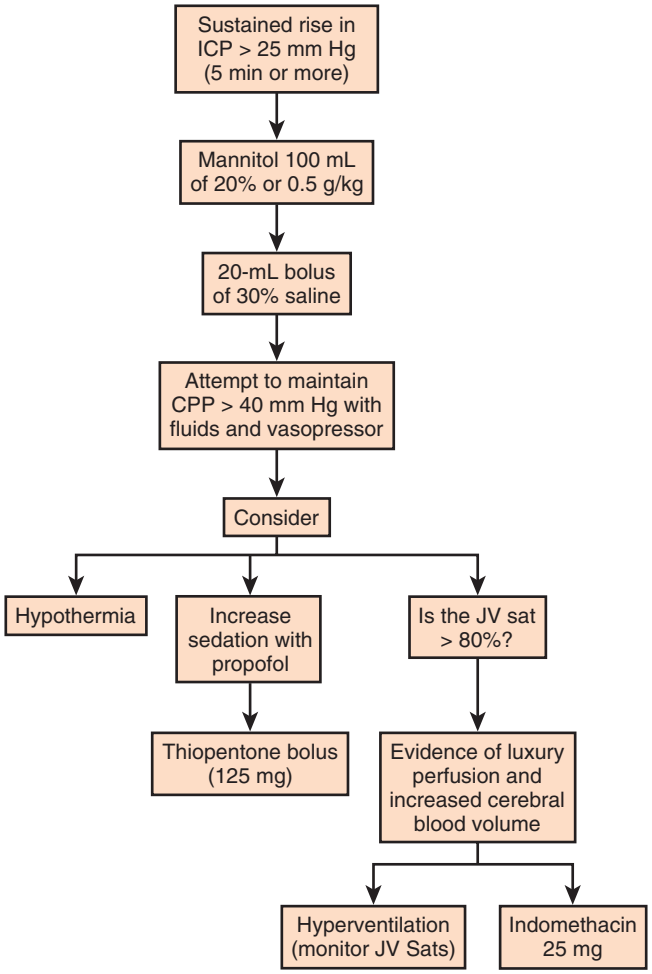
In patients at risk of or with suspected cerebral edema, prophylactic measures should be instituted. The decision whether or not to insert an ICP bolt will have to be made by the clinical team. If a bolt is inserted, there is the potential to manage ICP.

ICP is normally less than 15 mm Hg in an adult. The definition of ICH is not precise and varies among patients. Available data are derived from patients with TBI; observational studies suggest that intervention to reduce pressure should be instituted between 20 and 25 mm Hg, although pupillary abnormalities and brain herniation can occur at lower pressures.[187] There have been no studies investigating a treatment threshold in ALF and so similar thresholds to TBI are used.

The management of ICH is usually escalated along standard algorithms (Figs. 71.13 and 71.14). Elevate the patient to an angle of 30 degrees and avoid tight straps around the neck to encourage venous drainage. ICP tends to increase during nursing intervention. If the ICP rises after nursing intervention and does not resolve after several minutes, it implies poor intracranial compliance. Treatment is usually instituted for a sustained rise in ICP (>10 minutes over the treatment threshold) or clinical signs suggesting cerebral ischemia or impending herniation.



• **Fig. 71.13** Initial management of patient with high-grade encephalopathy. *CVVH,* Continuous venovenous hemofiltration; *ICH,* intracranial hypertension; *ICP,* intracranial pressure.



• **Fig. 71.14** Management of a sustained rise in intracranial pressure. *CPP,* Cerebral perfusion pressure; *ICP,* intracranial pressure; *JV,* jugular venous; Sats, saturation.

- Sedation should be increased. Propofol is probably the agent of choice.[194]
- Osmotherapy is the mainstay of treatment following these simple measures.
  - Mannitol as a rapid infusion (0.5–1.0 g/kg) has been shown to reduce ICP reliably in ALF.[197] The dose can be repeated but care must be used in renal failure owing to accumulation, and multiple administrations can result in a hyperosmolar syndrome. Plasma osmolality should be monitored if multiple doses are used. Current practice is to remove 500 mL of ultrafiltrate via CVVH after each bolus dose of mannitol.
  - Bolus doses of 20 mL hypertonic saline solution (30%) have an effect similar to mannitol in this setting in the authors' experience. Hypertonic saline solution has a higher reflectance coefficient at the blood-brain barrier compared with mannitol and there appears to be less tachyphylaxis to multiple administrations.[119]

In patients with a raised ICP and cerebral hyperemia, suggested by a JV oxygen saturation of 80% or greater (luxury perfusion), short-term hyperventilation induces cerebral vasoconstriction and reduces blood volume. This maneuver has been shown not to impair cerebral oxygenation, but close monitoring of cerebral oxygenation should be used if it is attempted.[195] Short-term hyperventilation has not been shown to improve outcome in ALF but does prolong survival in the ICU.[198] Hyperventilation may be lifesaving and may buy time for definitive treatment (transplantation). Indomethacin induces cerebral vasoconstriction and reduces ICP in patients with both TBI and ALF without impairing cerebral oxygenation, although confirmatory studies are needed.[169]

Seizures

Ammonia toxicity and cerebral edema are associated with seizure activity and it has been recognized that subclinical seizures occur more commonly than previously thought.[183] The use of mechanical ventilation facilitated by sedatives and muscular paralysis can mask clinical signs. Seizures adversely affect cerebral oxygen consumption and may contribute to cerebral edema and are a cause of low jugular oxygen saturation. The use of prophylactic phenytoin has been suggested in all patients with ALF and high-grade encephalopathy. Others have questioned this approach because of the significant side effects and apparent lack of effect on outcome.[199] If confirmed, seizure activity should be managed according standard management guidelines.

Infection and Immunosuppression

Patients with ALF have multiple immune defects and are susceptible to infections.[200] Infection is a common cause of progression and complication in ALF. Antibiotic prophylaxes have not been shown to reduce the incidence of infection or improve survival.[201] Selective decontamination of the digestive tract has not been shown to be superior to intravenous antibiotics alone.[200,202] More recent work has shown how the microbiologic flora of a liver unit has changed over the past 20 years—for example, bacteremia appearing later in the ICU stay and being predominantly gram-negative in nature.[203]

It is current practice to prescribe broad-spectrum antibacterial and antifungal medication to patients with ALF depending on local sensitivities. There is a general trend to the timing of infection with gram-positive infections occurring earlier than with gram-negative infections. Early gram-negative infections tend to be less resistant "endogenous" bacteria followed later by resistant hospital-acquired organisms.[204,205]

Nutrition

Within the general intensive care literature there is a consensus toward enteral nutrition (EN) as the route of choice.[206] There are few additional data on which to base decisions in patients with ALF. There is, however, wide regional variation in the prescribing of parenteral nutrition compared with EN. The reason for this is unclear as EN is associated with a reduction in infectious complications.[206] However, it is clear that some centers prefer parenteral nutrition.[207] Nutritional requirements in ALF are not well understood.

See the online supplement for additional text on nutrition.

Artificial Liver Support

At the present time liver transplantation is the only form of definitive therapy for severe hepatic failure. However, the scarcity of organs and potential for delay in transplantation, together with a proportion of patients who will make a full recovery if supported while the liver regenerates, suggest that there would be a role for some kind of liver support system.

The liver is a complex organ, and to be an ideal liver replacement, any system has to support a wide range of biosynthetic and metabolic functions. Any working system will also have to counter the systemic burden of the necrotic, dying liver.[216]

Artificial liver support can be split into two main approaches. In the first there is an attempt to simulate or replace all or most of the functions of the liver. These systems include hepatocytes either from human or animal sources. Another view of liver failure suggests that toxins either excreted by the dying liver or not metabolized because of an acute reduction in function are responsible for the majority of the signs and symptoms. In this view extracorporeal blood purification with dialysis or adsorption techniques are employed and serum proteins not produced are replaced with plasma (Box 71.3).

Biologic Systems

Biologic systems consist of a bioreactor within which the cellular biomass is contained and a mechanism of containing and separating the biomass from the circulation of the patient. They require an extracorporeal system to deliver blood or plasma to the bioreactor and may also contain an adsorption or dialysis component. Data from liver resection suggest that approximately 250 mL of liver by volume is required to prevent death from liver failure. This typically represents 20% to 30% of liver mass.[217]

See the online supplement for additional text on biologic systems.

• BOX 71.3 Functions of the Liver

Excretion of bilirubin, cholesterol, hormones, and drugs
Metabolism of fats, proteins, and carbohydrates
Enzyme activation
Storage of glycogen, vitamins, and minerals and regulation of glucose levels
Synthesis of plasma proteins such as albumin, clotting factors, and bile production
Blood detoxification and purification
Immune regulation

Nonbiologic Systems

Many of the molecules that accumulate within the blood during ALF are small or middle-sized. These molecules can be targeted by a variety of extracorporeal purification techniques, including dialysis through various types of membranes and adsorption onto carriers such as charcoal, resins, or albumin. Nonbiologic systems are attractive because they are relatively inexpensive (compared with biologic systems) and logistically much easier to implement.[216]

See the online supplement for additional text on nonbiologic systems.

Liver Transplantation

When and Whom to Transplant

Liver transplantation for ALF was used sporadically during the 1980s but gained pace in the late 1980s and now has a huge impact. It remains the only definitive form of therapy for some.

Timing is important, and in those with severe liver injury there is a window of opportunity beyond which transplantation often becomes futile because of deteriorating organ function.[228] It was recognized early in the history of transplantation for ALF that the challenge was to develop robust prognostic indicators. These need to be sensitive, early enough to provide maximum advantage to the patient, and specific enough not to result in unnecessary transplants.

A "super-urgent" designation exists in the national transplant sharing scheme in the United Kingdom with a similar "category 1A" designation in the United States (see http://www.unos.org/ for details). These categories recognize the role of early transplantation in ALF and the detrimental effect of delay in this setting.

In the United Kingdom, the super-urgent designation (Table 71.4) is closely linked to the prognostic score developed in King's College Hospital in the late 1980s using retrospective multivariate analysis with prospective validation.[229] The prognostic criteria have been subsequently validated in other centers and shown to be robust.[230] Other criteria have been developed.[231]

The criteria are not perfect. First, despite their good specificity (i.e., if the patient meets criteria the patient is likely to die), the sensitivity and negative predictive value are not as good, and there is a substantial proportion of patients who will die without ever reaching transplant criteria. In addition, awaiting positive criteria can lead to delay in listing and worsening of organ failure that often then preclude listing. This contributes to the fact that published rates of transplantation in those who reach criteria are

Energy expenditure is raised during ALF. This is surprising considering the normal contribution of the liver, a large metabolically active organ, on the overall energy expenditure, illustrated by the effects of hepatectomy on energy expenditure during elective liver transplantation.[208] There is organ-specific lactate production in both the liver and the lungs and evidence of a systemic inflammatory response in many patients.[201,209,210] The cause of systemic inflammation in ALF is activation of inflammatory cells (leukocytes and endothelium) and the release of systemic cytokines. This may be initiated by infection.[201] Patients in the early stages of ALF are markedly catabolic with insulin resistance despite the frequent presence of a hypoglycemic state.[211] The Harris-Benedict equation is inaccurate in ALF and indirect calorimetry should be used if energy requirements are sought.

Hypoglycemia is common as a result of the failure of both glycogenolysis and gluconeogenesis. Massive hepatic necrosis can result in a precipitous fall in serum glucose concentration. For this reason an infusion of 50% glucose should be used at least until feeding is established. Low-volume, high concentrations of glucose are preferred to reduce the infusion of large quantities of water and the resultant hyponatremia if lower concentrations are used.

Serum amino acids are consistently deranged during liver failure. There is a low or normal concentration of glutamine, branched-chain amino acids, and tryptophan and an increase in others.[212] High brain concentration of ammonia is thought to contribute to cerebral edema and encephalopathy in ALF. Manipulation of ingested amino acids has been investigated in an attempt to reduce ammonia concentration. L-Ornithine and L-arginine (LOLA) infusion encourages alternate pathway metabolism and reduces hepatic encephalopathy in chronic liver disease.[213] LOLA has been investigated in animal models of ALF and resulted in normalization of plasma ammonia concentration, significant delay in the onset of encephalopathy, and a reduction in brain water concentration.[214] LOLA was investigated in 2009 with a randomized controlled clinical trial in ALF. Despite theoretical promise, the investigators were unable to show any reduction in mortality rate or ammonia between the groups.[215]

NAC is primarily used as a glutathione precursor and antidote in acetaminophen poisoning, but it is used widely in patients with ALF induced by other causes and later in its subsequent course. Results of a recent randomized controlled clinical trial have shown efficacy with NAC in patients with low-grade encephalopathy and non–acetaminophen-induced liver failure. The mechanism of action is unknown.[70]

There is little evidence that protein restriction has any role in ALF, and protein requirements based on total calorie ingestion should be used.

Serum electrolytes are often deranged in the early stages of ALF. Hypophosphatemia is common in patients with ALF and is a good prognostic sign. High or normal phosphate may indicate a lack of hepatic regeneration and renal impairment.[120] Hypomagnesemia is also common and should be corrected.

Possible cell types for use as the biomass include animal or human primary hepatocytes or other forms of cell line with hepatocyte phenotype. Primary hepatocytes outperform other cells lines but are of limited availability and tend to have a time-dependent loss of hepatic phenotype. In addition, scaling up production with primary hepatocytes is difficult, as they do not readily undergo cell division under laboratory conditions. Instead, they have to be directly seeded into the bioreactor either immediately after harvest or after a period of storage and cryopreservation. Human cells are limited in availability but can be obtained from unused livers, after donation, and from cut-down grafts. Theoretically, animal cells are readily available but uncertainty about possible cross-infection from animal pathogens to the patient with organisms such as PERV (porcine endogenous retrovirus) and incompatibility of secreted antigens render them far from ideal, and regulatory authorities are often reluctant to sanction their use.

Immortalized cell lines that proliferate in culture, while retaining some liver-specific functionality, can be used in an attempt to overcome the limitations of primary hepatocytes. Many lines have been created by retroviral transfection with regulatory genes that stimulate cell division. The insertion of "terminator" genes that give the cells a limited life or enable switching the immortalizing gene off have also been developed to improve safety.[218] Other sources of immortal and readily cultured cells are tumor derived such as the ubiquitous HepG2/C3A hepatoblastoma line. Finally, stem cell sources appear to offer the most hope in terms of a readily available and functional supply of differentiated hepatocytes.[219]

Clinical trials in the use of bioartificial liver support have been relatively disappointing. The bioartificial liver uses porcine hepatocytes and a charcoal column in series. The largest trial published so far in the field was powered for survival advantage in ALF and primary nonfunction after liver transplantation.[220] The study was terminated early by the data and safety monitoring board because the trial was likely to be futile based on the results at interim analysis.[220] Post hoc analysis suggested some effect in the ALF group alone. The extracorporeal liver assist device system uses the HepG2/C3A hepatoblastoma line and has been investigated in a number of phase I and phase II studies designed to report safety and activity. A randomized controlled study, not powered for mortality, showed a trend for improved survival in the treatment group.[221, 222] Since then, in a more robust study of 203 ACLF patients with alcoholic hepatitis, the extracorporeal liver assist device failed to demonstrate an improvement in outcome.[223,224]

Early work with hemodialysis was unsuccessful and was largely abandoned with the conclusion that the toxemia of ALF was not due solely to small water-soluble molecules. The advent of synthetic membranes in the 1970s rekindled the interest in convective therapy for ALF. These allowed larger molecules to pass through compared with the cuprophane alternatives. Cardoso reported clinical improvement (reduction in ammonia) with the use of hemofiltration in patients with ALF.[225] Hemofiltration, as a form of renal support, is used in most liver critical care units as part of general supportive care and there is some evidence that increased convective exchange, with high-volume hemofiltration (>35 mL/kg per hour), is associated with improved ammonia clearance and mortality in ALF patients.[145,225]

Charcoal hemoperfusion has been extensively investigated. Initial trials were encouraging, but later larger randomized controlled trials were unable to show an improvement in outcome.[137] Large-volume plasma exchange showed some improvement in hemodynamics and other parameters in initial studies.[226] Recently Larsen and colleagues published a large multicenter randomized controlled clinical trial of high-volume plasma exchange (10 L/day for 3 days) in ALF that demonstrated an improvement in transplant-free survival (likely in patients using acetaminophen), and it may become a standard form of therapy.[227]

In an attempt to improve the efficacy of dialysis techniques, adsorbents have been added to the dialysis fluid to widen the range of molecules removed. A number of approaches are used for this. One is dialysis of blood or plasma against albumin solution. This is done via a recycled circulation in the Molecular Adsorbent Recirculating System (MARS; Gambro/Baxter International, Lakewood, CO) machine or via single-pass albumin dialysis. Another is the use of plasma separation, adsorption, and filtration and then recombining the "cleaned" plasma with the patient's blood.[223]

Nonbiologic systems have been shown to improve blood pressure, increase vascular resistance, and improve short-term encephalopathy scores in patients with ACLF. Three large studies have been reported, two in the management of ACLF (the RELIEF study and the HELIOS study) and the FULMAR study in patients with ALF. Unfortunately, none of the studies has shown an improvement in outcome.[223]

TABLE 71.4 Prognostic Indicators for Liver Transplantation

Acetaminophen-Related Acute Liver Failure[a]	Nonacetaminophen-Related Acute Liver Failure[a]	ALFSG Prognostic Index[b]
A. Single criterion • pH <7.30 or lactate >3.0 mmol/L after adequate fluid resuscitation B. Three criteria • Grade III-IV (West Haven) hepatic encephalopathy • INR >6.5 • Creatinine >3.4 mg/dL	A. Single criterion • INR >6.5 B. Three of 5 criteria • Age <10 or >40 years • Time from jaundice to coma >7 days • INR >3.5 • Bilirubin >17 mg/dL • Unfavorable etiology: drug-induced liver injury, Wilson disease, or seronegative liver injury	• Hepatic coma grade 3 or 4 (West Haven) • Favorable etiology • Acetaminophen, ischemia, hepatitis A, pregnancy • Vasopressor use • INR • Bilirubin

[a]From O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology.* 1989;97:439–445.
[b]From Koch DG, Tillman H, Durkalski V. Development of a model to predict transplant-free survival of patients with acute liver failure. *Clin Gastroenterol Hepatol.* 2016;14:1199–1206.
ALFSG, Acute Liver Failure Study Group; *INR,* international normalized ratio.

only 50% following acetaminophen toxicity.[232] Clinical practice has changed since this designation was first defined. For example, it is rare to see a patient after acetaminophen-induced ALF with a pH below 7.3 or a creatinine above 300 mmol/L because of improved resuscitation and early renal support at the referring hospital. Because of these factors, ongoing efforts continue to establish markers that increase sensitivity and occur even earlier in the course of the syndrome, while maintaining good specificity and not reducing the positive predictive value to unacceptable levels leading to unnecessary transplants.

Serum phosphate levels are higher in nonsurvivors after both acetaminophen toxicity and in other causes of ALF.[120,233] However, there appears to be an unacceptable overlap and others have suggested that the use of serum phosphate does not provide any additional benefit to existing markers.[121,234,235] Other factors investigated include α-fetoprotein levels and nuclear magnetic resonance analysis of peripheral blood.[120,236] Acute physiologic scoring as a basis for prediction has also been used.[237]

The liver plays a central role in lactate metabolism. In fact, in patients with severe liver necrosis the liver changes from being a consumer of lactate to being a net producer.[209] Arterial blood lactate levels have been shown to improve the sensitivity and maintain the specificity if added to the original King's College Hospital criteria and are achieved earlier in the course of the syndrome.[149]

More recently the ALFSG (Acute Liver Failure Study Group) prognostic index has been published from prospectively collected data from 1974 patients with ALF based on five variables (coma grade, etiology, vasopressor use, bilirubin, and INR).[238] Its performance characteristics (C statistic 0.84) significantly improve on KCC (0.55–0.65) and are available as a smartphone app.

Outcome From Transplantation

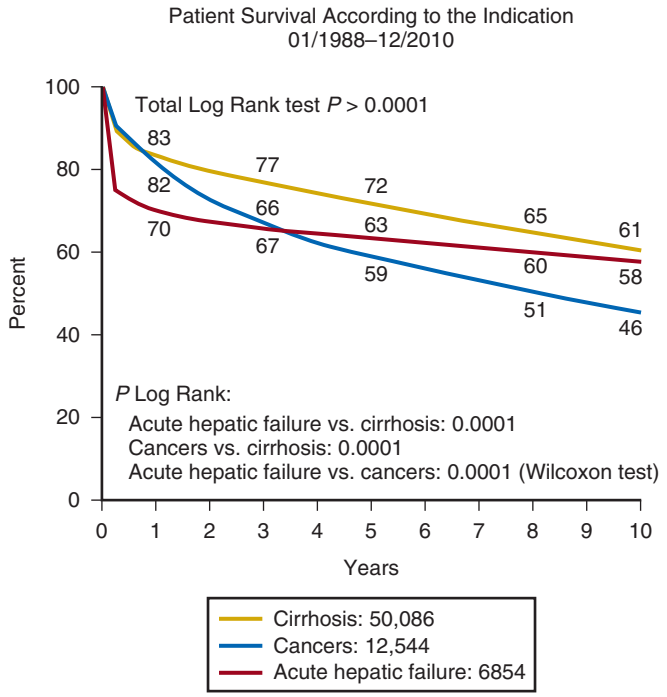
In Europe the 1-year survival rate after transplantation for ALF is worse than that seen in chronic liver disease. The excess mortality rate is seen in the first month or so after transplantation. This represents the severity of organ dysfunction seen before transplantation in ALF. After this initial period, the curve flattens and the survival rate is actually better than that of patients with chronic liver disease (Fig. 71.15). This probably represents a younger age group and less disease recurrence. There is a huge degree of heterogeneity in ALF, and those with seronegative hepatitis who receive transplants display a better survival profile than patients receiving transplants for other causes, although they exhibit a similar early mortality rate while in the ICU.[89]

Tremendous research efforts have gone into the search for prognostic criteria on which to base the decision to perform transplantations in patients with ALF; however, much less information is available about the prediction of fatality after transplantation. This is important, as decisions to withdraw from the waiting list based on severity are difficult.

There appear to be both recipient and donor factors that help predict the outcome from transplantation in ALF.[89,232,239] In theory, the severity of illness and organ dysfunction before transplantation should predict outcome. However, because patients whose conditions are unstable tend to be either not listed or withdrawn from the waiting list, there is inherent bias in retrospective analysis. Age of the recipient is a significant factor, certainly for seronegative ALF, but also in acetaminophen-induced failure, in which age is often used to exclude listing.[232] In non–acetaminophen-induced ALF, serum creatinine at the time of transplantation is a predictor of 2-month survival. After acetaminophen overdose, time from ingestion to transplantation has been shown to be a good predictor of 2-month survival; all patients who receive transplants later than 6 days from ingestion died. The APACHE III score at transplantation and the severity of metabolic acidosis are also predictive.[239]

Donor factors found to be important are the use of reduced size grafts in acetaminophen-induced ALF and evidence of early graft dysfunction as defined by a high AST or INR in the early postoperative period. In addition, a high donor body mass index is a risk factor for death in seronegative hepatitis.[89,232]

In 2012 a review of the European liver transplant database for patients receiving transplants after ALF evaluated 4903 patients. The 1-, 5-, and 10-year patient and graft survival rates were 74%, 68%, and 63%, respectively. Death and graft loss were independently associated with male recipients, recipients older than 50 years, incompatible ABO matching, donors older than 60 years, and reduced size graft. Recipients older than 50 years who received a



• **Fig. 71.15** Patient survival according to the first indication for liver transplant. (From European Liver and Intestine Transplant Association, accessed at http://www.eltr.org.)

graft from a donor older than 60 years had a 57% 1-year mortality rate or graft loss.[240]

The conclusions from this review suggest that older recipients with severe preoperative organ dysfunction are less able to tolerate poor early graft function, often seen with marginal grafts. Therefore to achieve the best graft and patient survival there should be matching of the organ to the recipient, but this is difficult because of time constraints.

Auxiliary Transplantation

Auxiliary partial liver transplantation has many theoretical advantages compared with standard orthotopic transplantation in ALF. It can be performed orthotopically (i.e., in the same place as the original liver) or heterotopically (e.g., in the left iliac fossa). These days it is always performed as a partial orthotopic transplant with a native left lobe in situ in adults and a right lobe in children using an adult left lobe graft, depending on size.

Auxiliary transplantation provides the potential to support the patient during the acute phase of liver failure, enabling regeneration of the native liver. This is attractive because in a number of patients immunosuppressive drugs can be withdrawn, allowing the graft to atrophy or be removed, and eliminating the risks associated with lifelong immunosuppression. Data on this procedure have been accumulating since the mid-1990s. Initial reports suggested that the procedure was associated with a high incidence of technical problems, primary dysfunction, and retransplantation. Later reports, however, suggest that many of these issues are resolving with greater experience in patient and graft selection. The best outcome has been seen in patients aged younger than 40 years with either acute viral hepatitis or acetaminophen hepatotoxicity in whom 1-year graft and patient survival are similar to those for standard transplantation for ALF. Withdrawal of immunosuppression can be achieved in 30% to 70% of patients receiving transplants.[241–243]

Living Related Lobe Donation

In many countries the only chance of transplantation for ALF is a living related donation of a liver lobe. This is most often performed in children when an adult left lobe can be used. In adults, a right lobe is usually required, increasing the risk to the donor. With the worldwide shortage of donor organs, living related transplantation for ALF is widely accepted in many countries but not all. There are significant issues related to living related transplantation in ALF, including a donor mortality rate of 1% and major morbidity rate of 40% to 60%. There are also ethical implications of adequately preparing the donor, medically and psychologically, in a time of acute crisis.[244]

Key Points

- Liver failure can occur with a background of cirrhosis, when it is often termed acute on chronic liver failure (ACLF), or it can occur de novo in a previously healthy individual owing to a toxic, immunologic, hypoxic, or infective cause, when it is termed acute liver failure (ALF) or fulminant liver failure.
- Liver failure, defined by the onset of hepatic encephalopathy and progressive failure in hepatic metabolic activity, progresses to multiple-organ failure and ultimately death in a large proportion of patients, and supportive care is the mainstay of therapy.
- ACLF is seen much more commonly than ALF. It is most often seen in the setting of advanced, decompensated cirrhosis with portal hypertension. It is usually precipitated by some intercurrent event such as sepsis or an upper gastrointestinal bleed. Therapy is aimed at the treatment of sepsis and aggressive management of the circulation.
- Worldwide, particularly in the developing world, approximately 95% to 100% of patients presenting with ALF have viral hepatitis.
- Acetaminophen poisoning is the most common cause of ALF in northern Europe and the United States. It can be treated successfully in the majority of patients with NAC, if given within the first 12 hours after nonstaggered ingestion.
- The presentation and clinical course of ALF depends on its cause and the rate of progression of the syndrome.
- Liver failure after viral hepatitis is rare and tends to run an acute or hyperacute course, with the onset of encephalopathy occurring within days or weeks of the first symptoms.
- The West Haven criteria, designed to assess coma grade in patients with cirrhosis, are often applied to patients with ALF and are useful because of their familiarity.
- Intracranial hypertension secondary to cerebral edema often complicates severe hyperacute liver failure and remains a leading cause of death.
- Management of ALF is complex, and liver transplantation is the only effective therapy in severe cases.

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Review Questions

1. A 27-year-old female with a history of depression and anxiety presents to her local emergency department with upper abdominal pain, jaundice, and lethargy. Her laboratories suggest a severe, acute liver injury. Her serologic investigations has been sent to the laboratory, but results are pending. Which of the following treatments has been shown to improve outcome of patients with the corresponding etiology of acute liver failure (ALF)?
   a. Lamivudine: hepatitis B
   b. Hepatitis A immune globulin: hepatitis A
   c. N-acetylcysteine (NAC): idiosyncratic drug-induced liver injury (DILI)
   d. Methylprednisolone: autoimmune acute liver failure
   e. Acyclovir: herpes simplex virus

   Answer: c. Use of NAC in non-acetaminophen ALF may improve transplant-free survival. Very few studies have had the statistical power to make firm conclusions about the efficacy of specific treatments for ALF by etiology. A randomized, controlled study of patients with severe hepatitis B found no improvement in patients who received lamivudine compared to placebo. There are no data to support the use of hepatitis A immune globulin. A retrospective review of corticosteroids for autoimmune ALF found no benefit. Case reports do not suggest benefit from acyclovir in patients with ALF owing to herpes simplex virus. These negative results do not argue against their use because all of the data are flawed to some extent.

   Although NAC has clearly been shown to improve the clinical course of patients with acetaminophen-induced ALF, its use in non–acetaminophen-induced ALF is less well documented. In one multicenter randomized, placebo-controlled study, NAC was found to improve liver transplant–free survival in patients with non–acetaminophen-induced ALF without high-grade hepatic encephalopathy. The two groups with the most benefit were those with hepatitis B and idiosyncratic DILI.
2. A 35-year-old female with a history of previous suicide attempts ingested a "handful" of extra-strength acetaminophen tablets at an unclear point in time and was found unresponsive by her sister. Results for her admission laboratory tests in the local emergency department include the following:

Aspartate aminotransferase (AST)	4567 IU/L
Alanine aminotransferase (ALT)	8459 IU/L
Total bilirubin	1.4 mg/dL
Creatinine	3.8 mg/dL
International normalized ratio (INR)	9.6
Ammonia	105 µmol/L

   Which of the following is the only prophylactic measure to prevent cerebral edema in patients with ALF supported by a randomized, controlled clinical trial?
   a. Mannitol
   b. Lactulose
   c. Hypertonic saline solution
   d. Hypothermia
   e. Renal replacement therapy

   Answer: c. Hypertonic saline has been shown to be effective as prophylaxis against cerebral edema in patients with ALF. Murphy et al. performed the only randomized and controlled clinical trial to prevent cerebral edema and intracranial hypertension. The trial showed that raising the serum sodium to 145 to 155 mEq/L with hypertonic saline solution decreased the mean intracranial pressure of study subjects with ALF and high-grade hepatic encephalopathy compared with patients managed with standard of care without hypertonic saline solution. Hypothermia was recently explored in a randomized, controlled, multicenter trial and was not shown to improve outcome or the development of intracranial hypertension.

   The other prophylactic measures listed have not been systematically studied in clinical trials. However, there are reasonable rationales behind their use and may be considered, particularly the early institution of renal replacement therapy in the presence of significant hyperammonemia (>150 µmol/L), even in the absence of azotemia.
3. A 27-year-old male is admitted with jaundice and altered mentation. There is no history of previous liver disease or acetaminophen ingestion, and the patient takes no over-the-counter or herbal remedies.

   After admission to the intensive care unit, the following data are obtained:

Sodium	147 mEq/L
ALT	3798 IU/L
AST	2857 IU/L
INR	8.5
Venous ammonia	135 µmol/L
Total bilirubin	2 mg/dL
Creatinine	0.8 mg/dL
Platelet count	56 x 10^9/L

   Hepatitis B surface antigen (HBsAg) and IgM anti-hepatitis B core antibodies (HBcAB) are positive.

   The patient has a mean arterial pressure of 70 mm Hg off vasopressors. He is lethargic and oriented only to person.

   You have entered the above data into the ALF Study Group Prognostic Score app on your smartphone, and determine the patient has a predicted transplant-free survival of ~5% at 21 days. An expedited liver transplant evaluation is nearly complete. Which of the following management options should be instituted next?
   a. Administer lactulose via nasogastric tube to effect three bowel movements.
   b. Administer plasma and platelets.
   c. Insert an intracranial pressure monitor.
   d. Intubate the patient.
   e. Administer an intravenous (IV) mannitol 0.5 g/kg bolus

   Answer: d. The progression of hepatic encephalopathy to higher than grade 2 is an absolute indication for endotracheal intubation and thereby airway protection. One of the worst mistakes a clinician can make in managing a patient with ALF is delaying intubation and losing control of the patient's airway long enough to result in aspiration. This patient has grade 3 hepatic encephalopathy, which is an informal, but widely accepted indication for immediate sedation and intubation. Lactulose is very unlikely to result in significant diminution of the ammonia to avoid the need for intubation or lower the risk of intracranial hypertension. Mannitol is given therapeutically after intracranial hypertension is suspected or established by head computed tomography (CT) or intracranial pressure (ICP) monitor criteria. The decision to place an ICP monitor is contentious and center and practitioner dependent, but it is usually reserved to manage

patients with deep coma who are at high risk of intracranial hypertension (i.e., those taking vasopressors, renal replacement therapy, and with severe hyperammonemia).

There is an emerging consensus that the INR should not be corrected unless a patient is actively bleeding. The reasons include that (1) patients with ALF seldom have clinically significant spontaneous (non–procedure-related) bleeding; (2) plasma transfusion obscures the trend in INR, a key prognostic indicator; and (3) plasma transfusion may be harmful. Sources of harm may include exacerbating a relative hypercoagulable state in patients with ALF, volume overload, transfusion-associated lung injury, and others. There are no data to support the transfusion of platelets in patients with ALF. Extrapolating from in vitro data in patients with cirrhosis, a platelet count of more than 60×10^9/L supports thrombin generation at the 90th percentile of normal. Therefore platelet transfusions in patients with ALF should be reserved for patients with significant spontaneous bleeding or in patients with counts below 60×10^9/L before undergoing high-risk procedures such as ICP monitor placement.

4. A patient with ALF as the result of hepatitis B is deeply comatose with no sedation for 48 hours and has received an offer of a liver from a deceased donor. Which of the following should be performed immediately before proceeding to the operating room for liver transplantation?
   a. Placement of an ICP monitor
   b. Electroencephalogram (EEG)
   c. CT scan of the head
   d. Optic nerve sheath diameter
   e. Transcranial Doppler ultrasound

   Answer: c. In a comatose patient with ALF, irreversible brain damage must be ruled out by head CT on the way to the operating room for liver transplantation. Predicting neurologic outcome after liver transplantation is often not possible in deeply comatose patients with ALF. The primary question at the time a patient has received an offer of a liver graft is which patient absolutely should not proceed to transplant. Placement of an ICP monitor remains a contentious management decision in patients with ALF, as several surveys and retrospective studies have failed to show an improvement in outcome or neurologic recovery. Furthermore, they are associated with uncommon but potentially fatal bleeding complications. ICP monitor placement is physician and center dependent, but is usually reserved for liver transplant candidates awaiting the offer of a graft in hopes of improving management of cerebral edema and would not be placed on the way to the operating room. However, patients with prolonged intracranial hypertension or low cerebral perfusion pressures assessed by an indwelling ICP monitor have been shown to have poor neurologic recovery after liver transplantation. Similarly, an EEG might be considered during the waiting period if seizures were considered. Transcranial Doppler and optic nerve sheath diameter are noninvasive procedures to estimate ICP. The single best test to determine whether a patient should absolutely not undergo liver transplantation is to do a head CT scan to look for evidence of irreversible brain damage, such as brainstem herniation.

5. The mental status of a patient with ALF caused by acetaminophen overdose has deteriorated from grade 1/2 hepatic encephalopathy to unresponsiveness over the previous 12 hours. Which of the following must be excluded urgently?
   a. Brainstem herniation
   b. Infection
   c. Acute kidney injury
   d. Acute respiratory distress syndrome and hypoxemia
   e. Hyponatremia.

   Answer: b. Sudden progression from low-grade to high-grade hepatic encephalopathy in a patient with ALF must be considered a sign of infection until proved otherwise. The most common risk factor for sudden, rapid, worsening of hepatic encephalopathy from mild to high-grade is infection. The other complications of ALF listed certainly would be expected to result in an exacerbation of encephalopathy, but they would occur in a patient with preexisting high-grade encephalopathy (brainstem herniation) or more gradually.

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Gastrointestinal Bleeding

LOUIS CHAPTINI AND STEVEN PEIKIN

CHAPTER OUTLINE

Clinical Presentation
- Initial Evaluation and Resuscitation
- History and Clinical Findings
- Diagnostic Tests
- Therapeutic Options

Upper Gastrointestinal Bleeding
- Differential Diagnosis
- Diagnostic Evaluation
- Therapeutic Alternatives

Stress-Related Mucosal Disease
- Prophylaxis
- Treatment

Lower Gastrointestinal Bleeding
- Differential Diagnosis
- Diagnostic Evaluation
- Therapeutic Alternatives

Obscure Gastrointestinal Bleeding
- Differential Diagnosis
- Diagnostic Evaluation

Conclusion

Gastrointestinal (GI) bleeding includes a wide range of diagnoses with multiple types of lesions and bleeding that can occur virtually anywhere in the GI tract. Acute GI bleeding is often an emergency that can be alarming to both the patient and physician. Management and the outcome of GI bleeding depend on both the severity of the bleeding and any comorbid conditions present at the time of the bleeding. Acute GI bleeding often requires close monitoring and management in an intensive care unit (ICU). Management of such bleeding relies on a team approach that involves the expertise of an intensivist, gastroenterologist (endoscopist), radiologist, and surgeon.

The annual hospitalization rate for GI bleeding of any cause in the United States is estimated to be at 150 per 100,000.[1] Upper GI bleeding accounts for most of these hospitalizations, with an incidence rate of 100 cases per 100,000,[2] whereas the incidence of lower GI bleeding is estimated at 20 to 27 cases per 100,000.[3,4] In recent years, a significant decline in incidence of all-cause acute upper GI bleeding has been reported in some but not all time-trend studies, especially peptic ulcer bleeding.[5] Mortality rates vary depending on the source of the bleeding, with an annual rate of 2.5% to 3.5% for any type of GI bleeding.[1] Most nonvariceal upper GI bleeding studies document mortality rates approximating 5% to 10%.[5–7] These rates have not changed over the past 2 decades despite the evolution of acid suppression therapy, which is probably explained by an aging population with increased comorbid diseases. Mortality rates for lower GI bleeding are usually in the range of 5%.[8,9]

Clinical Presentation

Initial Evaluation and Resuscitation

The clinical findings in a patient with GI bleeding are crucial in determining the site, cause, and rate of bleeding. The first step in clinical evaluation is to assess the severity of the bleeding. This is done primarily by measuring hemodynamic parameters in an attempt to quantify the amount of blood volume lost (Table 72.1).[10] Because bleeding can represent a dynamic ongoing situation, continuous monitoring of hemodynamics is necessary to guide resuscitation efforts and provide key prognostic information. In patients with GI bleeding, two large-bore intravenous (IV) catheters should be placed immediately on arrival to restore euvolemia.

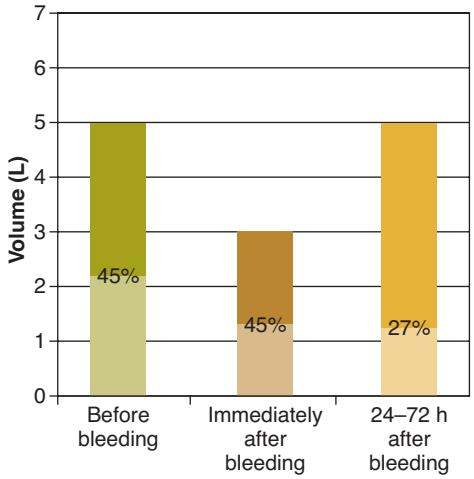
The hematocrit at initial evaluation may not reflect the severity of the bleeding because very recent loss of both plasma and red blood cells (RBCs) leads to a percentage of RBCs in the remaining blood (which defines the hematocrit) that is close to the same value. The hematocrit drops when hemodilution occurs as extravascular fluid enters the vascular space to restore volume, a process that may take up to 72 hours (Fig. 72.1).[11]

The rapidity of blood and colloid infusion depends in part on the patient's cardiovascular condition. Placement of a central venous pressure catheter can help one base decisions on more objective findings. Several recent studies found that transfusion was associated with a higher risk for nosocomial infection, multiorgan dysfunction, acute respiratory distress syndrome, and death.[12] Current transfusion trends are to administer blood to patients with hemoglobin less than 7 mg/dL and to avoid transfusion when it is above 10 mg/dL. However, the threshold for blood transfusion should take into consideration the patient's underlying condition, hemodynamic status, and markers of tissue hypoxemia.[13] A study evaluating blood transfusion for upper GI bleeding found a significantly higher survival rate and lower rebleeding rate when a restrictive transfusion threshold of 7g/dL was followed compared with a threshold of 9 g/dL.[14] In patients with conditions associated with defects in platelet or coagulation factors, these substances should be replaced. Patients requiring massive transfusion of packed red blood cells require fresh frozen plasma and platelets. Hypocalcemia can develop in these patients because of the large amount of citrate received

TABLE 72.1 Hemodynamics, Vital Signs, and Blood Loss

Hemodynamics and Vital Signs	% Blood Loss (Fraction of Intravascular Volume)	Bleeding Type
Shock (resting hypotension)	20–25	Massive
Postural (orthostatic tachycardia or hypotension)	10–20	Moderate
Normal	<10	Minor

From Rockey DC. Gastrointestinal bleeding. *Gastroenterol Clin North Am.* 2005;34:581–588.



• **Fig. 72.1** Plasma volumes *(solid bars)*, red blood cell volumes *(pale bars)*, and hematocrit values (%) before bleeding and after blood loss of 2 L. A baseline hematocrit level of 45% is assumed. (From Rockey DC. Gastrointestinal bleeding. In: Feldman M, Friedman LS, Sleisenger MH [eds]. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 7th ed. Philadelphia: WB Saunders; 2002:221–248.)

TABLE 72.2 Blatchford Score for Gastrointestinal Bleeding[a]

Admission Parameter	Score Value
Urea (mg/dL)	
≥6.5 to <8.0	2
≥8 to <10	3
≥10 to <25	4
≥25	6
Hemoglobin (g/dL)	
Men	
≥12 to <13	1
≥10 to <12	3
<10	6
Women	
≥10 to <12	1
<10	6
Systolic Blood Pressure (mm Hg)	
100–109	1
90–99	3
<90	3
Other Parameters	
Pulse >100 beats/min	1
Melena at presentation	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

[a]The score is calculated by adding the points from each variable. A score of zero is associated with a low risk of the need for endoscopic intervention.
From Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet.* 2000;356:1318–1321.

with massive transfusion, and thus calcium replacement should be considered, especially in individuals with end-stage liver disease and heart failure, in whom citrate metabolism may be impaired.[15]

The initial evaluation of patients with nonvariceal upper GI bleeding should include risk stratification of patients into low- and high-risk categories for rebleeding and death based on clinical, laboratory, and when available, endoscopic criteria.[12] This allows appropriate intervention and minimizes morbidity and mortality risks. The most extensively validated scores for risk stratification are the Blatchford and Rockall scores[16,17] (Tables 72.2 and 72.3). Similarly, risk stratification in lower GI bleeding helps in guiding the management of these patients. Hemodynamic instability, ongoing hematochezia, age older than 60 years, history of diverticulosis or angioectasia, and comorbid illnesses have been consistently associated with poor outcome in lower GI bleeding.[18,19]

History and Clinical Findings

After hemodynamic stabilization is achieved, a careful history and clinical examination are imperative to make a preliminary assessment of the location and cause of the bleeding. Important historical features in the evaluation of GI bleeding are shown in Box 72.1.[10]

Hematemesis typically points to an upper source of bleeding, proximal to the ligament of Treitz. In rare cases, hematemesis can be a sign of swallowed blood from oral, pharyngeal, or nasal bleeding. Melena is defined as black tarry stool with a glistering sheen and results from degradation of blood in the GI tract. At least 50 mL of blood in the upper GI tract is required to cause melena, although volumes up to 100 mL may be clinically silent.[20] Melena usually indicates upper GI bleeding, but its source may be the small bowel and sometimes even the proximal part of the colon when the volume of blood is too small to cause hematochezia. Coffee-ground emesis is typically a sign of recent, but currently inactive, upper GI bleeding, and its appearance is caused by the acid's effect on blood in the lumen. Hematochezia is generally associated with colonic bleeding but can also be caused by more proximal bleeding. Proximal bleeding in association with hematochezia is usually more hemodynamically significant.

Other symptoms at initial evaluation can help in narrowing the differential diagnosis. Abdominal pain before or at the time of the bleeding episode can be a sign of underlying peptic ulcer disease (PUD), mesenteric or colonic ischemia, perforation, or even intestinal infarction. Multiple episodes of vomiting and retching preceding the bleeding episode should alert one to the presence of a Mallory-Weiss tear (MWT).

TABLE 72.3 Rockall Scoring System for Risk of Rebleeding and Death in Acute Gastrointestinal Bleeding[a]

	POINTS			
Variable	**0**	**1**	**2**	**3**
Age (years)	<60	60–79	>80	
Shock	No shock (systolic BP >100 mm Hg, pulse <100 beats/min)	Tachycardia (systolic BP >100 mm Hg, pulse >100 beats/min)	Hypotension (systolic BP <100 mm Hg, pulse >100 beats/min)	
Comorbidity	Nil major		Cardiac failure, ischemic heart disease, any major comorbid condition	Renal failure, liver failure, disseminated malignancy
Diagnosis	Mallory-Weiss tear, no lesion, and no SRH	All other diagnoses	Malignancy of upper GI tract	
Major SRH	None or dark spot		Blood in upper GI tract, adherent clot, visible or spurting vessel	

[a]The score is calculated by adding the points from each variable. A score of 2 or less is associated with a low risk of further bleeding or death.
BP, Blood pressure; *GI,* gastrointestinal; *SRH,* stigma(ta) of recent hemorrhage.
From Rockall TA, Logan RF, Delvin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut.* 1996;38:316–321.

• BOX 72.1 Historical Features in the Assessment of Gastrointestinal Bleeding

Age
Previous bleeding
Previous gastrointestinal disease
Previous surgery
Underlying medical disorder (especially liver disease)
Nonsteroidal anti-inflammatory drugs
Abdominal pain
Change in bowel habits
Weight loss or anorexia
History of oropharyngeal disease

From Rockey DC. Gastrointestinal bleeding. Gastroenterol Clin North Am. *2005;34:581–588.*

A previous history of bleeding from PUD, esophageal or gastric varices, diverticulosis, or vascular ectasia puts these diagnoses high on the differential diagnosis list. A history of abdominal vascular surgery adds aortoenteric fistula to this list. In patients with known liver disease, the possibility of bleeding from conditions associated with portal hypertension, such as esophageal or gastric varices and portal gastropathy, should be raised. One should also look for risk factors for chronic liver disease, such as a history of chronic alcohol abuse and chronic hepatitis.

GI bleeding in elderly patients is usually caused by conditions less commonly encountered in younger patients (i.e., diverticulosis, vascular ectasia, ischemic colitis), whereas in younger patients, bleeding from sources such as varices, ulcer disease, and esophagitis is more common.

Ingestion of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) increases the risk of bleeding from PUD. In patients taking anticoagulant medications, bleeding most often results from underlying GI disease such as ulcer disease or vascular ectasia, even in the setting of a supratherapeutic international normalized ratio, and should not be attributed to the anticoagulation itself.

Other medical conditions present at the time of the bleeding can have a large impact on the resuscitation efforts and subsequent management. Bleeding patients with a history of coronary artery disease are at increased risk for myocardial infarction, and restoration of volume and oxygenation should be an immediate goal. Patients with pulmonary disease may need airway intubation before sedation when endoscopy is being contemplated.

Physical examination should look for evidence of chronic liver disease, such as spider angiomas, gynecomastia, splenomegaly, and ascites. The presence of these signs suggests the possibility of portal hypertension. Telangiectases of the skin or mucous membranes and lips raise the possibility of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Acanthosis nigricans can be a sign of GI malignancy (especially gastric cancer). The presence of purpura suggests vascular diseases such as Henoch-Schönlein purpura or polyarteritis nodosa. Tenderness with or without peritoneal signs on abdominal examination may indicate PUD, ischemia, or perforation. The abdominal examination should include percussion and palpation to look for organomegaly and masses. Bedside examination of the character of the stool is a necessary measure that provides critical information about the source and severity of the bleeding episode. Bright red blood per rectum, maroon-colored stools, and melena suggest active bleeding, whereas brown stools indicate less aggressive bleeding.

The use of a nasogastric tube in patients presenting with GI bleeding is a common practice but at the same time controversial. The presumed benefits of nasogastric lavage include confirmation of an upper GI source of bleeding, better visualization during endoscopy, and prediction of high-risk lesions, such as an oozing or spurting lesion and nonbleeding visible vessel. A bloody aspirate suggests, with some degree of certainty, an upper source of bleeding because false-positive results are rare and generally related to nasogastric trauma.[21] In one study of patients presenting with suspected upper GI bleeding, 45% of cases with a bloody aspirate were associated with a high-risk lesion on endoscopy versus 15% when the aspirate was clear or bilious.[22] Identifying patients with high-risk lesions is important because those patients have the worst outcome and early endoscopic therapy may have the most benefit.

However, the positive and negative predictive values of a bloody aspirate for high-risk lesions are only 45% and 85%, respectively, which makes basing the decision of an early endoscopy on the information obtained by the nasogastric lavage controversial. In a retrospective study of the impact of performance of nasogastric lavage, this practice was associated with earlier time to endoscopy but had no effect on mortality rate, length of hospital stay, surgery, or transfusion requirements.[23] In another recent randomized trial of nasogastric tube placement in patients with acute upper GI bleeding, routine nasogastric placement did not improve physicians' ability to predict the culprit bleeding lesion, did not affect rebleeding rates or mortality, and was complicated with pain and nasal bleeding in more than 25% of patients.[24] In our opinion, if an upper endoscopy is planned in the next 12 to 24 hours after presentation of a patient with suspected upper GI bleeding, nasogastric lavage should be avoided owing to lack of proven benefit and major discomfort and pain inflicted to the patient. In the setting of hematochezia with hemodynamic instability, extremely brisk upper GI bleeding should be suspected, and a positive nasogastric aspirate result can confirm this suspicion.

Diagnostic Tests

The initial laboratory evaluation in patients with GI bleeding should include a complete blood cell count, liver enzymes, prothrombin time, blood urea nitrogen, and creatinine. As mentioned earlier, the first hematocrit level may be falsely reassuring, so management decisions should rely on other parameters such as hemodynamics and the nature of the bleeding. A high white blood cell count should alert one to the presence of ischemia or infarction. Thrombocytopenia can be a sign of portal hypertension, and a critically low platelet count, as well as a high prothrombin time, should be addressed immediately by transfusion of platelets and fresh frozen plasma. An elevation in the blood urea nitrogen level disproportionate to creatinine is compatible with upper GI bleeding but may also be seen with intravascular volume depletion from any source of bleeding. In one study, this ratio was significantly higher in patients with upper GI bleeding than in those with lower GI bleeding (22.5 ± 11.5 vs. 15.9 ± 8.2; $P = 0.001$); however, the degree of overlap shows the poor discriminatory value of this ratio.[25] In another study, a ratio greater than 36 had a specificity of 27% and a sensitivity of 90% for upper GI bleeding.[26]

After initial resuscitation and stabilization, a diagnostic plan should be initiated. Several diagnostic tools are available, including endoscopy, radionuclide imaging, and angiography. These tests are aimed at detecting the location, source, and activity of bleeding. Other tests may be necessary in specific clinical situations, such as computed tomography (CT) scanning when abdominal pain is a prominent complaint to rule out ischemia, infarction, and perforation. Endoscopy and to some extent angiography have the advantage of allowing both diagnosis and therapy.

Therapeutic Options

In addition to controlling the current episode of bleeding, treatment is also aimed at preventing recurrent bleeding. The available forms of therapy are pharmacologic, endoscopic, angiographic, and surgical. They are often complementary and require a multidisciplinary team approach. Use of these different modalities varies with the specific cause and source of bleeding.

Advances in potent acid suppression with the advent of proton pump inhibitors (PPIs) and the progress made in endoscopic technology have revolutionized the management of GI bleeding. Effective acid suppression has an established role in decreasing bleeding recurrence. Different endoscopic treatment modalities can be used alone or in combination during endoscopy and have been shown to decrease bleeding recurrence. Such modalities include injection, cautery, and mechanical therapy.

Detailed approaches to the diagnostic and therapeutic options are highlighted in specific sections of this chapter.

Upper Gastrointestinal Bleeding

Differential Diagnosis

Nonvariceal Bleeding

Nonvariceal upper GI bleeding remains a significant cause of death and morbidity despite recent advances in pharmacologic and endoscopic therapy. The cause of nonvariceal bleeding encompasses a large array of diagnoses involving multiple organs above the ligament of Treitz and at times outside the GI tract. The causes and frequency of nonvariceal bleeding are listed in Table 72.4.[27]

Peptic Ulcer Disease

PUD traditionally refers to gastric and duodenal ulcers, gastritis, and duodenitis. A number of population-based and prospective studies rank PUD as the most common source of acute upper GI bleeding, with PUD representing up to 50% of all such cases.[28] However, analysis from the Clinical Outcomes Research Initiative database reported that the most common endoscopic finding in persons with acute upper GI bleeding was "mucosal abnormality" (40%), and gastric or duodenal ulcers were found in 20.6%.[29] Eradication of *Helicobacter pylori* and extensive use of PPIs are probably responsible for this observed decline in the frequency of PUD.

The most important factors predisposing to ulcer disease include acid, *H. pylori* infection, and NSAIDs; however, the role of some of these risk factors in inducing ulcer bleeding remains unclear. Indirect evidence regarding the role of acid in ulcer bleeding comes from data showing that acid suppression by PPIs in patients with active or recent bleeding reduces the risk for rebleeding.[30] Evidence of the association between NSAIDs and ulcer bleeding is strong and comes from both placebo-controlled and case-control studies.[31,32]

TABLE 72.4 Causes of Nonvariceal Upper Gastrointestinal Bleeding

Diagnosis	Incidence (%)
Peptic ulcer	30–50
Mallory-Weiss tear	15–20
Erosive gastritis or duodenitis	10–15
Esophagitis	5–10
Malignancy	1–2
Angiodysplasia or vascular malformations	5
Other	5

From Ferguson CB, Mitchell RM. Nonvariceal upper gastrointestinal bleeding: standard and new treatment. *Gastroenterol Clin North Am.* 2005;34:607–621.

The pathogenesis of bleeding from an ulcer involves aneurysmal dilation with an intense arteritis associated with a marked inflammatory response.[33] When eroding into large vessels, ulcers can cause catastrophic bleeding. This most commonly occurs in the posterior portion of the duodenal bulb, where ulcers can erode directly into the pancreaticoduodenal artery.

Other Sources of Nonvariceal Upper Gastrointestinal Bleeding

MWTs are mucosal and occasionally submucosal lacerations caused by sudden increases in pressure within the cardia and lower esophagus produced by retching. MWTs are responsible for 5% to 15% of upper GI bleeding.[28] The majority of upper GI bleeding caused by MWTs stops spontaneously and does not require any blood transfusion or endoscopic treatment. However, some cases are severe enough to require endoscopic hemostasis and occasionally angiography with embolization or even surgery. A history of retching on arrival at the emergency department is not always present.[34] Endoscopically, tears are usually 1.5 to 2 cm in length and occur at the gastroesophageal junction or, most commonly, in the proximal part of the stomach (Fig. 72.2).

Angiodysplasia, also referred to as arteriovenous malformation or vascular ectasia, is another source of upper GI bleeding and accounts for approximately 5% to 10% of cases.[28] It occurs in inherited syndromes such as hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) and blue rubber bleb nevus syndrome, but most cases are acquired.[35] The association of angiodysplasia with medical conditions such as renal failure, aortic stenosis, connective tissue disease (scleroderma), and von Willebrand disease has been recognized, but the evidence for these associations is limited.[28,36]

Dieulafoy lesion is an underrecognized cause of upper GI bleeding and is described as a visible vessel protruding from a small mucosal defect without any underlying ulcer.[28] It has also been called "caliber-persistent artery" in submucosal tissue. Bleeding from Dieulafoy lesion represents less than 5% of cases of upper GI bleeding.[37,38] The lesion is generally located on the lesser curvature within 6 cm of the gastroesophageal junction and can be difficult to detect because of its small size and normal surrounding mucosa (Fig. 72.3).[36]

Benign and malignant neoplasms are responsible for less than 5% of upper GI bleeding.[39] Bleeding can be the initial symptom of tumors originating from the esophagus, stomach, or small intestine. These neoplasms can be primary malignancies, such as adenocarcinoma of the esophagus, stomach, or duodenum; squamous cell carcinoma of the esophagus; and gastric or duodenal lymphomas. GI stromal cell tumors, carcinoid tumors, and lipomas are examples of benign tumors that can cause upper GI bleeding.[28]

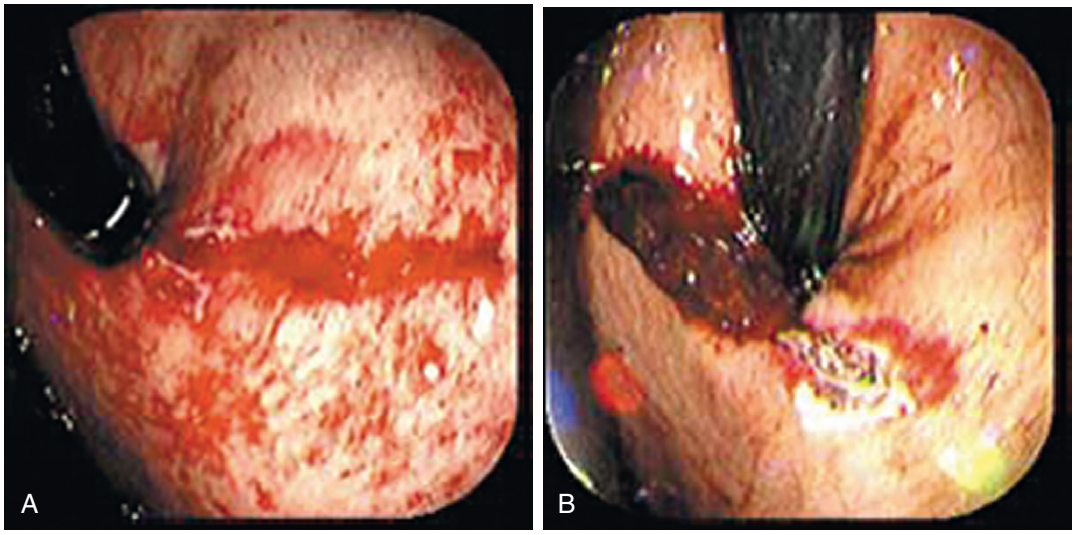
Upper GI bleeding from an aortoenteric fistula is very rare but should be considered in the appropriate clinical setting (such as a patient with a history of aortic aneurysm repair). Fistulas are generally located in the third portion of the duodenum. Patients frequently have a small hemorrhage first, known as a "herald bleed," that occurs before a major hemorrhage.[40]

Another rare cause of upper GI bleeding is hemobilia. It can occur after liver biopsy or hepatobiliary tree instrumentation (such as with endoscopic retrograde cholangiopancreatography) or from biliary tumors.

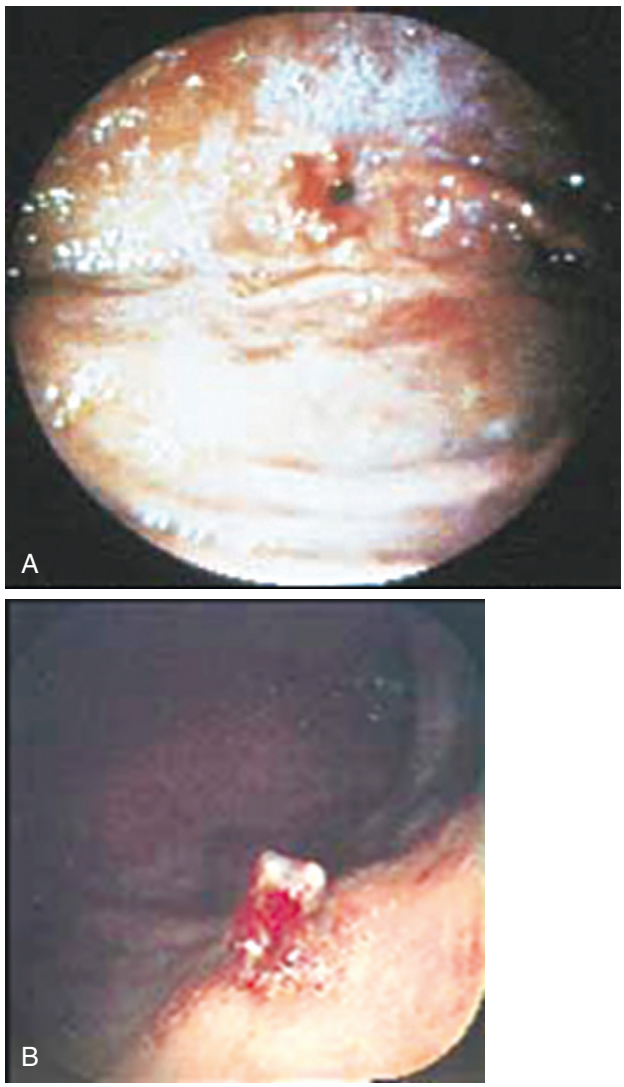
Hemosuccus pancreaticus is an uncommon cause of upper GI bleeding that occurs secondary to pseudoaneurysm formation and rupture into the pancreatic duct as a complication of a pancreatic pseudocyst in patients with chronic pancreatitis.[41]

Bleeding Secondary to Portal Hypertension

Portal hypertension is defined by a hepatic venous pressure gradient (HVPG) greater than 5 mm Hg. HVPG represents the difference between portal vein pressure and free hepatic vein pressure. Portal hypertension is most commonly related to cirrhosis but can be secondary to a variety of other conditions. It has been classified as prehepatic, hepatic, and posthepatic, depending on the location of the obstruction to flow. Examples of noncirrhotic portal hypertension include portal vein thrombosis, Budd-Chiari syndrome, and constrictive pericarditis. In the presence of portal hypertension, the development of portosystemic collateral venous drainage results



• **Fig. 72.2** A, Mallory-Weiss tear in the cardia of the stomach. Active bleeding is seen. B, The same tear seen in A after injection with epinephrine and coagulation. The bleeding is controlled. (From Schmulewitz N, O'Connor JB. Esophageal disease caused by medication, radiation and internal trauma. In: DiMarino AJ, Benjamin S [eds]. *Gastrointestinal Disease: An Endoscopic Approach.* 2nd ed. Thorofare, NJ: Slack; 2002:245–262.)



• **Fig. 72.3** A and B, Endoscopic appearance of Dieulafoy lesion in the proximal part of the stomach. (From Bashir RM, Al-Kawas FH. Vascular lesions of the stomach. In: DiMarino AJ, Benjamin S [eds]. *Gastrointestinal disease: An endoscopic approach*. 2nd ed. Thorofare, NJ: Slack; 2002:535–550.)

in the formation of varices. Varices develop most commonly in the distal portion of the esophagus and the stomach. Ectopic varices can be seen in the duodenum, jejunum, or colon; at the level of stomas (ileostomy and colostomy); and in the anorectal region. Most portal hypertensive bleeding results from ruptured esophageal varices, but clinically significant bleeding can also be secondary to gastric varices, portal gastropathy, and ectopic varices.

Esophageal Varices

The incidence of varices among all patients with cirrhosis is around 50%. However, if monitored long enough, varices eventually develop in most cirrhotics.[42] Variceal hemorrhage occurs in a third of cirrhotic patients with varices. Although portal hypertension is defined by an HVPG greater than 5 mm Hg, Garcia-Tsao and colleagues showed that varices do not develop and hence do not bleed as long as the HVPG is less than 12 mm Hg.[43] However, once this threshold is reached, there is poor correlation between the pressure gradient and the risk for bleeding. Other risk factors associated with variceal bleeding include the degree of liver disease (provided by the Child classification), variceal location and size (higher risk near the gastroesophageal junction and with large varices), and the presence of particular endoscopic signs (red wale markings suggestive of dilated longitudinal venules, cherry-red spots, and hematocystic spots consisting of small red dots or a reddish blister-like formation on the variceal surface and the white or purple nipple sign on a varix) (Fig. 72.4).[42,44]

Gastric Varices

Sarin and colleagues classified gastric varices into two groups: (1) isolated gastric varices and (2) gastroesophageal varices (GEVs) that are continuous with esophageal varices and extending to the cardia (GEV 1) or to the fundus (GEV 2).[45] The authors found that GEV 1 was the most common type of gastric varix but isolated gastric varices were the type that bleeds the most. Although the incidence of bleeding from gastric varices is in the range of 10% to 36%, it is usually massive and associated with high mortality rates.[46]

Diagnostic Evaluation

Endoscopic Examination

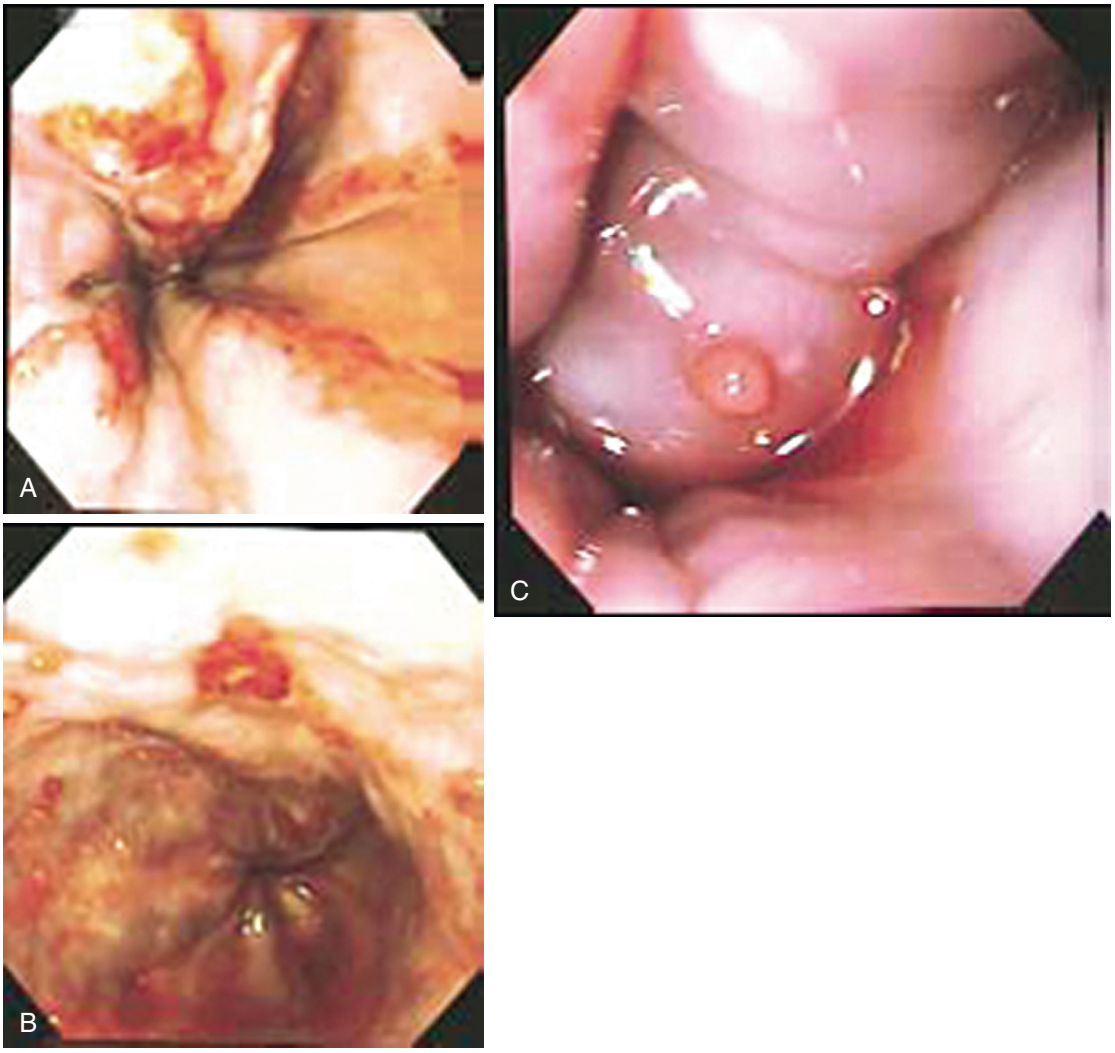
After the initial evaluation, resuscitation, and stabilization of a patient with upper GI bleeding, effort is directed at localization and treatment of the hemorrhage. Endoscopy has become the preferred diagnostic and therapeutic modality for upper GI bleeding because of its accuracy and low complication rate. With its use, a specific diagnosis can be achieved in 95% of patients. The use of promotility agents such as metoclopramide and IV erythromycin (250 mg by IV bolus or 3 mg/kg over a 30-minute period) before the endoscopic examination can significantly improve mucosal visibility by promoting gastric motility and emptying of gastric contents.[47–49] Two meta-analyses of the benefit of prokinetics showed a significant reduction in the need for repeat endoscopy.[50,51] The QT-interval–prolonging effect of erythromycin should be taken into consideration and an electrocardiogram first performed.

The optimal timing of endoscopy remains a balance between clinical need and resources and is still subject to controversy.[27] Endoscopy has to be delayed or deferred in selected high-risk patients such as patients with bowel perforation or acute coronary syndrome. In a meta-analysis of the timing of endoscopy, no significant reduction in rebleeding, surgery, or mortality rate was found with urgent endoscopy (1–12 hours) compared with later endoscopy (>12 hours).[13] In a subset of patients with bloody gastric lavage, length of hospital stay and blood transfusion requirements were significantly lower in the urgent endoscopy group (within 12 hours).[52] Guidelines from American and European societies recommend the performance of upper endoscopy within 24 hours in patients with suspected nonvariceal upper GI bleeding, and within 12 hours in patients with higher-risk clinical features (e.g., tachycardia, hypotension, bloody emesis, or nasogastric aspirate in the hospital).[53,54]

One major role of endoscopy is to identify stigmata of recent hemorrhage known to correlate well with an increased risk for rebleeding and thus a need for endoscopic therapy. Rates of rebleeding with these specific endoscopic findings are summarized in Table 72.5.[55]

Nonendoscopic Assessment

When endoscopy cannot be performed or has not yielded a definitive diagnosis, angiography and radionuclide imaging may be useful



• **Fig. 72.4** A to C, Esophageal varices with red color and white nipple signs. (From Sheikh RA, Prindiville TP, Trudeau W. Gastrointestinal bleeding in portal hypertension. In: DiMarino AJ, Benjamin S [eds]. *Gastrointestinal Disease: An Endoscopic Approach.* 2nd ed. Thorofare, NJ: Slack; 2002:605–644.)

alternatives. Such endoscopic failures are most often related to anatomic situations (i.e., strictures or surgical alterations) preventing full endoscopy. Esophagography and upper GI series are no longer used as part of the diagnostic evaluation of patients with upper GI bleeding.

Therapeutic Alternatives

Nonvariceal Bleeding

Pharmacotherapy

Acid suppression has been shown to play a role in the inactivation of pepsin, optimization of platelet function, and inhibition of fibrinolysis. Subsequently, clot stabilization and ulcer healing may be more effective and rapid within a less acidic environment. This constitutes the rationale for acid suppressive therapy in patients with bleeding peptic ulcers.

Treatment with PPIs before the performance of upper endoscopy has been shown to down-stage the endoscopic lesion and decrease the need for endoscopic intervention.[13] However, a meta-analysis of six randomized trials showed that a PPI given to patients with upper GI bleeding soon after presentation did not significantly reduce the risks of further bleeding, surgery, or death.[56]

Once endoscopy is performed, the role of PPI therapy becomes more obvious. In patients found to have high-risk lesions treated endoscopically, the guidelines recommend an IV bolus followed by continuous-infusion PPI therapy.[13,53,54] The use of a continuous infusion is supported by data showing that maintenance of intragastric pH at greater than 6 after endoscopic hemostasis is associated with the lowest rebleeding rates and that this goal can be achieved only by bolus administration of a PPI followed by a constant infusion.[57] However, a recent meta-analysis showed that intermittent oral or IV PPI therapy resulted in outcomes that were noninferior to those after continuous infusion.[58]

Other agents with different mechanisms of action have been studied in patients with upper GI bleeding. A reduction in splanchnic blood flow with somatostatin and its analogs (such as octreotide) is an attractive measure in patients with upper GI bleeding and has been the subject of several trials, with conflicting results.[59–61] To date, the available data are not convincingly in favor of using these agents in patients with nonvariceal upper GI bleeding,

TABLE 72.5 Stigmata of Ulcer Hemorrhage and Risk for Recurrent Bleeding Without Endoscopic Therapy

Endoscopic Finding	Risk for Recurrent Bleeding Without Therapy
Active arterial (spurting) bleeding	Approaches 100%
Nonbleeding visible vessel ("pigmented protuberance")	Up to 50%
Nonbleeding adherent clot	30%–35%
Ulcer oozing (without other stigmata)	10%–27%
Flat spots	<8%
Clean-based ulcers	<3%

From ASGE Standards of Practice Committee. ASGE guideline: the role of endoscopy in acute nonvariceal upper GI-hemorrhage. *Gastrointest Endosc.* 1999;49:145–152; and ASGE Standards of Practice Committee. ASGE guideline: the role of endoscopy in acute nonvariceal upper GI-hemorrhage. *Gastrointest Endosc.* 1999;49:145–152.

even though some authors find them useful in patients who are bleeding uncontrollably while awaiting endoscopy or surgery or in whom surgery is contraindicated.[59]

Endoscopic Therapy

Endoscopic therapy for nonvariceal upper GI bleeding in patients with high-risk lesions has been shown to reduce the rate of rebleeding, need for surgery, and mortality rate.[62] It is indicated in patients with active bleeding, spurting arterial vessels, and nonbleeding visible vessels in an underlying ulcer.[55] When a clot is found in an ulcer bed, targeted irrigation in an attempt at dislodgment with treatment of the underlying lesion is indicated. If the clot remains adherent after irrigation, endoscopic therapy (injection followed by snaring of the clot) may be considered but intensive PPI therapy alone may be sufficient.[13] Different forms of endoscopic therapy include injection technique, thermal technique, mechanical technique, and topical spray. In many cases, a combination of these modalities is used to treat a single bleeding lesion or one at high risk of bleeding.

Injection therapy results in hemostasis, probably from a combination of vascular tamponade and the pharmacologic effect of the injected agent. Agents used for injection include normal saline solution, epinephrine, and sclerosants such as ethanol, ethanolamine, and polidocanol. In addition to the local tamponade effect of normal saline solution and epinephrine, the latter has a vasoconstricting effect. Sclerosant agents work by causing direct tissue injury and thrombosis.[55] Epinephrine at a concentration of 1 : 10,000 or 1 : 20,000 is the most commonly used agent, sometimes in conjunction with other agents or techniques.

Thermal therapy consists of the delivery of heat to the mucosa, which results in edema, coagulation of tissue proteins, and contraction of arteries. When heat is delivered through a contact probe, an additional effect is achieved by mechanical compression of the target artery before delivery of the heat.

Thermal energy can be delivered through noncontact techniques, such as the neodymium-yttrium-aluminum garnet and argon lasers and argon plasma coagulation (APC). The laser technique has been abandoned because of its high cost and the high risk of complications associated with its use. In APC, the argon gas forms a plasma and acts as an electrical conductor of the current, thereby resulting in coagulation of superficial tissues. Despite comparable results with the heater probe technique when used for ulcer bleeding,[63] APC is used primarily for the treatment of superficial lesions such as vascular abnormalities.[55]

Contact thermal techniques refer to the delivery of heat through direct contact of the mucosa with heater probes or electrocautery probes (monopolar and bipolar probes). The heater probe is an aluminum cylinder that delivers a programmed amount of energy (heat) through its end or sides to the tissue. The catheter tip can also be used to apply firm pressure on the bleeding point or the visible vessel. Electrocautery probes use an electrical current that passes from the electrode tip through the patient's body to a grounding plate (monopolar) or flows between two or more electrodes at the probe tip (bipolar or multipolar). The advantage of the bipolar (multipolar) probe is that the concentration of current at the level of the tip results in less depth of tissue injury and lower potential for perforation.

Mechanical therapy refers to the use of a device that causes physical tamponade of a bleeding site. Such devices include metallic clips, sewing devices, rubber band ligation, and endoloops. Metallic clips are the most studied of these devices and have shown variable success, probably because of the difficulty encountered with their placement. Some authors have suggested the use of clips in combination with other endoscopic treatments.[59]

Topical hemostatic sprays have been recently introduced with promising results. They consist of absorbent powder that rapidly concentrates clotting factors at the bleeding site. The advantages of topical therapy include ease of use, access to lesions in difficult areas, and the ability to treat large surfaces. However, the role of this new modality remains ill-defined in the absence of trials comparing it to other traditional hemostasis methods.[64]

The choice of endoscopic therapy depends on the stigmata of ulcer hemorrhage and the experience of the endoscopist. Monotherapy with epinephrine injection has been shown to be more effective than medical therapy in patients with high-risk lesions. However, it is inferior to other monotherapies (thermal or mechanical) or to combination therapy that uses two or more methods.[13] Epinephrine plus a second method significantly reduces rates of rebleeding, surgery and mortality when compared with epinephrine alone.[65]

Angiographic Therapy

Angiography can be useful as a potential diagnostic and therapeutic modality in specific cases of upper GI bleeding when endoscopy cannot be performed or fails to reveal the bleeding site and when endoscopic hemostasis is unsuccessful. It is also considered in patients who are poor surgical candidates.

Angiographic or "transcatheter" intervention in cases of upper GI bleeding involves two techniques: infusion of vasoconstricting medication and mechanical occlusion (embolization) of the arterial supply responsible for the hemorrhage. Vasopressin infusion induces vasoconstriction and results in cessation of bleeding in 70% to 80% of cases initially, but rebleeding occurs in up to 20%. Complications can range from problems related to arterial access to pulmonary edema and myocardial depression.[66] Vasopressin infusion has lost favor with the advent of embolization. Transcatheter embolization has become the mainstay for the radiographic treatment of nonvariceal upper GI bleeding and ranks second after endoscopic therapy in most centers.[67] The embolic material used

can be temporary (such as a gelatin sponge and autologous clot) or permanent (such as coils). Clinical success with embolization ranges from 52% to 91%. Potential complications of embolization include ischemia and perforation.[67]

Surgical Therapy

When endoscopic hemostasis fails to control the bleeding or when hemorrhage recurs after successful control of bleeding, surgical intervention provides an alternative therapeutic option. The main goal of surgery is control of active bleeding and prevention of exsanguination, with a secondary aim to prevent recurrent ulceration. The choice of operation depends on the location of the bleeding lesion and the surgeon's expertise. Truncal vagotomy with antrectomy and vagotomy with pyloroplasty are examples of operations performed in cases of nonvariceal upper GI bleeding. Total gastrectomy is rarely indicated. Because recurrent ulcers can be prevented by avoiding NSAIDs, eliminating *H. pylori* if present, or administering prophylactic PPI therapy, most ulcer operations for acute bleeding focus on oversewing the ulcer rather than performing the more definitive surgeries just listed.

Variceal Bleeding

Pharmacotherapy

Pharmacologic agents used in the treatment of acute variceal bleeding are aimed at reducing portal pressure by either decreasing portal blood flow or reducing intrahepatic resistance. Infusion of vasoactive agents constitutes an adjunct to endoscopic therapy and often precedes endoscopy when suspicion of variceal bleeding is high.

Vasopressin, terlipressin, somatostatin, and somatostatin analogs (octreotide and lanreotide) all induce constriction of the splanchnic vasculature and result in a decrease in portal blood flow. Vasopressin causes systemic vasoconstriction, as well as splanchnic vasoconstriction, and can lead to adverse effects, such as myocardial ischemia and infarction and cerebrovascular accidents.[68] These dangerous side effects led to the combination of vasopressin with other agents and the search for analogs with a better safety profile.

In one study, the combination of vasopressin with nitroglycerin resulted in a reduction in side effects and improved efficacy over vasopressin alone.[68] Nitroglycerin, a potent venous dilator, decreases the hemodynamic side effects of vasopressin and at the same time reduces intrahepatic resistance, thereby resulting in a further reduction in portal pressure.

Terlipressin is a synthetic analog of vasopressin with a longer duration of action and fewer side effects than vasopressin. Unlike other vasoactive agents, terlipressin has been shown to reduce mortality rate when compared with placebo.[69] At present, terlipressin is not available nor approved for use in the United States.

Somatostatin is a naturally occurring peptide that induces splanchnic vasoconstriction without affecting the systemic circulation and thus results in a decrease in portal pressure. When compared with vasopressin, somatostatin was equivalent in bleeding control but had significantly fewer side effects.[70] Further data suggested that somatostatin has the greatest effect when used in conjunction with endoscopic therapy.[71,72] Octreotide, a somatostatin analog, is approved for use in variceal bleeding in the United States. Meta-analyses of the efficacy of octreotide led to controversial results.[70,73] One meta-analysis of trials of somatostatin analogs in general showed a negligible effect.[74] However, octreotide appears to be useful as an adjunct to endoscopic therapy.[75,76] At present, because of its excellent safety profile and easy availability, octreotide (50-µg bolus followed by a 50-µg/h continuous infusion for 3–5 days) is almost always used in conjunction with endoscopic therapy.

The use of prophylactic antibiotics in patients with variceal bleeding has been shown to decrease the mortality rate in several randomized controlled trials.[71] The rationale behind antibiotic prophylaxis derives from the fact that bacterial infection is present in up to 20% of patients with cirrhosis who are admitted with variceal bleeding and that infection develops in as many as 50% of patients while hospitalized.[77] The mortality rate is significantly higher in infected patients with cirrhosis than in those with cirrhosis who are noninfected.[78,79] Furthermore, infected patients with cirrhosis have a higher rate of variceal rebleeding.[80] This is probably due to the presence of cytokines and endotoxins that induce hematologic abnormalities, such as platelet dysfunction and activation of the coagulation and fibrinolytic systems.[71] An updated meta-analysis showed that antibiotic prophylaxis significantly reduced the all-cause mortality rate, bacterial infection mortality rate, rebleeding events, and length of hospital stay.[81] Prophylaxis benefits were observed regardless of the type of antibiotic used. Nonabsorbable antibiotics, quinolones, and more recently cephalosporins have all been used with good success. Recent concerns have been raised about bacterial resistance and potential decreased benefit with quinolones in some geographic areas.[81]

Endoscopic Therapy

Endoscopic sclerotherapy and endoscopic band ligation are the mainstays of therapy for acute variceal bleeding. These procedures are successful in achieving hemostasis in 80% to 90% of patients.[71]

Sclerotherapy consists of intravariceal or paravariceal injection of a sclerosant agent such as sodium tetradecyl sulfate or ethanolamine. These agents provoke a severe inflammatory reaction within or around the varix that leads to variceal thrombosis and obliteration. Despite its high effectiveness in controlling bleeding, the complication rate with sclerotherapy can be as high as 40%.[84] Complications range from local effects, such as deep ulcers causing rebleeding, odynophagia, and in some cases perforation to bacteremia and systemic complications such as pleural and pericardial effusion. Esophageal stricture is the most common long-term side effect of sclerotherapy. Once the acute bleeding is controlled, repeated sessions of sclerotherapy are required to eradicate the varices and prevent rebleeding.

Endoscopic band ligation consists of the placement of a ligating device on the tip of the endoscope, and elastic rings are placed over the targeted varix (Fig. 72.5). With the availability of multiband ligating devices, 5 to 10 bands can be deployed in one session. Band ligation has a lower rate of complication (including the rebleeding rate in some but not all studies[85]) than sclerotherapy does, but it can be difficult to perform during acute bleeding.[71] Superficial mucosal ulceration occurs when the elastic ring and underlying tissue slough off. Transient chest discomfort and dysphagia are common after band ligation. Band ligation also has the advantage of achieving eradication of varices with fewer endoscopic sessions than are typically needed for sclerotherapy.[85]

A meta-analysis of 10 randomized clinical trials showed an almost significant benefit of endoscopic band ligation over sclerotherapy in the initial control of bleeding.[86] A practice guideline by the American Association for the Study of Liver Diseases recommends the use of endoscopic band ligation as the preferred form of endoscopic therapy and the use of sclerotherapy when band ligation is not technically feasible.[76]

The management of gastric varices depends on their location: GEV 1 (gastroesophageal varices extending to the cardia) are managed the same way as esophageal varices, whereas banding is not effective for GEV 2 (varices extending to the fundus) and

• **Fig. 72.5** Esophageal varices immediately after band ligation. (From Bashir RM, Al-Kawas FH. Vascular lesions of the stomach. In: DiMarino AJ, Benjamin S [eds]. *Gastrointestinal Disease: An Endoscopic Approach*. 2nd ed. Thorofare, NJ: Slack; 2002:245–262.)

isolated gastric varices. Fundic varices are usually treated with injection of cyanoacrylate glue. However, although used extensively in Europe and Asia with excellent outcomes, cyanoacrylate glue is not approved by the U.S. Food and Drug Administration.[87]

Balloon Tamponade

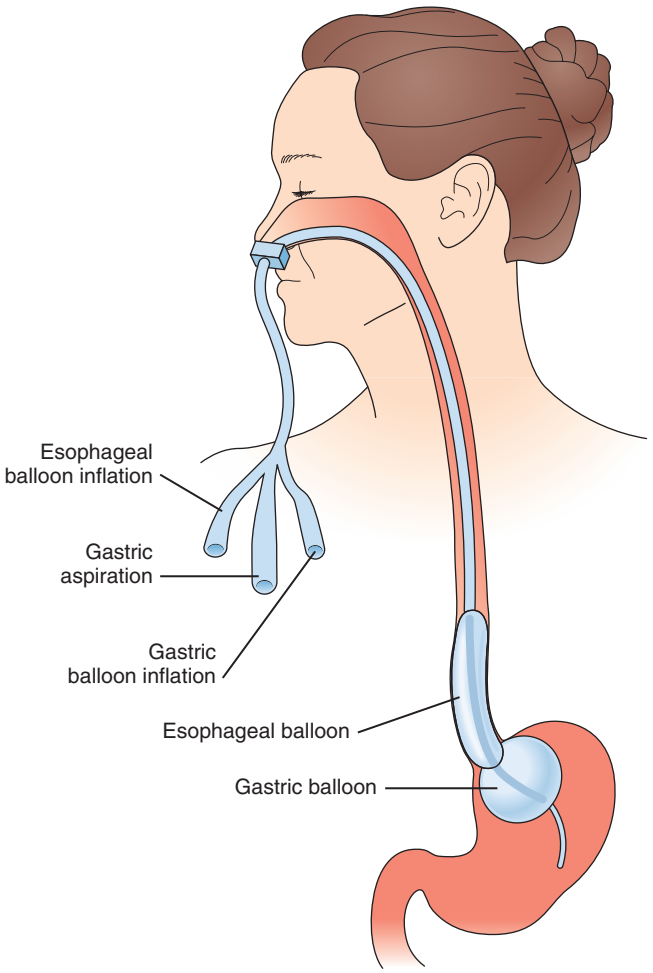
The use of balloon tamponade in the control of active variceal bleeding comes as a last resort when other forms of therapy are not available or fail to achieve hemostasis. Three balloons have been used for this purpose: the Minnesota tube, the Sengstaken-Blakemore tube, and the Linton-Nachlas tube. Control of bleeding with these tubes depends on patient selection, the concomitant use of other therapies, and the experience of the staff using them. With the advent of other therapies and the increasing experience of endoscopists in sclerotherapy and endoscopic banding, experience in the use of tamponade balloons decreased substantially. A major concern with the use of these tubes is the high risk of rebleeding after deflation of the balloon, in addition to the risk of esophageal rupture. Balloon tamponade should be used only as a temporary means of stabilization and as a bridge to a more definitive form of therapy. Fig. 72.6 illustrates the steps used to control bleeding with a balloon.

Esophageal Stenting

A recent randomized controlled trial compared balloon tamponade with the use of esophageal covered metal stent in patients with cirrhosis and acute refractory esophageal variceal hemorrhage. Success of therapy, defined as 15-day survival without serious adverse events or GI bleeding, was significantly more frequent in the esophageal stent group. Moreover, control of bleeding was higher and transfusional requirements and serious adverse events were lower in the esophageal stent group.[88]

Transjugular Intrahepatic Portosystemic Shunt

The transjugular intrahepatic portosystemic shunt (TIPS) procedure involves the creation of a low-resistance channel between the portal vein and the hepatic vein through which blood is shunted from the portal to the systemic circulation. Via an angiographic technique, an expandable metal stent is deployed across this channel and

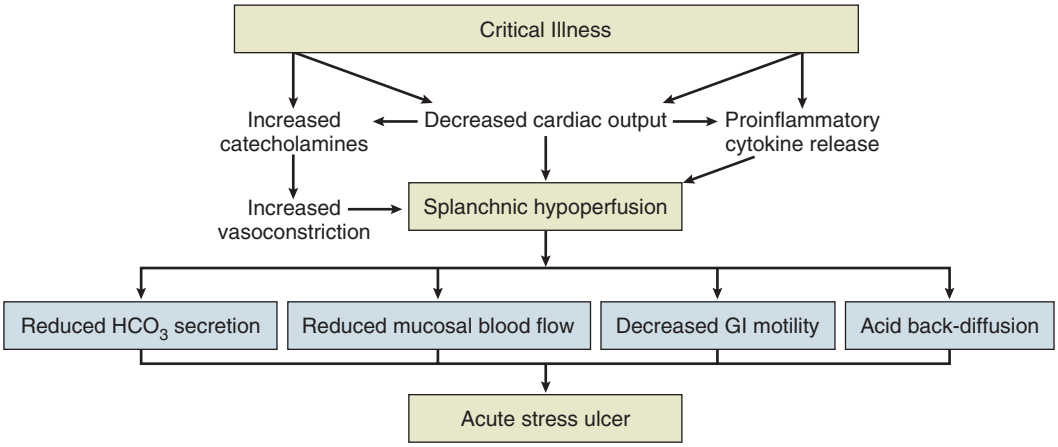


• **Fig. 72.6** Sengstaken-Blakemore tube. The tube is passed to at least the 50-cm mark. The gastric balloon is then inflated with the full recommended volume of air (usually 450–500 mL). A portable chest radiograph should be obtained to check for proper placement. The tube is pulled back gently until resistance is felt against the diaphragm. If bleeding persists from the aspiration port, the esophageal balloon is inflated to the lowest pressure needed to stop bleeding (usually 30–45 mm Hg).

results in a significant decrease in portal pressure. This technique allows the creation of a portosystemic shunt without requiring general anesthesia and major surgery. The TIPS procedure is indicated in situations in which acute variceal bleeding is refractory to endoscopic and pharmacologic therapy. It has been shown to control bleeding in more than 90% of patients, with a rebleeding rate of less than 20%.[89,90] In 2010 Garcia-Tsao and colleagues showed that an early TIPS procedure (within 24–48 hours of admission) was associated with significant decrease in mortality rate in high-risk patients (with HVPG >20 mm Hg or with Child-Pugh class C disease).[91] However, the mortality rate after the TIPS procedure in the setting of acute uncontrollable variceal bleeding is between 30% and 40%.[71] A major complication associated with this procedure is the development of encephalopathy in 10% to 20% of patients. Stenosis and complete occlusion of the shunt occur in 5% to 15% of the cases, requiring revision.

Surgical Therapy

Surgical creation of portosystemic shunts has been used for decompression of the portal system to treat and prevent variceal



• **Fig. 72.7** Pathophysiology of stress ulcers. *HCO_3,* Bicarbonate. (From Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest.* 2001;119:1222–1241.)

bleeding. The various forms of surgical shunts include portacaval shunts, distal splenorenal shunts, and partial shunts. Revascularization of the esophagus is another surgical option for the treatment of variceal bleeding. Interest in surgery has declined over the years because of the advent of the less invasive endoscopic and TIPS procedures. At present, surgery is considered only when medical and endoscopic therapy fails to control bleeding and the TIPS procedure is not available.[71]

Stress-Related Mucosal Disease

The term *stress-related mucosal disease* (SRMD) covers a spectrum of conditions ranging from superficial mucosal damage to focal deep mucosal damage (stress ulcers). The terms *stress ulcer, stress gastritis, stress erosions,* and *stress lesions* are used interchangeably in the literature. SRMD is defined as mucosal abnormalities of the upper GI tract that occur with extreme physiologic stress, typically in the ICU.

The incidence of endoscopically documented gastric lesions in patients in the ICU ranges from 74% to 100%.[92] The lesions are typically, but not exclusively, located in the fundus and body of the stomach. However, most of these lesions are of little significance because healing occurs rapidly. Clinically evident bleeding, defined as blood in a nasogastric aspirate, hematemesis, and melena, occurs in 5% to 25% of patients in the ICU. Clinically important bleeding, however, is defined as overt bleeding associated with one of the following within 24 hours of the onset of the bleeding: a drop in systolic blood pressure of greater than 20 mm Hg, an increase in the pulse rate of more than 20 beats/min and a 10-mm Hg drop in systolic blood pressure, or a decrease in hemoglobin of greater than 2 g/dL requiring blood transfusion and failure of hemoglobin to increase by the number of units transfused minus 2 g/dL.[93] Clinically important bleeding affects only 3% to 6% of critically ill patients.[94]

The pathogenesis of SRMD involves a disruption in the balance between aggressive and protective factors that leads to gastric mucosal damage. Adequate microcirculation in the upper GI tract is the most important defense mechanism against luminal aggressors such as acid and enzyme secretion, as well as infection. The role of the microcirculation is to provide nutrients and eliminate toxic oxygen-derived free radicals. In the presence of severe physiologic stress, disruption of intramucosal blood flow leads to a number of events, including the formation of toxic oxygen-derived radicals, a decrease in the synthesis of cytoprotective prostaglandins and mucus production, and a reduction in bicarbonate secretion resulting in an increase in intramural acidity (Fig. 72.7).[92,94] These events create a favorable setting for mucosal injury and ulceration.[95,96] Subsequent reperfusion also plays a major role in the development of lesions.[96]

Identification of critically ill patients at risk for significant bleeding from SRMD has been the subject of several studies. A landmark study by Cook and associates[93] demonstrated a significant increase in the risk for bleeding from SRMD in patients requiring mechanical ventilation for more than 48 hours and in those with coagulopathy (defined as thrombocytopenia [platelet count <50,000/mL^3], an international normalized ratio above 1.5, or a partial thromboplastin time more than 2.0 times the control value). Other risk factors such as shock, sepsis, renal failure, liver failure, and glucocorticoids were identified, but the association with bleeding was not statistically significant. Risk factors associated with the presence of SRMD (not necessarily bleeding) include recent major surgery, major trauma, severe burns (Curling ulcers), head trauma or coma (Cushing ulcers), and multiple organ failure.[97–99] Further understanding of the risk factors associated with bleeding from SRMD will help in directing prophylactic therapy to patients who will benefit most from this therapy.[100]

The reported mortality rates in critically ill patients with bleeding from SRMD ranges from 46% to 77%.[93,101,102] These high rates are most likely due to the underlying disease and not directly related to GI bleeding. However, they reveal the importance of significant bleeding as a sign of the degree of severity of the primary illness.

Prophylaxis

As mentioned earlier, the risk for bleeding from SRMD is significantly increased in patients undergoing prolonged mechanical ventilation and in those with coagulopathy. Such patients should benefit from the different forms of prophylaxis available.

The role of enteral nutrition in prophylaxis for SRMD is controversial.[103,104] The rationale behind the use of enteral nutrition derives from its ability to improve blood flow to the stomach and sustain mucosal immunity and integrity.[105]

When compared with placebo, antacids have been shown to decrease bleeding in patients with SRMD.[106] However, antacids require frequent dosing and monitoring of pH and are not practical

to use, especially with the advent of other effective agents for prophylaxis.

Sucralfate works by coating the gastric mucosa and forming a thin protective layer between the mucosa and the gastric acid in the lumen without affecting acid secretion and intragastric pH. The use of sucralfate for the prevention of bleeding in patients with SRMD gained interest because of theoretical concern about gram-negative bacterial overgrowth when the pH of the stomach is increased by the use of histamine 2 receptor agonists (H_2RAs) or PPIs, which can potentially lead to nosocomial pneumonia. Conflicting results were reported regarding this issue, but a large trial by Cook and colleagues in which ranitidine and sucralfate were compared showed no significant difference in the development of nosocomial pneumonia.[107] In this same trial, the incidence of clinically important bleeding was significantly lower with ranitidine. Other studies demonstrated comparable efficacy between sucralfate and antacids and H_2RAs in terms of prevention of SRMD.[108,109] One drawback to the use of sucralfate is that it may decrease the absorption of other concomitantly administered oral drugs.

IV H_2RAs are the most widely used pharmacologic agents for the prophylaxis of bleeding in patients with SRMD. A meta-analysis of studies looking at the role of H_2RAs in SRMD demonstrated a decrease in the incidence of clinically important bleeding.[106] Furthermore, H_2RAs were more effective than antacids in preventing bleeding.[106,110] Despite better control of gastric pH with continuous infusion of H_2RAs, bolus infusion has been shown to be as effective in preventing bleeding.[106,111] One major concern is the development of tolerance to H_2RAs when administered for a prolonged period.

In recent years PPIs have gained wider use in the prevention of bleeding from SRMD because of their ease of dosing, effective and predictable acid suppression, lack of need for regular gastric pH monitoring, and lack of tolerance as encountered with H_2RAs.[105] A recent meta-analysis compared the efficacy of PPIs versus H_2RAs in the prophylaxis of stress-related mucosal bleeding in critically ill patients at risk of bleeding. It demonstrated that PPI prophylaxis significantly decreased rates of clinically significant bleeding compared with H_2RAs without affecting the development of nosocomial pneumonia or mortality rates.[112]

The development of adverse events owing to acid suppression, including nosocomial pneumonia and *Clostridium difficile* infection, has been the subject of many reports with conflicting but concerning results.[113] Drug interactions, liver and bone marrow toxicity, and hypomagnesemia represent other concerns relevant to patients in ICU. These concerns should alert providers to the importance of discontinuation of acid suppression in the absence of proper indication.

Treatment

Endoscopy is the principal diagnostic and therapeutic procedure used in patients with bleeding from SRMD. The same endoscopic techniques used for hemostasis in peptic ulcer bleeding are used in SRMD when an actively bleeding lesion is found. Surgery is reserved for patients with uncontrolled hemorrhage and usually involves vagotomy, oversewing of bleeding sites, and in rare cases, subtotal or total gastrectomy.[105] In poor surgical candidates with severe uncontrolled hemorrhage, angiography may be a useful diagnostic and therapeutic option.

Lower Gastrointestinal Bleeding

Differential Diagnosis

Lower GI bleeding is defined as bleeding that originates from a source distal to the ligament of Treitz. It is caused by a diverse range of bleeding sources and can range from trivial to life-threatening bleeding. It can also be acute, arbitrarily defined as less than 3 days' duration and possibly resulting in hemodynamic compromise, or chronic, extending over a period of several days or longer and usually less severe in terms of the amount of blood loss.[114] Sources of lower GI bleeding and their incidence from several large studies are listed in Table 72.6.[115–122]

TABLE 72.6 Sources of Lower Gastrointestinal Bleeding

	NO. OF AFFECTED PATIENTS (%)							
Study	Diverticulosis	Angiodysplasia	Cancer/Polyp	Colitis/Ulcers[a]	Anorectal[b]	Others[c]	Unknown	Totals
Jensen and Machicado[116]	13 (20)	24 (37)	9 (14)	7 (11)	3 (5)	3 (5)	5 (8)	64
Longstreth[117]	91 (41)	6 (3)	20 (9)	35 (16)	10 (5)	31 (14)	26 (12)	219
Farrands and Taylor[118]	30 (29)	6 (6)	38 (36)	20 (19)	5 (5)	5 (5)	1 (1)	105
Bramley et al.[119]	60 (24)	17 (7)	25 (10)	52 (21)	22 (9)	11 (4)	64 (25)	251
Colacchio et al.[120]	98 (55)	13 (7)	14 (8)	11 (6)	5 (3)	5 (3)	32 (18)	178
Richter et al.[121]	51 (48)	13 (12)	12 (11)	6 (6)	3 (3)	7 (6)	15 (14)	107
Rossini et al.[122]	60 (15)	16 (4)	122 (30)	92 (22)	0 (0)	47 (11)	72 (18)	409
Totals	403 (33)	95 (8)	240 (19)	223 (18)	48 (4)	109 (8)	215 (16)	1333

Studies cited in this table may be found in the complete list of references for this chapter provided online.

[a]Includes inflammatory bowel disease, infectious colitis, ischemic colitis, radiation colitis, vasculitis, and inflammation of unknown origin.

[b]Includes hemorrhoids, anal fissure, and idiopathic rectal ulcers.

[c]Includes postpolypectomy bleeding, aortocolonic fistula, trauma from fecal impaction, and anastomotic bleeding.

From Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. *Gastrointest Endosc.* 1999;49:228–238.

Diverticular Bleeding

Diverticular bleeding, the most common source of lower GI bleeding, accounts for up to 40% of cases.[114] Diverticular disease is more common in the elderly. It affects up to two-thirds of people older than 80 years. Only 3% to 15% of patients with diverticulosis experience diverticular bleeding.[114]

Patients with diverticular bleeding typically have painless hematochezia. Most patients stop bleeding spontaneously, but the bleeding can recur in 10% to 40% of cases.[123]

The bleeding is thought to occur after repetitive trauma to the vasa recta (nutrient arteries) that stretch over the diverticular dome.[124] NSAIDs have been associated with increased risk for diverticular bleeding.[125]

Ischemic Colitis and Other Forms of Colitis

Ischemic colitis accounts for up to 19% of lower GI bleeding.[114] It results from a sudden reduction in mesenteric blood flow. As opposed to acute mesenteric ischemia, this reduction is transient and reversible. The typical regions affected are the "watershed" areas of the colon: the splenic flexure, the rectosigmoid junction, and the right colon. Ischemia is precipitated by any event that compromises colonic blood flow. Clinically, patients have a sudden onset of abdominal pain, followed by hematochezia within 24 hours. Endoscopically, ischemia is suspected in the presence of bluish hemorrhagic nodules from submucosal bleeding, cyanotic or necrotic mucosa with hemorrhagic ulcerations, or segmental distribution with an abrupt transition between injured and normal mucosa (Fig. 72.8).[114] Most cases of ischemic colitis resolve spontaneously with supportive treatment. Rare cases require surgery (if peritoneal signs are present) or develop chronic ischemic colitis with stricture formation. Ischemic colitis is a common cause of lower GI bleeding in patients in the ICU because of the frequent hemodynamic instability in this setting.[126]

Infectious colitis, radiation colitis, and inflammatory bowel diseases can also result in bloody diarrhea, but the bleeding is rarely severe.

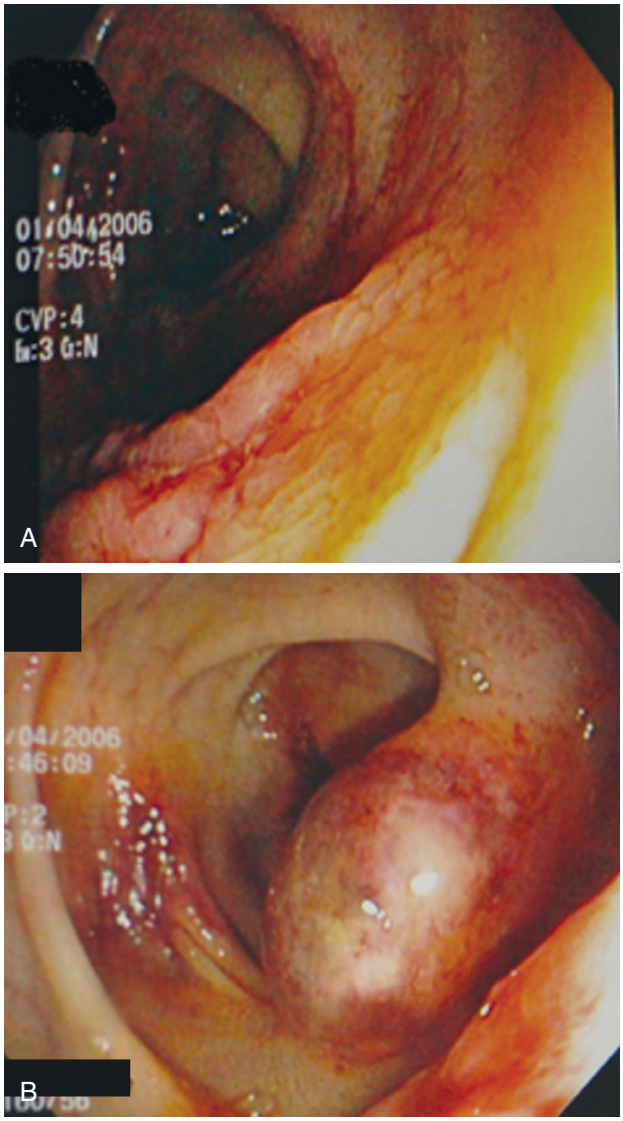
Angiodysplasia

Estimates of angiodysplasia as a source of lower GI bleeding vary widely and reach 37% in some reports.[117] Current data suggest that acute bleeding caused by angiodysplasia is less frequent than previously thought, with most cases demonstrating iron deficiency anemia and occult blood loss.[124] These lesions are seen predominantly in the elderly. They appear endoscopically as red, flat lesions with ectatic blood vessels radiating from a central feeding vessel, usually in the right colon (Fig. 72.9). Overt bleeding from angiodysplasia is usually brisk and painless and cannot be distinguished from diverticular bleeding. Endoscopic treatment is highly effective and safe and prevents bleeding episodes from recurring.

Other Sources of Lower Gastrointestinal Bleeding

Acute significant bleeding from colonic neoplasia and polyps is uncommon despite reports in which it accounts for up to 36% of cases.[121] Cancer and polyps are thought to bleed from erosions on the surface.

Postpolypectomy bleeding occurs in 1% to 6% of patients undergoing colonoscopic polypectomy.[124] Bleeding can be immediate or delayed up to 3 weeks after the procedure. Risk factors for postpolypectomy bleeding include large size, sessile morphologic appearance, and right colonic location.[127]



• **Fig. 72.8** A and B, Ischemic colitis.

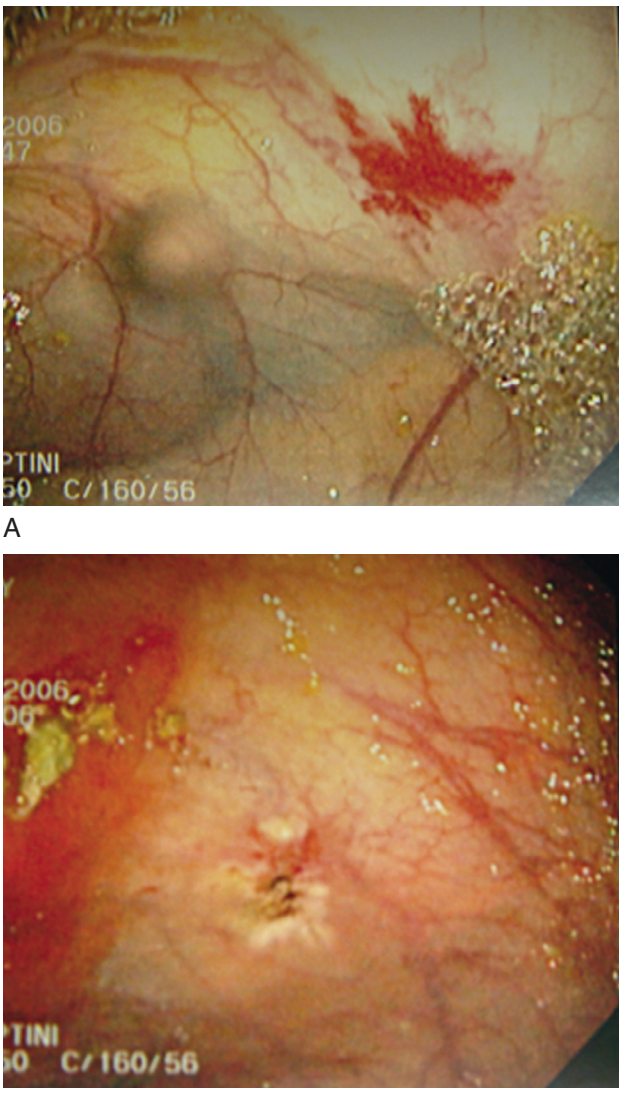
Anorectal sources of lower GI bleeding include hemorrhoids, anorectal fissures, stercoral ulcers, and proctitis. Hemorrhoids can cause significant bleeding and may sometimes require endoscopic or surgical intervention. Bleeding from rectal ulcers is common in elderly bedridden patients and in critically ill patients.[115]

Small bowel sources of lower GI bleeding include angiodysplasia (most frequent), lymphoma, small bowel ulcers, and Crohn disease.[124] Small bowel lesions are typically more difficult to identify and require more diagnostic procedures.[128]

Diagnostic Evaluation

Colonoscopy

After initial evaluation, stabilization, and exclusion of an upper GI source, management shifts to localization of the lower GI bleeding site. Colonoscopy is an attractive choice in this setting because it offers the best opportunity for early diagnosis and subsequent management. In the past, colonoscopy used to be performed in an expectant manner, after cessation of bleeding and



• **Fig. 72.9** A, Angiodysplasia in the cecum. B, Same lesion after thermal therapy (electrocauterization).

colonic preparation. Concern about poor visibility, the potential for complications, and the adverse effects of bowel preparation in the setting of bleeding is behind the reluctance in performing "urgent" colonoscopy. Over the past decade, early colonoscopy has gained interest in the management of lower GI bleeding. Several reports have shown that early (or urgent) colonoscopy is safe and has high diagnostic yield in patients with hematochezia.[129–133] The definition of "urgent" varied in these reports, from within 8 hours to within 24 hours of initial evaluation. This approach was also associated with shorter hospital stay.[134] Bowel preparation is generally recommended before urgent colonoscopy to improve visibility and prevent complications related to poor visibility. Polyethylene glycol lavage solution by mouth or through a nasogastric tube is commonly used in these cases. It can be administered at a rate of approximately 1 L every 30 to 45 minutes.[114] Some authors have proposed the use of colonoscopy without bowel preparation and have shown high diagnostic yield with this approach.[135] Despite the fact that urgent colonoscopy improves the diagnostic yield and leads to more frequent endoscopic therapy, there is still controversy regarding its impact on important outcomes, such as mortality rate, rebleeding, and the need for surgery.[131,133]

Jensen and colleagues[131] showed that urgent colonoscopy with endoscopic treatment in a group of patients with active diverticular bleeding (versus a historical group that did not receive endoscopic treatment) may prevent recurrent bleeding and the need for surgery. Another randomized trial compared urgent colonoscopy with a standard care algorithm in which radionuclide scanning, followed, if positive, by angiography, was used in patients with suspected active bleeding versus expectant colonoscopy in those without active bleeding. This trial showed that a definite source of bleeding was found more often in urgent colonoscopy patients. However, no difference in mortality rate, surgery, and rebleeding was found in the two groups.[133] A more recent trial of the benefit of urgent versus elective colonoscopy (<12 hours vs. 36–60 hours from presentation) showed no evidence of improving clinical outcomes, such as rebleeding, transfusion requirements, and hospital length of stay. A major limitation of this trial was that the study was terminated before reaching the prespecified sample size.[136] A recent guideline on acute lower GI bleeding recommends the performance of colonoscopy within 24 hours of patient presentation in patients with high-risk clinical features and signs or symptoms of ongoing bleeding as this approach can potentially improve diagnostic and therapeutic yields.[19]

Radionuclide Scanning

The use of radionuclide scanning (also known as a technetium-labeled RBC scan) in patients with lower GI bleeding is highly controversial. It has been used for several decades as a method for localization of the bleeding source.[124] A main advantage of radionuclide scanning is its sensitivity for bleeding at a rate as low as 0.05 to 0.1 mL/min, in addition to its noninvasive nature.[124] It also can be repeated in cases of intermittent bleeding. On the other hand, this diagnostic modality lacks therapeutic capability, has variable accuracy, and may delay other diagnostic and therapeutic procedures. A review of data from several studies of radionuclide scanning for lower GI bleeding in which radionuclide scintigraphy findings were confirmed by a different test found the accuracy of a positive test to be 66%.[18] Localization improves when scan results are positive within 2 hours of injection. A common practice in the setting of ongoing lower GI bleeding is to perform radionuclide scanning as a screening test before angiography and in some cases as a guide to surgery. The problem with this approach is the inconsistent and widely variable accuracy and the high rate of false-positive results in different reports.[124,137,138]

Angiography

Angiography is less sensitive than radionuclide scanning in the detection of active bleeding. It can detect bleeding at a rate of 0.5 to 1.0 mL/min. In addition to its role in accurate localization of bleeding lesions, angiography offers therapeutic possibilities. As with radionuclide scanning, the ability of angiography to detect the bleeding source varies widely among studies, from 20% to 70%.[124] This variation is due to several factors, including patient selection (higher diagnostic yield in patients with positive radionuclide scanning results), the severity and intermittent nature of the bleeding, procedural delay, and venous or small vessel bleeding.[124] In one study, a systolic blood pressure of less than 90 mm Hg and a requirement of at least 5 units of blood within a 24-hour period have been shown to predict positive angiography results (85% when both criteria were present).[139] Angiography is usually performed in patients with ongoing lower GI bleeding with or without

a positive radionuclide scan. This sequence in management was the standard approach to ongoing bleeding until recently, when colonoscopy started gaining interest in the setting of acute bleeding (as opposed to expectant elective colonoscopy). When angiographic therapy fails or is not available after localization of the bleeding, the findings are used to guide surgical resection. Angiography can cause serious complications, such as contrast reactions, arterial thrombosis and dissection, and catheter site infection and bleeding. Thus it should be used in carefully selected patients.

Computed Tomography

CT angiography gained interest in the setting of GI bleeding after the recent introduction of multidetector row CT. It enables the accurate acquisition of arterial images, which can show contrast extravasation in areas of active bleeding.[18] It can detect bleeding rates as low as 0.3 to 0.5 mL/min. The yield for lower GI bleeding ranges from 25% to 95% and is highest in severe ongoing bleeding. The advantages of CT are its wide availability and the added diagnostic yield of cross-sectional imaging, but exposure to radiation and contrast and, like radionuclide scanning, the inability to deliver therapy constitute some of the disadvantages of this technique.[18]

In a recent retrospective study comparing CT angiography with radionuclide scanning, the two modalities showed similar diagnostic yields but the site of bleeding was accurately localized with CT angiography in a significantly higher proportion of cases.[140] CT angiography should be considered if a diagnostic test is desired for localization of the bleeding site before angiography.[19]

Therapeutic Alternatives

Endoscopic Therapy

Data on the effectiveness of endoscopic therapy for lesions causing lower GI bleeding are limited. However, the experience from published series suggests that this form of therapy is likely to be beneficial. Methods of endoscopic hemostasis are similar to those used for upper GI bleeding and include injection therapy, thermal therapy (APC and heater and electrocautery probes), and mechanical therapy (hemoclips).[141] Several studies showed that clipping is very effective modality for diverticular bleeding with a low rate of early rebleeding.[18]

Angiographic Therapy

When angiography identifies the bleeding site in cases of lower GI bleeding, hemostasis can be achieved by the intraarterial infusion of vasopressin or superselective embolization. Infusion of vasopressin can control bleeding in up to 91% of cases,[141] but complications develop in 10% to 20% and include arrhythmia, pulmonary edema, and ischemia.[141] Furthermore, rebleeding occurs in as many as 50% of cases.[141] In early studies, transcatheter embolization carried a high risk for bowel infarction, but current superselective techniques using smaller catheters with various agents (gelatin sponge, microcoils, and polyvinyl alcohol particles) appear to be more effective and safer than the old techniques. Review of several studies using superselective techniques showed that immediate hemostasis was achieved in 96% of cases and rebleeding within 30 days occurred in 22%.[18] Since the advent of these new techniques, embolization has become the preferred modality when angiographic therapy is contemplated.

Surgical Therapy

Surgery is indicated in cases of recurrent bleeding (especially diverticular) and massive ongoing bleeding with high transfusion requirements (generally >6 units of packed RBCs in a 24-hour period).[114] Accurate localization of the site of bleeding preoperatively is crucial so that segmental rather than subtotal colectomy can be performed. Unfortunately, the accuracy of radionuclide scanning in localization of the bleeding is variable, and hence it should not be used as a guide for surgery. Colonoscopy and angiography may be used as a guide for surgery in cases in which bleeding is initially identified and possibly treated through these modalities, and then recurs and requires surgery.

Obscure Gastrointestinal Bleeding

Obscure GI bleeding is bleeding that persists or recurs without an obvious source identified on upper and lower endoscopy. Obscure bleeding can be occult (positive fecal occult blood testing without frank recognizable blood loss) or overt (clinically evident). Obscure bleeding can be very challenging to the physician and, in cases of overt massive bleeding, life-threatening to the patient. The initial approach to the problem is the same as with upper and lower GI bleeding and includes resuscitation and stabilization, followed by a search for the source.

Differential Diagnosis

Missed lesions on upper and lower endoscopy should be considered first in the workup of obscure bleeding. Causes difficult to identify on routine endoscopy include hemosuccus pancreaticus, hemobilia, aortoenteric fistula, Dieulafoy ulcer, and extraesophageal varices. Small bowel lesions are another source of obscure bleeding and include tumors (lymphomas, carcinoids, adenocarcinomas), vascular ectasia, NSAID-induced ulcers, Meckel diverticulum, and other less common causes.[142]

Diagnostic Evaluation

Repeat upper and lower endoscopy is usually warranted at least once after the index endoscopy, with the uncommon and subtle lesions just listed kept in mind. When the patient has active ongoing bleeding, radionuclide scanning and angiography should be considered. In young patients, Meckel diverticulum scan may be helpful. If results of all these tests are negative, the focus should shift to evaluation of the small bowel. Radiographic, endoscopic, and surgical modalities are used for this purpose.

Radiographic imaging of the small bowel may help when Crohn disease or malignancy is suspected. These modalities have lost favor with the advent of capsule endoscopy and device-assisted enteroscopy (except in cases in which there may be narrowing of the small bowel). Small bowel push enteroscopy can be very helpful in identifying and, in some cases, treating lesions in the small bowel that are responsible for obscure bleeding. Unfortunately, it can examine only 50 to 150 cm of small bowel.[143] Device-assisted enteroscopy (double- and single-balloon enteroscopy and spiral enteroscopy) has comparable diagnostic yield to capsule endoscopy but has the advantage of performing therapeutic interventions and obtaining biopsies.[144]

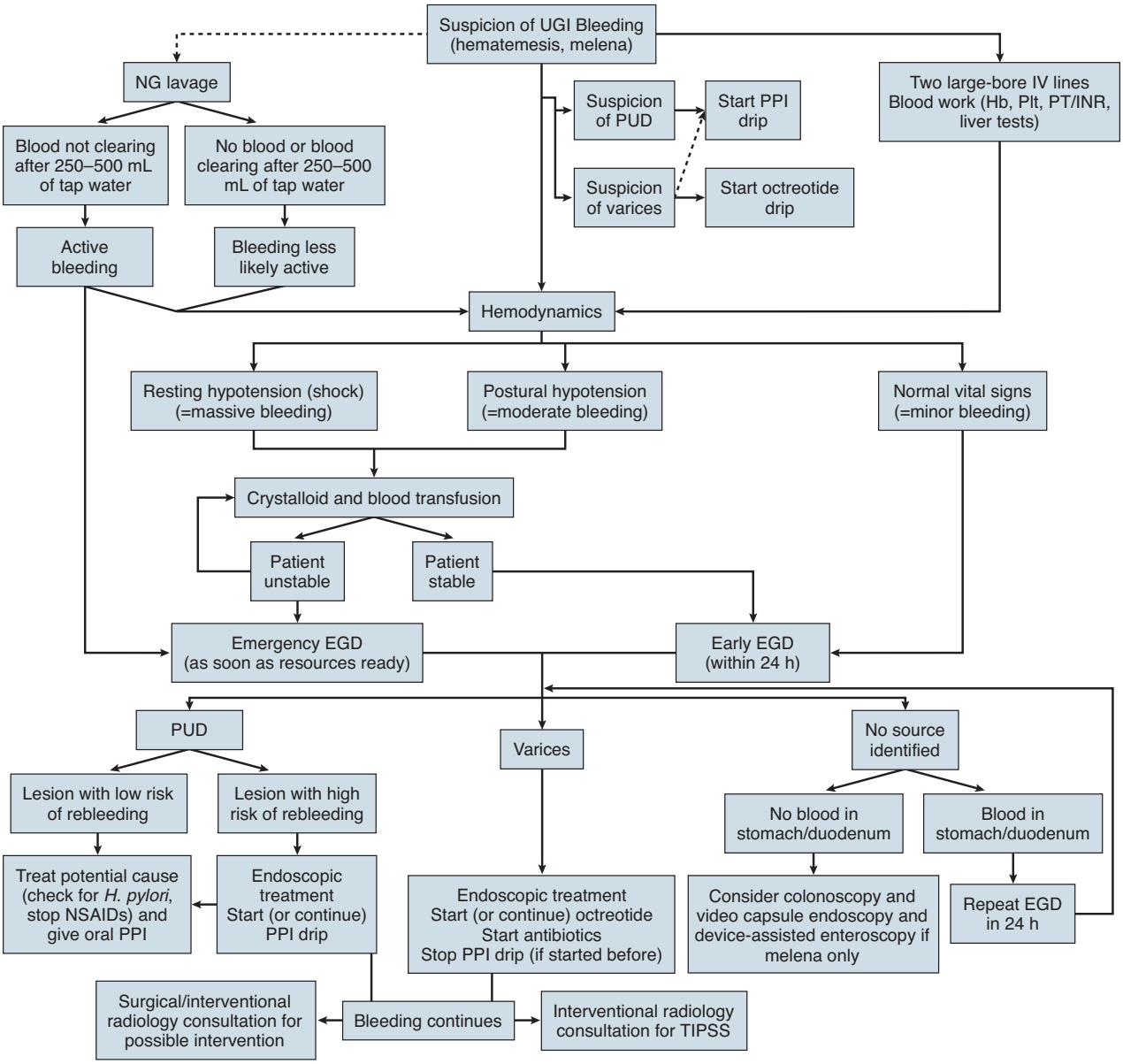
Capsule endoscopy gained great interest in evaluation of the small bowel because of its ability to examine the entire small bowel and its noninvasive nature. It consists of swallowing a pill-sized camera with sufficient battery life to image the entire small bowel. Studies have supported the role of capsule endoscopy in the evaluation of obscure GI bleeding with an overall diagnostic yield of 55% to 70%.[142] The diagnostic yield is even higher when it is

administered to patients with ongoing bleeding (87%–92%).[145,146] In our opinion, efforts should be made to perform capsule endoscopy in patients with obscure overt bleeding while they are still in the hospital instead of waiting until discharge (which is the current standard practice in most centers). In patients who can tolerate an invasive procedure, device-assisted enteroscopy can be used when available and has the advantage of therapeutic ability. However, this procedure achieves total enteroscopy in only 29% of patients. Other limitations include limited availability, time, and sedation requirements. The procedure's risk of complications is low (<1%).[144]

Exploratory laparotomy is generally the last option in the evaluation of obscure GI bleeding. When combined with intraoperative enteroscopy, the diagnostic yield reaches 50% to 100%.[142]

Conclusion

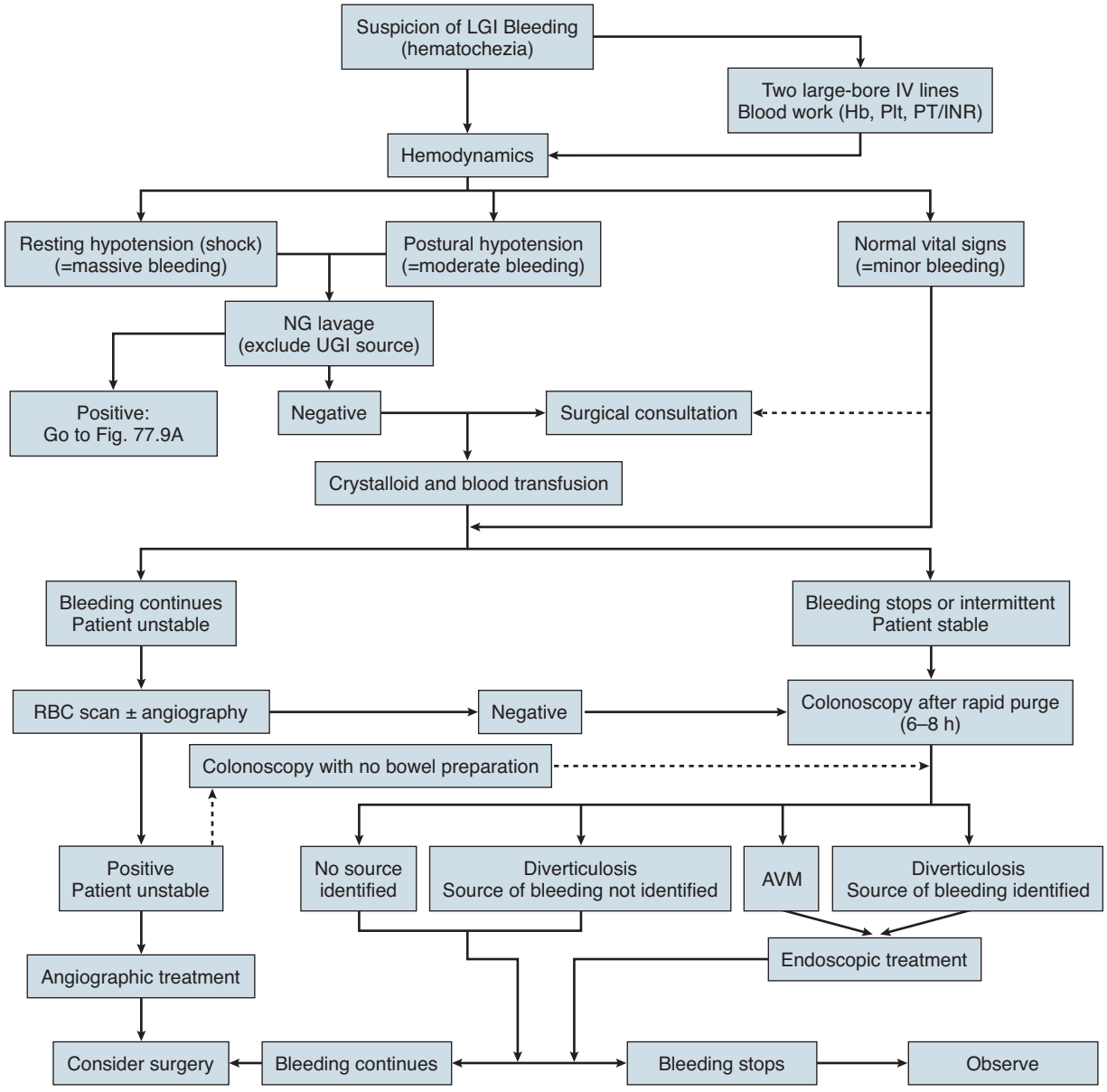
In summary, acute GI bleeding is a life-threatening emergency that requires a quick response and a coordinated team approach. Acute management is the same regardless of the source of bleeding (Fig. 72.10) and should be orchestrated by a critical care team. The prime direction in resuscitation should be restoration of euvolemia. Once a source is suspected, specific management and therapeutic options are considered and may require communication with gastroenterologists, surgeons, and interventional radiologists. Prevention of bleeding from SRMD is indicated in a specific population of critically ill patients. Endoscopy plays a major role in the diagnosis and management of acute GI bleeding. Endoscopic therapy with standard and innovative techniques has been shown to have a major impact on the prognosis of bleeding patients.



A

• **Fig. 72.10** A, Approach to managing upper gastrointestinal bleeding in critical care patients.

Continued



B

• **Fig. 72.10, cont'd** B, Approach to managing lower gastrointestinal bleeding in critical care patients. *AVM,* Arteriovenous malformation; *EGD,* esophagogastroduodenoscopy; *Hb,* hemoglobin; *H. pylori, Helicobacter pylori*; *INR,* international normalized ratio; *LGI,* lower gastrointestinal; *NG,* nasogastric; *NSAIDs,* nonsteroidal antiinflammatory drugs; *Plt,* platelets; *PPI,* proton pump inhibitor; *PT,* prothrombin time; *PUD,* peptic ulcer disease; *RBC,* red blood cell; *TIPSS,* transjugular intrahepatic portosystemic stent shunt; *UGI,* upper gastrointestinal.

Key Points

- The patient's history provides important clues regarding the cause of the acute GI bleeding and helps direct initial management.
- Management of GI bleeding relies on a team approach involving an intensivist, endoscopist, radiologist, and surgeon.
- The prime direction of evaluation and resuscitation in a bleeding patient should be restoration of euvolemia.
- SRMD is a common source of upper GI bleeding in physiologically stressed patients, and prophylaxis with acid suppressants should be given to patients with coagulopathy and those undergoing prolonged mechanical ventilation.
- PPIs in drip form should be given to patients with upper GI bleeding after endoscopic treatment of lesions with a high risk of rebleeding.

- Antibiotic therapy decreases the mortality rate in patients with variceal bleeding. It should be given empirically along with vasoactive agents (octreotide).
- Several forms of endoscopic therapy are effective for nonvariceal bleeding, including injection, thermal, and mechanical therapy.
- Endoscopic band ligation is the most commonly used and preferred technique for the treatment of bleeding varices.
- Early colonoscopy has become an attractive choice in lower GI bleeding because of its diagnostic and therapeutic abilities.
- Videocapsule endoscopy has an important role in the evaluation of patients with obscure overt GI bleeding, and efforts should aim at performing it in hospitalized patients. Device-assisted enteroscopy has the benefit, when available, of therapeutic ability and should be performed in the appropriate setting.

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Review Questions

1. A 46-year-old man with no significant medical problems presents to the emergency department after multiple episodes of melena with palpitation and dizziness. He has been taking NSAIDs for acute onset back pain for 1 week. On presentation, his pulse is 122 beats/min, blood pressure 98/52 mm Hg. His hemoglobin level is 7.8 g/dL, and results of liver tests and coagulation factors are normal. Which one of the following statements is most correct?
   - **a.** The presence of melena indicates with a high degree of certainty the origin of the bleeding as being in the upper GI tract proximal to the ligament of Treitz.
   - **b.** In addition to hemodynamic resuscitation, blood transfusion should be immediately administered with the goal to reach a hemoglobin level of 10 mg/dL.
   - **c.** Endoscopy should be performed within 6 hours of presentation, as this will decrease both the rebleeding risk and overall mortality.
   - **d.** Nasogastric tube placement should be avoided, given the lack of proven benefit in decreasing mortality or rebleeding rates and in predicting the culprit lesion.

   Answer: d. The source of melena may be the small bowel distal to the ligament of Treitz and sometimes even the proximal part of the colon. Blood transfusion should be avoided if hemoglobin is above 7 g/dL. A study evaluating blood transfusion for upper gastrointestinal (GI) bleeding found a significantly higher survival rate and lower rebleeding rate when a restrictive transfusion threshold of transfusing only if the hemoglobin level is below 7g/dL was followed compared with a threshold of 9 g/dL. Although urgent endoscopy (within 12 hours of presentation) may decrease the length of hospital stay and transfusion requirements in patients with high-risk clinical features, it has no impact on rebleeding risk and mortality. Nasogastric tube placement should be avoided for the reasons mentioned in option d.
2. In the previous case, an upper endoscopy was performed and showed a large gastric ulcer with an adherent clot. Which one of the following statements is most correct?
   - **a.** Unlike an ulcer with a visible vessel, an ulcer with adherent clot has a low risk of rebleeding
   - **b.** Acid suppression with an intravenous proton pump inhibitor (PPI) should be administered immediately after the endoscopy as this will decrease the risk of rebleeding.
   - **d.** Endoscopic therapy with topical hemostatic spray is the simplest and most effective way to treat the ulcer described.
   - **d.** A repeat endoscopy in 72 hours is indicated to assess the response to treatment and need for further endoscopic intervention.

   Answer: b. An ulcer with adherent clot has a high rebleeding risk (see Table 72.5). Although topical hemostatic sprays have shown some promising results, the role of this new modality remains ill-defined in the absence of trials comparing it to other traditional hemostasis methods. A repeat endoscopy is not indicated unless there are signs or symptoms of recurrent bleeding. In patients found to have high-risk lesions treated endoscopically, the guidelines recommend an intravenous bolus followed by continuous-infusion PPI therapy.
3. 76-year-old man presents with five episodes of moderate to large amounts of hematochezia and complains of lightheadedness. His pulse is initially 130 beats/min with hypotension. After fluid bolus his blood pressure normalized and his pulse decreased to 112 beats/min. He has another episode of hematochezia in the emergency department.

   After placement of a Foley catheter and further fluid resuscitation targeting blood pressure, heart rate, and urine output, which one of the following statements concerning the management of this patient is most correct?
   - **a.** A radionuclide scan should be done next for the purpose of confirming the site of bleeding is in the colon in anticipation of surgical intervention.
   - **b.** Colonoscopy should be performed within 24 hours of presentation for diagnostic and therapeutic purposes.
   - **c.** Proceeding directly to surgical intervention is the most appropriate course of action as this patient is at high risk of catastrophic rebleeding.
   - **d.** Radionuclide scan is preferred over computed tomography (CT) angiography as a modality to localize the site of bleeding before angiography.

   Answer: b. Colonoscopy should be performed within 24 hours of presentation for diagnostic and potential therapeutic purposes. The role of radionuclide scanning is controversial because of inconsistent and widely variable accuracy in localizing the bleeding and the high rate of false-positive results. CT angiography can better localize the bleeding source when compared with radionuclide scanning. Surgery is indicated in cases of continued bleeding (especially diverticular) and massive ongoing bleeding with high transfusion requirements (generally >6 units of packed red blood cells in a 24-hour period).

73

Acute Pancreatitis

DAVE D. PASKAR AND JOHN C. MARSHALL

CHAPTER OUTLINE

Definitions and Terminology

Pathogenesis

Etiology and Risk Factors

Clinical Presentation and Diagnosis

Early Management of the Critically Ill Patient With Acute Pancreatitis
- Initial Resuscitation
- Infection Prophylaxis
- Nutritional Support
- Adjuvant Therapy
- Endoscopic Retrograde Cholangiopancreatography in Acute Gallstone Pancreatitis

Management of the Late Complications of Severe Acute Pancreatitis
- Pancreatic Pseudocysts
- Infected Necrosis and Pancreatic Abscess
- Vascular Complications of Necrotizing Pancreatitis

Long-Term Outcome and Quality of Life

Conclusions

Acute pancreatitis is a complex disease with a highly variable clinical course. It is responsible for more than 275,000 hospital admissions each year in the United States[1] and has an annual incidence of 10 to 80 cases/100,000 in the developed world.[2–5] Incidence rates have been increasing over recent decades, reflecting the obesity epidemic, an independent pancreatitis risk factor in its own right, as well as the strong association with the most common etiology of acute pancreatitis, gallstones.[1,6] The crude mortality rate for patients hospitalized with acute pancreatitis is less than 2%.[7] The majority (80%) of patients with acute pancreatitis experience a benign and self-limited disease, resulting in a hospital stay usually lasting only a few days with no significant lasting sequelae.[7] In the remaining proportion of patients, however, acute pancreatitis is severe enough to lead to admission to an intensive care or high-dependency unit, and a prolonged clinical course with a mortality risk of that may exceed 15% depending on the presence and degree of infectious complications and associated end-organ failure.[1,8,9] These patients can present intensivists with formidable challenges during the course of their illness; however, those who recover, as most do, can return to their premorbid state of health with no significant reduction in quality of life.[10–13]

The prognosis for patients with severe acute pancreatitis has improved considerably over the 40 years since Ranson proposed his widely known severity criteria.[14] In the mid-1970s, the mortality for patients with severe pancreatitis approached 100%[14]; today the risk is now less than 20%.[15–17] This improved outcome can be ascribed in part to general improvements in critical care but, more importantly, to fundamental changes in the treatment approach to the patient with acute pancreatitis that, in turn, reflect an evolving understanding of the pathophysiology of the disease and a growing shared experience in treating patients affected by it.

Definitions and Terminology

Pancreatitis is an acute inflammatory disorder that arises as a consequence of the activation of pancreatic digestive enzymes present within the parenchyma of the gland, and in severe cases, the surrounding tissues of the peritoneal cavity and retroperitoneum. The most widely used classification system is the Atlanta classification,[18] created in 1991 and revised in 2012. Its original reproducibility was poor,[19] and as such, the revision[20–21] (Table 73.1) sought to clarify and standardize the terminology used to classify the range of acute pancreatitis severity based on whether the primary parenchymal process is interstitial edema or glandular necrosis and the presence, if any, and duration of associated multiorgan failure. Similarly, it sought to define the spectrum of local (peripancreatic) complications that may result.[20] In the mildest form of the disease, leakage of activated enzymes is minimal, and the most prominent manifestation is pancreatic interstitial edema secondary to a local inflammation. In more severe cases, the presence of extraductal enzymes results in glandular necrosis, when pancreatic ductal disruption results in leakage of pancreatic enzymes into adjacent tissues (Fig. 73.1). If the leakage occurs anteriorly into the "lesser sac" (retrogastric portion) of the peritoneal cavity, fluid collections are evident. The resulting local peritoneal inflammatory response triggers coagulation and fibrin deposition, walling off the collection, and in time (usually 4–6 weeks), creating a pancreatic pseudocyst—so-called as it is a fluid collection that lacks an epithelial lining. Alternatively, if leakage is into the retroperitoneum, necrosis of pancreatic tissue and surrounding fat predominates, although loculated necrotic fluid collections can result. In time, pancreatic necrosis may become walled off by fibrin deposition and the influx of granulation tissue, resulting in the demarcation of viable from nonviable tissue. In patients with severe acute pancreatitis, both intraperitoneal and retroperitoneal involvement is often present.

Drainage of pancreatic ascites into the chest via diaphragmatic lymphatics can create a pleural effusion, typically on the left side. Marked elevation of amylase in the pleural fluid establishes the

TABLE 73.1 Atlanta Classification System for Acute Pancreatitis (2012 Revision)[20]

Term	Definition
Acute pancreatitis	Acute inflammation of the pancreas with variable involvement of peripancreatic tissues
Mild acute pancreatitis	Interstitial edema of pancreas; typically benign clinical course with minimal organ dysfunction and full recovery
Moderately severe acute pancreatitis	Evidence of pancreatic necrosis with infectious complications and/or organ failure that resolves within 48 h of onset
Severe acute pancreatitis	Pancreatitis with associated organ failure that persists beyond 48 hours' duration
Acute fluid collection	Pancreatic or peripancreatic fluid, evident early in course of disease; lacks wall/organization
Pancreatic pseudocyst	Collection of pancreatic juice contained within a capsule of fibrous tissue that arises after an episode of acute pancreatitis
Pancreatic necrosis	Diffuse or focal loss of viability of pancreatic parenchyma or peripancreatic fat, evident as nonenhancing tissue on a contrast-enhanced CT scan
Pancreatic abscess	Localized collection of pus within pancreatic or peripancreatic tissue, containing little or no necrotic material

CT, Computed tomography.

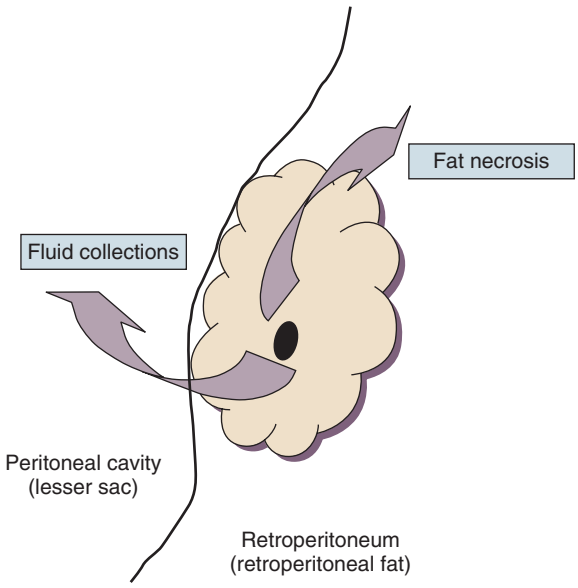
collection as pancreatic fluid, rather than as a reaction to an inflammatory process on the abdominal side of the diaphragm.

Pancreatic fluid collections can become secondarily infected by microorganisms from the gastrointestinal (GI) tract, giving rise to infected pancreatic or peripancreatic necrosis, infected pseudocysts, or pancreatic abscesses—the latter terms being largely interchangeable.

The older term, *hemorrhagic pancreatitis,* describes the sequelae of extension of necrosis into blood vessels of the retroperitoneum causing bleeding. Extraperitoneal tracking of the resulting hematoma gives rise to the physical examination findings of Grey-Turner sign, where the ecchymosis is evident in the flanks, and Cullen sign, when it tracks anteriorly through the falciform ligament to present at the umbilicus.[22]

Pathogenesis

Acute pancreatitis arises as a result of the leakage of activated pancreatic enzymes into pancreatic and peripancreatic tissues after ductal obstruction or disruption. The characteristic clinical syndrome (described later), however, reflects the activation of a massive systemic inflammatory response to that local tissue injury, mediated through the activation of the inflammasome—a multiprotein intracellular complex that leads to the activation of the key inflammatory cytokine, interleukin (IL) 1.[23]



• **Fig. 73.1** Disruption of the pancreatic ductal system results in leakage of activated digestive enzymes into the peripancreatic tissues. When the predominant direction is anteriorly into the lesser sac, the result is one or more fluid collections that either resolve or coalesce to form a pseudocyst. Leakage posteriorly into the fatty tissues of the retroperitoneum results in fat necrosis.

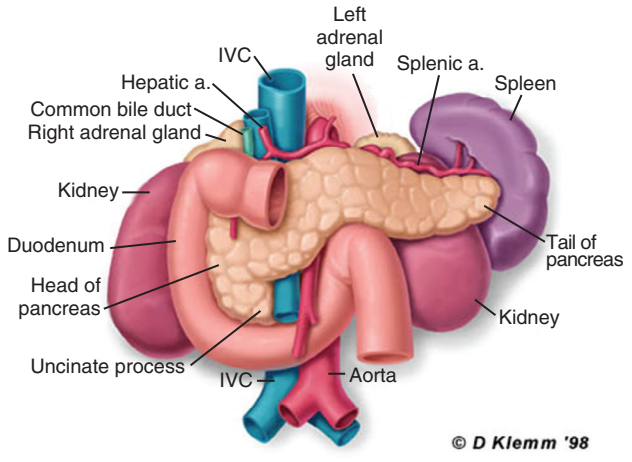
Beyond its role as an endocrine organ, the pancreas plays a fundamental role in the digestion of foodstuffs through the production of enzymes that degrade the major constituents of ingested food—protein (proteases), fat (lipases), starch (amylase), and nucleic acids (nucleases). Pancreatic enzymes are synthesized by the acinar cells lining the pancreatic ductal system and then released from the cell as inactive zymogens.[24] They pass via the pancreatic duct into the lumen of the duodenum, where they are activated by mucosal enzymes such as enterokinase, and become capable of degrading their target substrates. Under normal circumstances, intrapancreatic activation is inhibited by sequestration of newly synthesized enzymes within zymogen granules, and further through the local action of a specific inhibitor of trypsin activation called SPINK (serine protease inhibitor, Kazal type).[25] The importance of this latter mechanism is underlined by the observation that genetic mutations in the *SPINK* gene that result in reduced activity have been implicated in the pathogenesis of hereditary pancreatitis.[26]

The activation of pancreatic enzymes within the pancreas initiates autodigestion of the gland and surrounding tissues.[27,28] Activation of trypsinogen to trypsin appears to be a critical event during the early pathogenesis of the acute process[29,30] and may be mediated by an increase in intracellular calcium concentrations.[31] Trypsinogen can also be activated by lysosomal cathepsin B within acinar cells.[32] Pancreatic acinar cells can die by either necrosis or apoptosis. Necrotic death is characterized by cell lysis, with leakage of intracellular constituents into the surrounding microenvironment, and the activation of an acute inflammatory response. Neutrophil recruitment in response to local tissue injury has been implicated in the amplification of cellular damage in acute pancreatitis.[33–35] Apoptotic death, in contrast, is noninflammatory. Cells are degraded into membrane-bound vesicles that are taken up by tissue macrophages. Phagocytosis of an apoptotic cell not only prevents the local activation of inflammation, but also triggers transcriptional

programs in the phagocytosing cell that are antiinflammatory and reparative in nature, with upregulation of counterinflammatory cytokines such as IL-10.[36] The local cellular injury in acute pancreatitis can also be conceptualized as an imbalance between necrotic and apoptotic cell death. Activation of caspases—the intracellular enzymes that mediate apoptosis—attenuate the severity of pancreatitis,[37] whereas severe pancreatitis is associated with reduced levels of IL-10.[38]

Activated pancreatic enzymes injure not only cells of the pancreas, but also those of surrounding tissues. Fat cells appear to be particularly vulnerable, and the disease tends to be more severe in the obese because of the greater volume of peripancreatic fat necrosis.[39] However, the degradative effects of pancreatic enzymes, and the secondary tissue injury resulting from the host response, can injure other structures in the vicinity of the pancreas, particularly the transverse colon, and major vessels such as the splenic artery and vein.[40] Thus pancreatitis can rapidly evolve from an inflammatory disease of the pancreas to a chemical burn of the retroperitoneum.

The pathogenesis of the clinical syndrome is further complicated by the presence of the GI tract immediately adjacent to the pancreas (Fig. 73.2). The head of the pancreas lies within the curve of the duodenum, immediately behind the stomach and above the transverse colon. Damage to terminal feeding vessels in the colonic fat can result in focal perforation of the colon, with leakage of colonic bacteria into the peritoneal cavity.[41] Although the stomach and duodenum are only lightly colonized in health, the local ileus induced by the acute pancreatic inflammation promotes proximal gut bacterial overgrowth.[42] In addition, changes in the function of the GI mucosal barrier function arising from local inflammation and the absence of enteral nutrients promote the translocation of luminal bacteria and their by-products, such as endotoxin, into the injured or necrotic peripancreatic tissues.[43] The clinical syndrome of acute pancreatitis evolves as a result of a systemically activated inflammatory response, with the same changes in microvascular blood flow, endothelial permeability, and inflammatory mediator release that also characterize bacterial sepsis, even in the absence of infection.[44]



• **Fig. 73.2** The pancreas is a retroperitoneal organ, lying posterior to the stomach, within the curve of the duodenum. It lies in immediate proximity to a number of large blood vessels including the splenic artery and vein, the superior mesenteric artery and vein, and the portal vein. *Hepatic a.,* Hepatic artery; *IVC,* inferior vena cava; *Splenic a.,* splenic artery.

Etiology and Risk Factors

Acute pancreatitis has many causes (Table 73.2), although 80% of cases in the developed world result from either alcohol or gallstones, with the latter being slightly more common. Alcohol-induced pancreatitis typically occurs after acute binge ingestion on a background of chronic use, occurring in 25% to 5% of chronic alcohol abusers.[1] The mechanism of alcohol-induced pancreatitis is unknown; acinar cells of the pancreas are capable of metabolizing alcohol, and appear to be the primary target of alcohol-mediated pancreatic injury.[45] In vitro studies show that alcohol reduces the sensitivity of isolated acini to zymogen activation by cholecystokinin.[46]

Gallstone pancreatitis appears to be a consequence of a transient acute increase in pancreatic ductal pressures associated with passage of a small gallstone through the sphincter of Oddi in patients with a common channel for the distalmost bile and pancreatic ducts.[47] True ductal obstruction is uncommon, and approximately 90% of affected patients are found to have gallstones in the stool, implicating the actual passage of the stone, rather than a fixed obstructive mechanism, in the etiology of the resulting pancreatic inflammation.

Drug-associated pancreatitis is typically mild and not common, representing less than 5% of cases.[1] The list of drugs implicated in the etiology of acute pancreatitis is long[48]; some of the more prominent associations are shown in Table 73.2.

Genetic factors have also been associated with the development of acute pancreatitis. A polymorphism in the secretory trypsin inhibitor *(SPINK1)* gene is associated with an increased risk for acute pancreatitis,[49] as are mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene,[50] and *PRSS1,* a peptidase-encoding gene.[51] Polymorphisms in the genes for tumor necrosis factor α and heat shock protein 70 have also been linked to increased risk for acute pancreatitis,[52] although the associations are less clear.

TABLE 73.2 Causes of Acute Pancreatitis

Congenital	
Anatomic abnormalities: Pancreas divisum, choledochocele, periampullary diverticulum	
Familial pancreatitis	
Cystic fibrosis	
Hereditary angioedema	
Acquired	
Toxic	Alcohol, scorpion venom
Obstructive	Gallstones, duodenojejunal intussusception
Metabolic	Hypercalcemia, hypertriglyceridemia
Trauma	Blunt/penetrating
	Endoscopic retrograde cholangiopancreatography–induced
	Operative
Drugs	Thiazides, corticosteroids, valproate, sulfasalazine
Ischemia	Low flow state
Infectious	Mumps, human immunodeficiency virus, cytomegalovirus, other viral infections, *Salmonella,* ascariasis, tuberculosis, brucellosis, leptospirosis
Autoimmune	Systemic lupus erythematosus, autoimmune (immunoglobulin G-related) pancreatitis
Carcinoma of the Pancreas	
Idiopathic	

Clinical Presentation and Diagnosis

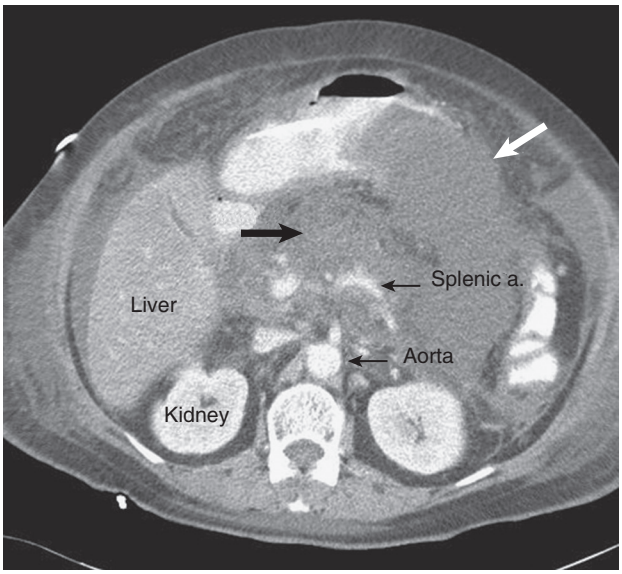
Acute pancreatitis typically presents as severe acute epigastric pain that radiates to the back, a reflection of the retroperitoneal position of the pancreas. Nausea and vomiting are common associated symptoms. From the perspective of the intensivist, the predominant manifestations of severe acute pancreatitis are those that reflect hemodynamic instability secondary to an activated systemic inflammatory response. These can evolve with alarming rapidity, and the severity of the process is frequently not appreciated until it is quite advanced.

The causes of shock in the patient with acute pancreatitis are multifactorial. Initially, the acute inflammatory process in the retroperitoneum elicits local inflammation, with an outpouring of fluid into the relatively confined space of the retroperitoneum, or into the peritoneal cavity itself. Intra-abdominal inflammation evokes secondary ileus of the GI tract, resulting in intraluminal fluid sequestration, increasing the relative intravascular volume deficit. Nausea, vomiting, and a reluctance to take fluids by mouth further exacerbate this fluid deficit. As the process evolves, a systemic inflammatory response to the local abdominal process results in diffuse vasodilatation and capillary leak syndrome. In aggregate, the effective loss of intravascular volume can be enormous, and thus the initial resuscitation often requires large volumes of intravenous fluid to achieve end-organ perfusion. Acute hypocalcemia, possibly driven by abnormal pancreatic enzyme activation,[31] may also contribute to the clinical picture of cardiovascular compromise. Indeed, the classical prognostic criteria articulated by Ranson (Table 73.3) emphasize the importance of secondary hemodynamic sequelae in determining the ultimate prognosis of the patient with acute pancreatitis.[14]

The diagnosis of pancreatitis is usually straightforward, based on the combination of clinical manifestations and characteristic biochemical findings of elevated (more than three times the local upper limit of normal) circulating levels of amylase and lipase, the latter being somewhat more diagnostically useful (higher specificity and sensitivity; earlier detection).[53,54] The diagnosis can be confirmed by computed tomography (CT) (Fig. 73.3), which can also be used to assess disease severity by using the grading system developed by Balthazar (Table 73.4).[55] Radiographic manifestations of acute pancreatitis tend to lag behind the clinical condition.

Other radiographic studies pertinent to the management of acute pancreatitis include focused abdominal ultrasound to assess for the presence of gallstones and/or biliary dilatation, and if further detail regarding possible biliary pathology is needed, magnetic resonance cholangiopancreatography.

An assessment of the initial severity of the disease is useful primarily in determining the optimal venue for the early management of the patient, because at least some of the delayed morbidity of acute pancreatitis can be reduced through aggressive initial resuscitation and support.[54] A variety of approaches have been used to quantify disease severity. Ranson identified 11 variables—5 at initial presentation and 9 over the ensuing 48 hours—that correlated in a graded fashion with the ultimate risk of mortality (see Table 73.3).[14] The Glasgow-Imrie criteria are a modification of the Ranson criteria and represent an alternate model of severity scoring. In head-to-head studies, APACHE II (Acute Physiology and Chronic Health Evaluation II)—a generic severity of illness scale—performs at least as well as the Ranson or Glasgow-Imrie criteria in predicting severe disease and hospital survival.[56] Moreover, even simpler scales appear to provide comparable prognostic



• **Fig. 73.3** Computed tomography findings in severe acute pancreatitis (Balthazar grade E). Note the combination of pancreatic necrosis *(black arrow)* and fluid and debris *(white arrow)* and the intimate relationship of inflamed pancreas to the splenic artery *(splenic a.)*.

TABLE 73.3 Ranson Criteria in Acute Pancreatitis

On Admission	Over First 48 h
Age >55 years	Po_2 <60 mm Hg
White cell count >16,000/μL	Estimated fluid sequestration >6 L
Blood glucose >1.1 mmol/L (200 mg/dL)	Calcium <2.00 mm/L (8 mg/dL)
	Hematocrit fall <10%
LDH >350 IU/L	BUN rise >1.8 mmol/L (5 mg/dL)
AST >250 IU/L	Base excess >–4 mEq/L

AST, Aspartate aminotransferase; *BUN,* blood urea nitrogen; *LDH,* lactate dehydrogenase; *Po_2,* partial pressure of oxygen.

From Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet.* 1974;139:69–81.

TABLE 73.4 Balthazar Grading of Computed Tomography Findings in Acute Pancreatitis

Grade	Findings
Grade A	Normal pancreas
Grade B	Pancreatic enlargement
Grade C	Pancreatic or peripancreatic inflammation
Grade D	Single peripancreatic fluid collection
Grade E	2 or more pancreatic collections and/or retroperitoneal air

From Balthazar EJ. CT diagnosis and staging of acute pancreatitis. *Radiol Clin North Am.* 1989;27:19–37.

information; however, most acute pancreatitis scoring systems tend to overcall "severe" pancreatitis.[23,49,54,57]

A variety of biochemical measures, including C-reactive protein, procalcitonin, interleukins 6, 8, 10, and trypsinogen activation peptide, are purported to differentiate mild and severe pancreatitis early in the disease course[1,58–60]; however, their clinical utility remains unclear. The degree of amylase/lipase elevation is not overly informative in regard to disease severity, and thus there is no role for repeated measurements once the diagnosis has been made.

Persistence of clinical manifestations of systemic inflammation beyond 48 hours is also associated with subsequent organ dysfunction and a higher mortality.[61] Precision in prognostication is less important than the early identification of patients for whom close monitoring and aggressive resuscitation in an intensive care environment may alter their clinical course.[62]

Early Management of the Critically Ill Patient With Acute Pancreatitis

Initial Resuscitation

Intravascular fluid deficits early in the course of pancreatitis can be substantial. Prompt and aggressive fluid resuscitation is the cornerstone of initial successful management.[63] Volume status should be monitored with a urinary catheter and serial laboratory investigations (serum creatinine, hematocrit, and so on). Although few studies specific to pancreatitis have been performed, there is every reason to believe that the principles of goal-directed resuscitation should be followed.[64,65] The key is to administer sufficient volumes rapidly enough to restore an adequate circulating volume and prevent (or reverse) hemoconcentration, which may in turn prevent or minimize pancreatic necrosis.[66] There is some evidence to suggest that use of Ringer lactate solution results in a reduced systemic inflammation, compared with normal saline solution, when used for the acute resuscitation of pancreatitis.[65]

Typically resuscitation requires many liters of fluid, and not infrequently, the sickest patients will receive more than 10 to 15 L of fluid resuscitation over the first 24 hours. Such aggressive resuscitation is best carried out within the well-monitored environment of the intensive care unit (ICU) to assess for resuscitation response in real time, as well as to facilitate interventions such as vasopressor administration or positive-pressure ventilation that severe cases often require.

Although aggressive fluid resuscitation can minimize later complications such as pancreatic necrosis and acute renal failure, in patients with increased vascular permeability, it carries a high risk of complications related to interstitial edema. Frequently patients will require endotracheal intubation and mechanical ventilation. Development of the abdominal compartment syndrome is a relatively common and underdiagnosed complication of resuscitated acute pancreatitis.[67] Intra-abdominal pressure can be measured by transducing a urinary catheter in the bladder. Normal pressures approximate the central venous pressure, whereas pressures greater than 12 cm H_2O indicate intra-abdominal hypertension. When the latter is associated with end-organ failure (renal failure, inability to ventilate, and so on), this represents formal abdominal compartment syndrome, which is usually associated with pressures in excess of 20 cm H_2O. The first-line management of abdominal compartment syndrome consists of nonsurgical interventions directed at reducing intra-abdominal contents (nasogastric decompression, paracentesis, and so on) and maximizing abdominal wall compliance (i.e., chemical paralysis).[68] In refractory cases, management requires abdominal decompression by formal laparotomy, sometimes even in the ICU, for very unstable cases. Anterior abdominal fasciotomy (without peritoneal violation) has been proposed as a less invasive alternative for surgical decompression.[69] Laparotomy complicates the subsequent management of pancreatitis, and so surgical decompression should be avoided if at all possible.

Infection Prophylaxis

Infection is a common complication of acute necrotizing pancreatitis, and its development is associated with an increased risk of morbidity and mortality.[70] For the patient with severe acute pancreatitis, these infections may arise within necrotic pancreatic or peripancreatic tissues, or at distant sites as nosocomial infections (i.e., ventilator-associated pneumonia). Infected pancreatic necrosis occurs in about one-third of cases of necrotizing pancreatitis, representing about 5% of all patients with acute pancreatitis.[1]

The characteristic microbial flora of peripancreatic infection includes organisms that normally reside within the GI tract,[71] as well as those that characteristically colonize the proximal GI tract of the critically ill patient (Box 73.1).[42] Anaerobes may be present but are uncommon, whereas organisms such as *Candida*, *Enterococci*, and coagulase-negative *Staphylococci* are encountered with increasing frequency.[72,73] These flora reflect the role of the GI tract as the reservoir of organisms that induce superinfection of acute pancreatitis.[74] Peripancreatic infections are typically monomicrobial.[1]

Infection of necrotic tissue in the retroperitoneum can arise by one of several routes. Bacteremic spread from a distant site, retrograde passage up the pancreatic duct, and direct extension through a defect in the adjacent GI tract are all plausible mechanisms. However, the most significant mechanism of infection appears to be the translocation of viable microorganisms across an anatomically GI tract, from either colon or small intestine. Bacterial translocation is readily demonstrable in animal models of acute pancreatitis,[75,76] and indirect evidence suggests that the phenomenon contributes to infectious complications in human pancreatitis.[77] Patients with severe pancreatitis, for example, have higher rates of proximal gut colonization with the same enteric organisms that produce infection,[78] and colonization invariably precedes the development of invasive infection.[79] Moreover, suppression of pathologic gut colonization reduces the risk of infection.[80]

• BOX 73.1 Common Microbial Isolates in Pancreatic and Peripancreatic Infections

Gram-negative aerobes
- *Escherichia coli*
- *Klebsiella*
- *Pseudomonas*
- *Proteus*
- *Enterobacter*

Gram-positive aerobes
- *Enterococcus*
- *Staphylococcus aureus*
- *Staphylcococcus epidermidis*

Anaerobes
- Bacteroides

Fungi
- *Candida*

Host-microbial interactions within the GI tract are complex,[81,82] and the changes that occur in pancreatitis are much more than a state of generalized leakiness. Colectomy, for example, increases rates of small bowel microbial colonization and bacterial translocation.[83] Moreover, the anaerobic flora of the gut provides a barrier to intestinal mucosal colonization with pathogenic aerobes, and thus inhibits bacterial translocation.[84] Anaerobes are uncommonly found in pancreatic infections, and the isolation of an anaerobic organism from an area of infected pancreatic necrosis is highly suggestive of a physical breach of the GI tract.

Infection of pancreatic necrosis is a relatively late event, occurring maximally during the second or third week after the onset of the acute disease.[85] Nevertheless, circulating bacterial DNA or endotoxins may be detected earlier during the course of the disease.[86,87]

The role of antibiotic prophylaxis, however, is controversial. An early meta-analysis of randomized controlled trials of prophylactic antibiotics for patients with acute pancreatitis concluded that prophylaxis can improve survival without significantly altered rates of pancreatic infection.[88] A consensus conference of critical care organizations, however, recommended that routine antibiotic prophylaxis should not be used in the absence of more compelling evidence,[62] and more recent compilations of data from clinical trials fail to show clear benefit for antibiotic prophylaxis.[89,90] A preference for conservatism is driven by three principal factors: the low methodologic quality of trials that support antibiotic prophylaxis, concerns regarding adverse ecologic consequences of prolonged broad-spectrum antibiotic administration (i.e., *Clostridium difficile* colitis, antibiotic resistance, and fungal infections), and the increasing use of an alternate prophylactic strategy, enteral feeding.[91] One of the most influential studies of prophylactic antibiotics in pancreatitis, for example, reported a significant survival improvement associated with antibiotic prophylaxis in a cohort of 60 patients; in that study, however, antibiotic use had no impact on rates of pancreatic infection, and three-quarters of patients in the control arm effectively crossed over by receiving antibiotics early in the course of their disease.[92]

The prevention of pathologic gut colonization through the use of selective digestive tract decontamination has been shown to reduce rates of pancreatic infectious complications[80] and to reduce mortality associated with gram-negative infections.[93] Whether antifungal prophylaxis is efficacious is also controversial.[94,95]

Nutritional Support

In contrast to the persistent controversy regarding the utility of antibiotic prophylaxis in severe acute pancreatitis, it is now generally accepted that patients fare better, and in particular, experience less infectious and inflammatory morbidity, if they are fed earlier and enterally rather than parenterally. This is contrary to historical thinking that espoused "bowel rest" as a core tenet of the acute management of pancreatitis. Enteral feeding is associated with maintained epithelial barrier function and reduced rates of translocation of endotoxin and viable bacteria in experimental animals.[96,97] A meta-analysis found lower rates of infectious complications (relative risk [RR] 0.39; 95% confidence interval [CI] 0.23–0.65), operative intervention (RR 0.44; 95% CI 0.29–0.67), organ failure (RR 0.55; 95% CI 0.37–0.81), and mortality (RR 0.50; 95% CI 0.28–0.91).[98] Shorter hospital lengths of stay and improved pain outcomes were observed.[98]

Current guidelines recommend the early institution of enteral feedings in patients with severe acute pancreatitis, supplemented with parenteral support to meet full nutritional requirements.[62,99,100] Evidence suggests "early" initiation should ideally be between 3 and 5 days after presentation, with no benefit evident for initiation before 3 days.[101] Although the frequent presence of gastric ileus in acute pancreatitis has resulted in a preference for the nasojejunal, rather than the nasogastric (or oral, if possible), route of feeding, there is no evidence to suggest the inferiority of nasogastric feeding.[102,103] Similarly, there is no compelling evidence at present to favor any particular nutritional formulation. Intestinal ileus may cause feeding intolerance and thus may mandate total parenteral nutrition; however, enteric feeding should be frequently retried.

Adjuvant Therapy

Despite a substantial body of literature suggesting a benefit for a variety of different adjuvant treatments in preclinical models, there is no evidence for any specific therapy in human disease. A systematic review of the use of cimetidine found no evidence that suppression of gastric acid secretion improved outcomes, but rather a trend to a higher risk of complications.[104] Pooled data from small studies have suggested that somatostatin or octreotide can improve survival for patients with severe acute pancreatitis,[105] but data from larger, more robust trials continue to be lacking.

Endoscopic Retrograde Cholangiopancreatography in Acute Gallstone Pancreatitis

Gallstone pancreatitis is caused by a gallstone that has migrated from the gallbladder into the common bile duct producing transient obstruction of the pancreatic duct. This pathogenetic mechanism raises the possibility that measures to relieve relative obstruction of the sphincter of Oddi (and facilitate bile flow) might reduce the severity of the disease. This possibility has been evaluated in at least four clinical trials, the pooled data from which suggest benefit for patients with severe pancreatitis in reducing subsequent complications.[106] It is unclear whether the benefit extends to all patients or simply to the subset of patients with persistent common bile duct obstruction and concomitant cholangitis.[107,108] In stable patients with uncomplicated gallstone pancreatitis, the definitive management is cholecystectomy to prevent relapse and other stone-related complications, ideally performed on the index admission to prevent interval relapse.[109] Endoscopic retrograde cholangiopancreatography can be used to minimize relapse risk in patients with prohibitive operative risk.

Management of the Late Complications of Severe Acute Pancreatitis

The initial management of severe acute pancreatitis is focused primarily on adequate resuscitation and organ support. Early lethal postresuscitation complications are uncommon[110] and include intestinal ischemia (typically secondary to a low flow state or mesenteric venous thrombosis after delayed resuscitation)[111] and bleeding secondary to erosion into a major vessel. In the absence of these catastrophic and fortunately rare complications, the subsequent management of the critically ill patient with acute pancreatitis involves optimal intensive care,[112] close monitoring, and patience. About 40% of cases of necrotizing pancreatitis require an invasive intervention for local management of complications of the disease.[113]

Pancreatic Pseudocysts

Serial evaluation by CT shows that the diffuse fluid collections evident in early pancreatitis coalesce to form discrete cystlike collections contained within an organized capsule of fibrin, termed a *pseudocyst.* Typically these arise in the lesser sac, between the pancreas and the posterior wall of the stomach (Fig. 73.4). Management is expectant in the absence of complications,[114] and rarely is intervention required in the ICU setting. The most common symptom precipitating drainage is persistent pain or symptoms of gastric obstruction. Other important complications include infection or hemorrhage into the cyst.

The classic approach to the management of a pancreatic pseudocyst involved waiting until the fibrous capsule of the cyst has matured (usually after 4–6 weeks), then draining the cyst into the back wall of the stomach. Open surgical pseudocyst gastrostomy has largely given way to less invasive approaches, creating a cyst gastrostomy by radiologic image–guided,[115] endoscopic,[116] or laparoscopic approaches.[117] A pseudocyst forms because of injury to the main pancreatic duct or one of its branches, and persists because of obstruction to the flow of pancreatic juice through the duct. If that obstruction persists, then external drainage will result in a persistent pancreaticocutaneous fistula. Drainage into the stomach avoids this complication by an internal pancreaticogastric fistula that is without clinical importance. Open operation may be required for massive hemorrhage; angiographic embolization of the bleeding vessel is a modern alternative in reasonably stable patients.[118]

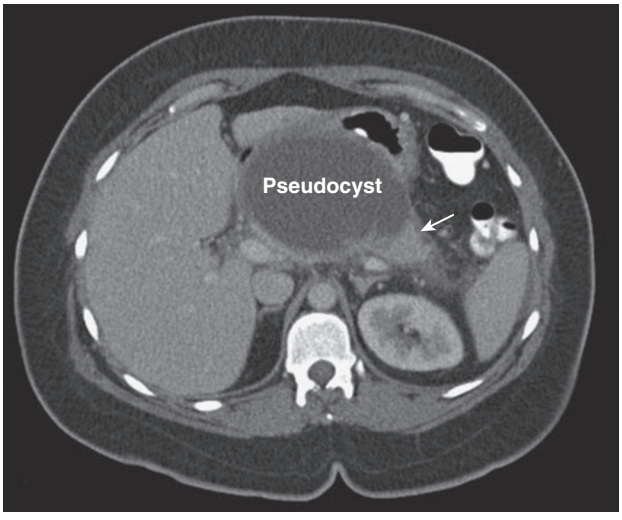
Infected Necrosis and Pancreatic Abscess

One of the more significant recent advances in the management of severe pancreatitis has been the adoption of a policy of surgical conservatism in managing patients with suspected pancreatic or peripancreatic infection. Case series demonstrate improved survival rates when surgery is delayed,[119–123] and a single randomized trial showed that delaying surgical intervention for at least 2 weeks in patients with necrotizing pancreatitis improves clinical outcomes.[124] This improvement can be attributed to a reduced frequency of major bleeding and systemic inflammatory complications associated with the debridement of necrotic, infected retroperitoneal tissue.

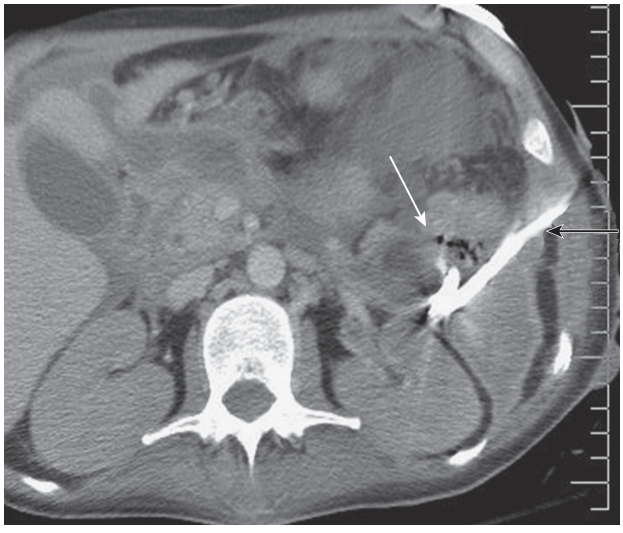
Just as serial CT evaluation reveals unification of pancreatic fluid collections, serial study of areas of pancreatic necrosis shows that they too coalesce with time, and importantly, become circumscribed by the development of a wall of granulation tissue between the areas of necrosis and viable surrounding tissues. It is this clear demarcation between viable and nonviable tissue that renders percutaneous drainage feasible and operative intervention safe and obviates the need for repeat operation or open abdomen approaches. Typically, the process of demarcation takes 3 to 4 weeks or longer to occur; thus surgical intervention, if contemplated, should be deferred. Repeat CT scans should be performed only as mandated by patient signs and symptoms and not according to a timed schedule. A strategy of surgical conservatism in the face of a patient with clinical manifestations of sepsis and ongoing organ dysfunction may appear counterintuitive, but it is both well tolerated and safer than the alternative.[125]

There is general consensus that the indication for operative intervention in a patient with severe pancreatitis is infected necrosis; sterile necrosis should be managed expectantly.[120,126,127] The diagnosis of infection of pancreatic necrosis can be challenging to establish, as the clinical manifestations of systemic inflammation are common in the acutely ill patient with pancreatitis, even in the absence of infection, as are nosocomial infections in sites other than the necrotic retroperitoneal tissues. A diagnosis of infection may be suggested by new elevation in levels of procalcitonin[128,129] or by CT findings of air in the necrotic tissues (Fig. 73.5). However, definitive diagnosis of infection is best established by CT-guided fine-needle aspiration of the peripancreatic necrotic tissues.[130] Aspiration should be performed only when infection is suspected on clinical grounds, and not as a matter of routine when fluid collections or necrosis are detected, as iatrogenic infection of these potentially sterile entities may occur.

Documentation of infection on a fine-needle aspirate is not an absolute indication for operative intervention. Antibiotics should be administered as guided by the results of culture and sensitivity and then source control options evaluated. Early in the course of the disease, before the demarcation of necrotic and viable tissues,



• **Fig. 73.4** A maturing pancreatic pseudocyst, evident as a well-circumscribed fluid collection in the lesser sac, compressing the residual pancreas *(white arrow).*



• **Fig. 73.5** Infected pancreatic necrosis *(white arrow)*; the fluid component of the collection was decompressed with a percutaneously placed drain *(black arrow),* allowing delayed laparoscopic debridement.

percutaneous drainage of the fluid component of the collection can temporize until operative intervention is safer (see Fig. 73.5). Percutaneous drainage alone is often curative.[16,131–134]

The surgical management of infected pancreatic necrosis entails the debridement of the necrotic retroperitoneal tissues and drainage of the resulting cavity. Approaches span the surgical spectrum from minimal access techniques[135–137] to open abdomen approaches.[138,139] Improved clinical outcomes have also been seen with the use of less invasive, staged procedures. van Santvoort and colleagues reported a randomized controlled trial of a staged "step-up" approach to pancreatic necrosectomy consisting of initial percutaneous drainage of the liquid elements of a pancreatic infection, followed by a minimally invasive necrosectomy, using the drain tract as a route of access.[16] The minimally invasive approach resulted in significantly lower rates of major complications and new-onset organ dysfunction, as well as lower rates of delayed complications including diabetes and incisional hernia. This same group has also reported lower rates of new organ dysfunction and pancreatic fistula when patients were managed by transgastric endoscopic necrosectomy compared with open necrosectomy.[140]

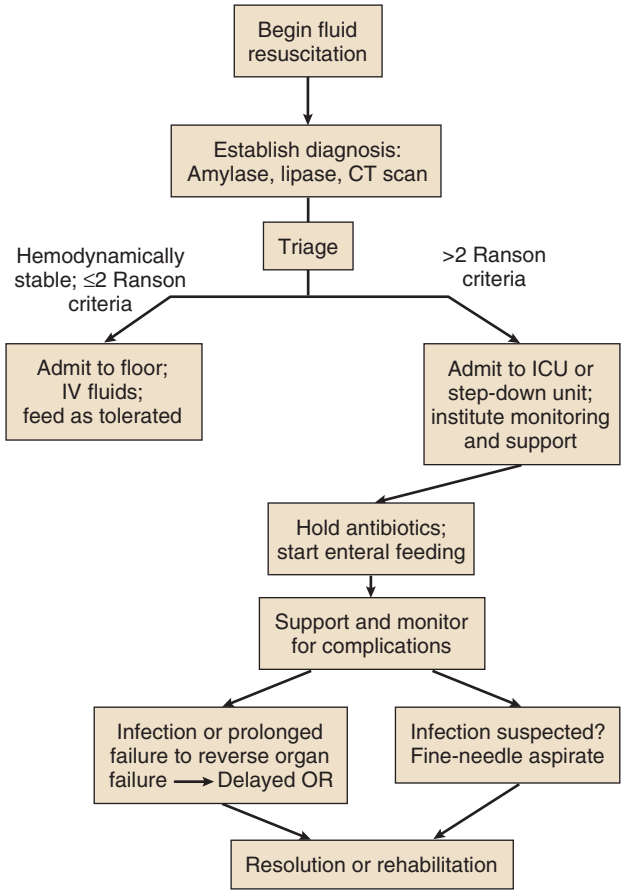
Overall, the optimal approach is the one that entails the least anatomic and physiologic upset to the patient. An open laparotomy can be performed using either a midline or bilateral subcostal incision. With the aid of a recent CT scan to guide the dissection, the infected retroperitoneal necrosis is approached either through the gastrocolic omentum and the lesser sac or through the inferior aspect of the transverse mesocolon. Dissection is performed largely blindly and bluntly, evacuating necrotic retroperitoneal fat and pus. Soft drains are left in the resulting cavity to provide egress for pancreatic juice, and the abdomen can usually be closed primarily. If there is evidence of significant involvement of the mesocolon or preoperative cultures yield anaerobic organisms, a proximal diverting ileostomy may be added to minimize contamination from the adjacent colon.

Laparoscopic techniques have the added advantage of permitting direct visualization of the abscess cavity,[137,141,142] but they may be challenging if there is extensive or multiloculated areas of necrosis. Infected necrosis can also be approached via the flank, using a nephroscope or laparoscope to aid in visualization of the abscess contents.[16,143] Further insights into the role of minimally invasive approaches should emerge from several ongoing clinical trials.[117,144] The role for open abdomen approaches in the management of infected pancreatic necrosis is diminishing as surgical practice shifts to delayed intervention with more minimally invasive techniques.[145]

Peritoneal lavage with the objective of evacuating activated pancreatic enzymes enjoyed a period of popularity[146] but is now used less frequently. Some authors recommend continuous postoperative lavage after pancreatic necrosectomy,[145] though the benefits of this approach are unproven.

Vascular Complications of Necrotizing Pancreatitis

The vascular complications of acute pancreatitis include both thrombosis and hemorrhage.[147,148] Thrombosis of the splenic, superior mesenteric, or portal vein develops as a consequence of the prothrombotic effects of the adjacent inflamed pancreas and reduced flow before full resuscitation. Less commonly, more distant vessels such as the inferior vena cava or renal veins may thrombose. Venous thrombosis may give rise to portal venous gas on CT; in the absence of clinical findings dictating a need for emergent intervention, both the venous thrombosis and the associated CT findings can be managed medically with anticoagulation and aggressive fluid resuscitation.[149] Intestinal infarction secondary to venous thrombosis in patients with acute pancreatitis carries a prohibitive mortality, even with surgery.



• **Fig. 73.6** Approach to the patient with acute pancreatitis. *CT,* Computed tomography; *ICU,* intensive care unit; *IV,* intravenous; *OR,* operation.

Erosion of the retroperitoneal inflammatory process into a major artery can produce bleeding into either the peritoneal cavity or the gut lumen, which may present as peritonitis and GI hemorrhage, respectively, and in either case, hemorrhagic shock if significant blood loss occurs. Commonly involved vessels include the splenic artery, the gastroduodenal artery, and the pancreaticoduodenal arcade.[150] Operative exposure is challenging in the face of acute retroperitoneal inflammation, and whenever feasible, bleeding is best managed by angiographic embolization.[118]

An algorithm summarizing the key elements in management of the patient with severe acute pancreatitis is provided in Fig. 73.6.

Long-Term Outcome and Quality of Life

Acute necrotizing pancreatitis can be an enormously challenging process to treat. Although the mortality for all cases of acute pancreatitis is only approximately 2% (and decreasing annually), the mortality for patients with end-organ failure persisting beyond 48 hours and/or infectious complications of pancreatic necrosis is higher, typically in the range of 15% to 20%. Additional risk factors for death include obesity (body mass index >30; >25 for

Asian populations), increasing age, and mounting preexisting comorbid conditions.[1]

For the survivors, the ICU and hospital stay is often prolonged, and in addition to procedures undertaken during the acute episode, there is often a need for later interventions, such as incisional hernia repair, cholecystectomy, or drainage of symptomatic pseudocysts. Yet there is ample evidence that most patients who survive their acute illness return to a health-related quality of life that is no different from age-matched controls.[10–13] Abnormalities of both endocrine and exocrine function are commonly evident at follow-up,[151] and approximately one-third of survivors of severe necrotizing pancreatitis develop diabetes.[152] Finally, about 10% will also progress to develop chronic pancreatitis, which manifests with chronic pain that can be quite debilitating.[153] Efforts to prevent recurrent episodes of pancreatitis should reflect the presumed underlying etiology of the individual patient's pancreatitis (cholecystectomy, alcohol cessation, lipid profile optimization, and so on).

Conclusions

Necrotizing pancreatitis is a challenging but often an enormously satisfying disease to manage. Current management approaches are supportive, with treatment directed at correcting complications of the disease process. Modern management is multidisciplinary involving the intensivist, surgeons, endoscopists, and allied health team members such as dieticians, and as such may ultimately mandate transfer to a specialist center to meet the needs of patients with complex disease. Adjunctive treatment strategies that target the pathologic host inflammatory response are not yet available but should emerge over the coming decade. Although the outcome is heavily dependent on disease severity, with early and aggressive resuscitation, optimal supportive care in an ICU, and judicious and delayed intervention to manage infected necrosis, the overwhelming majority of patients survive and are rehabilitated to an excellent quality of life.

Key Points

- The incidence of acute pancreatitis is increasing over time; the most common etiologies are gallstones and excessive consumption of alcohol.
- The initial presentation of severe acute pancreatitis can be subtle; early objective assessment of disease severity is important in guiding the vigor of resuscitation and informing patient disposition.
- Aggressive fluid resuscitation is the cornerstone of successful management. Large volumes of intravenous fluids are often required, and the development of acute respiratory failure with a need for mechanical ventilation and admission to the ICU is not uncommon.
- The use of prophylactic antibiotics is discouraged and should be limited to cases in which there is a high likelihood of infectious complications.
- Nutritional support should be instituted early, prioritizing the enteral route. Parenteral nutrition should be reserved for patients who cannot meet their full caloric needs enterally.
- Serial CT scans can document the severity of the disease and monitor its progression. CT-guided fine-needle aspiration is the diagnostic technique of choice to confirm infected necrosis; the presence of gas formation within tissue necrosis on CT scans serves as a surrogate.
- The management of infected necrosis consists of culture-guided systemic antibiotics and source control, of which the first line measures are minimally invasive techniques of pancreatic debridement, including endoscopic and interventional radiology options. Surgical debridement is now reserved for refractory cases.
- Despite the complexity and morbidity of acute episodes, long-term health-related quality of life for survivors of acute necrotizing pancreatitis is excellent.

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Review Questions

1. Which of the following statements regarding the provision of nutrition to patients with complicated acute pancreatitis is the most correct?
   - **a.** In the acute phase, parenteral nutrition is preferred over enteral nutrition to prevent stimulation of the pancreas.
   - **b.** Early initiation of enteral nutrition reduces the frequency of infectious complications.
   - **d.** Nasojejunal (postpyloric) administration of enteral feedings is superior to nasogastric feeding.
   - **d.** Paralytic gastrointestinal (GI) ileus is a rare complication of complicated pancreatitis.

   Answer: b. Early (day 3–5) initiation of enteral nutrition in patients with severe pancreatitis has been demonstrated to be safe and results in improved survival and infectious outcomes relative to parenteral nutrition. Parenteral nutrition, either partial or total, may still be required in the setting of paralytic GI ileus, which remains common in the setting of complicated, especially infected, pancreatitis. Owing to the proximity of the stomach to the pancreas, isolated gastric ileus may be a concern in some cases, and in which case, patients may benefit from the placement of a nasojejunal feeding tube to bypass the stomach to provide ongoing enteric nutrition. A commonly held belief has been that routine nasojejunal feeding may be beneficial by minimizing pancreatic stimulation; however, outcomes have been shown to be equivalent comparing nasogastric and nasojejunal approaches to feeding.
2. A 57-year-old man was admitted to the intensive care unit (ICU) with necrotizing pancreatitis secondary to alcohol. He has received massive fluid resuscitation, transient vasopressor support, and invasive positive-pressure ventilation. His status had been improving, but as he enters the second week of his admission, he develops new fevers and reinitiation of vasopressor support. Infected pancreatic necrosis is suspected. With respect to infected pancreatic necrosis, which of the following statements is the most correct?
   - **a.** Anaerobic bacteria are the most commonly isolated microorganisms from cultures of infected pancreatic necrosis.
   - **b.** Early drainage of pancreatic pseudocysts upon detection prevents infection.
   - **c.** Prophylactic antibiotics reduce the risk of pancreatic infection.
   - **d.** Approximately one-third of patients with necrotizing pancreatitis will develop infected necrosis.

   Answer: d. About one-third of patients with necrotizing pancreatitis develop infected pancreatic necrosis. The use of prophylactic antibiotics has not been clearly shown to prevent pancreatic infection. The most likely source of causative microbes is translocation of aerobic GI flora, especially from the upper GI tract. Anaerobic bacterial infection of pancreatic necrosis is less common, and is likely the result of discrete intestinal breach (i.e., colonic perforation secondary to ischemia).

   Pancreatic pseudocysts arise from the leakage of pancreatic enzymes from the ducts of the damaged gland in the retrogastric lesser sac of the peritoneal cavity. Pseudocysts may become symptomatic owing to mass effect (i.e., pain, gastric outlet obstruction) or secondary infection. In such cases, drainage via surgical, endoscopic, or radiographic means is beneficial. However, pseudocysts are initially sterile and routine drainage may result in iatrogenic infection; thus is not encouraged. In addition, percutaneous drainage may result in the formation of a persisting pancreatic-cutaneous fistula.
3. With respect to gallstone pancreatitis, which of the following statements is most correct?
   - **a.** The definitive management of gallstone pancreatitis is endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy.
   - **b.** The incidence of gallstone pancreatitis is declining.
   - **c.** Cholecystectomy is the most effective therapy to prevent recurrence.
   - **d.** Gallstone pancreatitis results from persisting bile duct obstruction by a gallstone.

   Answer: d. Gallstone pancreatitis is the most common cause of acute pancreatitis. Its incidence is increasing, reflecting the growing global obesity burden. The underlying pathophysiology results from a transient increase in intraductal pressure within the biliary tree upon stone passage from the gallbladder into the duodenum, rather than from persistent obstruction of the common bile duct by a gallstone.

   Patients with proven or suspected persisting ductal gallstones should undergo ERCP to clear the stones; in patients with prohibitive operative risk, ERCP with sphincterotomy can be used to decrease the risk of subsequent bouts of gallstone pancreatitis. However, the most effective means of preventing subsequent bouts of gallstone pancreatitis is to remove the source of the gallstones by removal of the gallbladder (cholecystectomy).

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Hemorrhagic and Thrombotic Disorders

NEIL A. LACHANT AND KAMYAR NADER

CHAPTER OUTLINE

Approach to a Critically Ill Patient With Hemorrhage or Thrombosis

Laboratory Tests of Coagulation

Disorders of Platelets
- Thrombocytopenia
- Acquired Platelet Dysfunction
- Thrombocytosis

Complex Thrombohemorrhagic Disorders
- Heparin-Induced Thrombocytopenia
- Thrombotic Microangiopathies
- Disseminated Intravascular Coagulation

Catastrophic Antiphospholipid Syndrome

Disorders of Hemostasis
- Artifacts
- Coagulation Factor Abnormalities
- Acquired Circulating Inhibitors
- Inherited Deficiencies of Procoagulants

Venous Thromboembolism
- Deep Venous Thrombosis Prophylaxis
- Therapy for Venous Thromboembolism
- Inferior Vena Cava Filter

Anticoagulants
- Heparin, Heparin Derivatives, and Heparinoid
- Direct Thrombin Inhibitors
- Direct Oral Anticoagulants
- Direct Oral Thrombin Inhibitors
- Direct Oral Factor Xa Inhibitors
- Warfarin

Approach to a Critically Ill Patient With Hemorrhage or Thrombosis

In the patient with acute hemorrhage or thrombosis, the history taker must be a detective interviewing the patient, family members, and outside health care providers. Useful information includes a personal or family history of a known bleeding disorder; bleeding after previous trauma, surgery, or dental procedures; a personal history of recent bleeding, bruising, or menorrhagia; and a history of liver or kidney disease, malabsorption, or recent chemotherapy. Perhaps the most challenging is obtaining a medication history, particularly as it may relate to covert heparin exposure. The use of anticoagulants, antiplatelet agents, aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and herbs should be determined. Recently started or intermittently used medications (e.g., quinine) that may cause thrombocytopenia should be elicited. In a hypercoaguable patient, a personal or family history of a known thrombophilia defect, thrombosis, recurrent miscarriage, or stillbirth may be useful.

Laboratory Tests of Coagulation

Although not reflective of the current model of coagulation, the integrity of coagulation is routinely tested by a limited set of in vitro assays (Fig. 74.1). The prothrombin time (PT) reflects the cascade of reactions traditionally called the extrinsic pathway, whereas the activated partial thromboplastin time (aPTT) reflects the intrinsic pathway. They intersect in the common pathway. The thrombin time (TT) measures the rate of conversion of fibrinogen to insoluble fibrin polymer after thrombin is added to plasma. A prolonged TT may be due to an inhibitor of thrombin (e.g., heparin, direct thrombin inhibitor [DTI]), hypofibrinogenemia or dysfibrinogenemia, fibrin degradation products (FDPs), and, rarely, paraproteins. The only specific coagulation factor that is routinely measured is fibrinogen. These four tests can usually localize abnormalities in the coagulation cascade.

Once a coagulopathy has been identified, the next step is to determine whether it is due to a factor deficiency or a circulating inhibitor. In the inhibitor or mixing study, the patient's plasma is mixed with an equal volume of normal pooled plasma. Normalization of the coagulation test in such a "mixing study" reflects a deficiency of one or more coagulation factors. It also implies that administration of fresh frozen plasma (FFP) should correct the coagulopathy. Further diagnosis requires specific factor assays. If there is partial or no correction in the mixing study, an inhibitor is suspected, most often contaminating heparin or a lupus anticoagulant in the nonbleeding patient or a factor VIII inhibitor in the patient with bleeding.

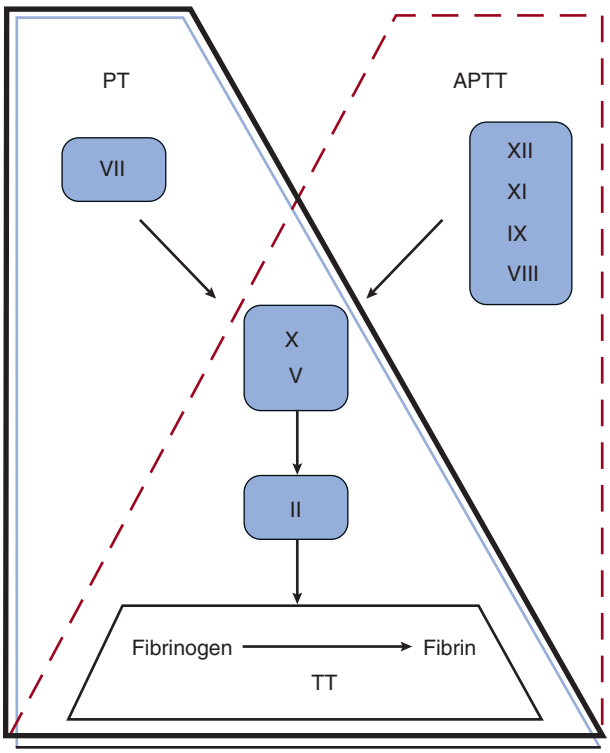
The template bleeding time (BT) is no longer used to assess in vivo platelet function given its technical issues and lack of reproducibility.

Disorders of Platelets

Thrombocytopenia

Mechanisms and General Management

Thrombocytopenia is common in the intensive care unit (ICU). It has been estimated that 23% to 50% of patients in the ICU



• **Fig. 74.1** Coagulation factors evaluated in routine coagulation assays. *aPTT,* Activated partial thromboplastin time; *IV,* intravenous; *PT,* prothrombin time; *STAT,* immediately; *TT,* thrombin time.

• BOX 74.1 Common Causes of Thrombocytopenia in Critically Ill Patients

Decreased Production
Drugs (e.g., thiazides, linezolid)
Ethanol
Liver disease
Right-sided heart failure

Increased Destruction/Consumption
Bacteremia/sepsis
Drugs
Disseminated intravascular coagulation
Massive bleeding/transfusions
Pulmonary artery catheter
Intraaortic balloon pump
Ventricular assist device
Idiopathic thrombocytopenic purpura
Burns
Posttransfusion purpura
Thrombotic thrombocytopenic purpura
Antiphospholipid syndrome

Splenic Sequestration
Portal hypertension
Hypothermia

have a platelet count below 100,000/μL, and 10% to 17% have a count below 5000/μL.[1,2] Common causes of thrombocytopenia in the ICU are shown in Box 74.1. In complex, acutely ill patients, many of these mechanisms may operate simultaneously. Sepsis is the most common cause of thrombocytopenia in the ICU.[2]

• BOX 74.2 Drugs Commonly Causing Thrombocytopenia in the Intensive Care Unit

Abciximab
Carbamazepine
Cephalosporins
Clopidogrel
Digoxin
Eptifibatide
Heparins
Hydrochlorothiazide
Linezolid
Quinidine
Quinine
Ranitidine
Tirofiban
Trimethoprim/sulfamethoxazole
Valproic acid
Vancomycin

Frequently, thrombocytopenia must be managed without a specific diagnosis. Medications should be reviewed for potential offending agents.[3,4] Inhibitors of platelet function should be avoided with platelet counts below 50,000/μL. Although not always evidence based, if there is bleeding or if invasive procedures are anticipated, platelet transfusions should be given, unless contraindicated. A platelet count above 20,000 to 50,000/μL may be used depending on the procedure.[2] In life-threatening situations, the goal should be a platelet count higher than 100,000/μL. In nonbleeding patients, maintenance of a platelet count above 10,000/μL (20,000/μL with fever or infection) with prophylactic transfusions is usually adequate.[2,5]

Although an uncommon cause of thrombocytopenia, hemophagocytic syndrome needs to be considered in any acutely ill patient with multisystem disease.

Pseudothrombocytopenia

Pseudothrombocytopenia is a laboratory artifact.[2,6] The platelet count is factitiously lowered because of the presence of naturally occurring antibodies that cause platelet agglutination in the presence of ethylenediamine tetraacetic acid (EDTA) at room temperature. The diagnosis is suspected by finding platelet clumps on the peripheral blood smear. Repeating the platelet count with a different anticoagulant such as citrate generally produces a normal platelet count.

Drug-Induced Thrombocytopenia

A limited number of drugs have evidence-based data to support a causal role in the development of thrombocytopenia.[3,4,7,8] Medications commonly used in the ICU can cause thrombocytopenia (Box 74.2). Drug-induced thrombocytopenia most commonly occurs 7 to 21 days after exposure to the offending agent. Clinical manifestations can range from an asymptomatic decrease in platelets to life-threatening bleeding. The diagnosis is established by (1) finding a temporal relationship between starting the drug and the fall in the platelet count, (2) having no alternative diagnosis, and (3) having the platelet count recover after removal of the putative offending agent. Unfortunately, this is usually difficult to establish in the typical ICU patient. Treatment is based on removing the putative offending agent and initiating a drug of another class if

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possible. Although often used, steroids in general have not been shown to hasten the rate of platelet recovery. In severe thrombocytopenia with bleeding such as seen with quinine, intravenous immunoglobulin (IVIG) (1 g/kg per day for 2 days) and platelet transfusion are beneficial.

Glycoprotein IIb/IIIa Inhibitors

All platelet glycoprotein IIb/IIIa inhibitors have been associated with severe thrombocytopenia that can occur within hours of exposure (up to 2 weeks with abciximab).[7] Heparin-induced thrombocytopenia (HIT) is the main differential diagnosis. Bleeding is very uncommon with HIT because of the strong prothrombotic state. Conversely, with glycoprotein IIb/IIIa inhibitor–associated thrombocytopenia, bleeding or hematoma formation may occur, especially at the site of the sheath. A platelet count less than 20,000/μL and clinical bleeding are indications for platelet transfusion. The use of IVIG and corticosteroids is not evidence based.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura results from the destruction of immunoglobulin (Ig) G–coated platelets in the reticuloendothelial system, primarily the spleen. There is no significant compensatory increase in thrombopoiesis. Anemia, if present, may be autoimmune (Evans syndrome) or due to bleeding and iron deficiency. Immune thrombocytopenia may be primary (idiopathic [ITP]) or secondary. The differential diagnosis includes pseudothrombocytopenia; immune thrombocytopenia secondary to systemic lupus, human immunodeficiency virus (HIV) infection, or hepatitis C; and drug-induced thrombocytopenia.

Guidelines for the diagnosis and management of ITP have been developed.[9,10] Indications for therapy in ITP are platelet count less than 20,000 to 30,000/μL or clinical bleeding. Corticosteroids (pulse dexamethasone, 40 mg/day for 4 days, or prednisone, 1 mg/kg per day) are the usual initial therapy for ITP.[9,10] Individuals with ITP in the ICU usually have severe or life-threatening bleeding. Several modalities of therapy should be used in concert to raise the platelet count in urgent situations (methylprednisolone, 1 g/day for 3 days, and IVIG, 1 g/kg per day for 2 days). Although platelets may be destroyed quickly, platelet transfusions should still be used as initial therapy. The response to platelet transfusion may improve after IVIG is given. Anti-Rh(D) IgG (WinRho), 50 to 75 μg/kg, has also been used.[11] Because the dose of anti-Rh(D) must be reduced in the face of anemia, its use may be problematic in a patient with severe bleeding. Anti-Rh(D) IgG is ineffective in Rh-negative patients and after splenectomy. ε-Aminocaproic acid (4–5 g intravenous [IV] followed by either 2–4 g IV every 4 hours or 0.5–1.0 g/h continuous IV infusion [maximum 24 g/24 h]) may be useful for mucosal bleeding and severe menorrhagia.

Posttransfusion Purpura

Posttransfusion purpura is a rare condition characterized by acute, severe immune-mediated thrombocytopenia. Posttransfusion purpura occurs in human platelet antigen-1 (HPA-1)-negative individuals who receive HPA-1–positive platelets (most commonly as a contaminant in packed red blood cells [RBCs]). These individuals have previously been sensitized to HPA-1 through transfusion or pregnancy. Usually 7 to 10 days after reexposure to HPA-1, an anamnestic response occurs, resulting in a precipitous fall in the platelet count. Petechiae and bleeding are common. IVIG and plasma exchange are effective.[12]

Acquired Platelet Dysfunction

Medication-Induced Abnormalities

Aspirin irreversibly acetylates cyclooxygenase (COX), inhibiting platelet function for the life of the platelet (7–10 days). The aspirin effect can be overcome with the infusion of desmopressin (DDAVP). Platelet transfusion can be tried but is not evidence based to improve outcome.[2] The effect of NSAIDs is reversible and disappears as the drug is cleared, usually within 24 to 48 hours for ibuprofen. The risk of bleeding from NSAIDs is lowest with ibuprofen and greatest with ketorolac. Three thienopyridines bind the platelet adenosine diphosphate (ADP) P2Y12 receptor. All should ideally be withheld for 7 days before invasive procedures with 5 days as a minimum for urgencies.[13,14] Clopidogrel tightly binds the platelet ADP P2Y12 receptor. In an emergency, platelet transfusion and DDAVP can be tried, but platelet function may not be fully restored because of circulating active clopidogrel metabolites, which have a half-life of 8 hours and bind to the transfused platelets.[14] Prasugrel irreversibly binds the P2Y12 receptor and has active metabolites with a 4-hour half-life and can affect platelet function. Platelet transfusion and DDAVP can be tried.[14] Ticagrelor reversibly binds the P2Y12 receptor. Its major metabolites have a 7 hour half-life. Platelet transfusion can be tried but is not evidence-based.[14] Cyclooxygenase 2 inhibitors do not affect platelet function.

Renal Failure

The hemorrhagic diathesis of renal failure is the result of metabolic derangements related to uremic toxins.[15] Bleeding may worsen when the hematocrit falls below 30% owing to a rheologic phenomenon in which rapidly flowing RBCs gravitate to the center of the streaming blood and force the platelets toward the vessel wall.[16] Uremic bleeding is uncommon in the modern era of dialysis.[16] For clinical bleeding, IV DDAVP (0.3 μg/kg given over 30 minutes) is often therapeutic.[15] If the hematocrit is less than 30%, the patient should have a transfusion of packed RBCs.[15,16] An alternative to DDAVP is cryoprecipitate (10 bags every 12–24 hours).[15] IV conjugated estrogen (0.6 mg/kg per day for 5 days) is also effective.[15] An unexpected "coagulopathy" (prolonged aPTT and TT) may develop as a result of delayed clearance of heparin after dialysis. If available, an anti–factor Xa assay will show the presence of heparin.

Thrombocytosis

Although not as common as thrombocytopenia, reactive thrombocytosis often the result of splenectomy, surgery, or bleeding may be seen in the ICU. Reactive thrombocytosis does not have an increased risk of thrombosis. Antiplatelet therapy is not needed even for platelet counts higher than 1,000,000/μL.

Complex Thrombohemorrhagic Disorders

Heparin-Induced Thrombocytopenia

Although commonly looked for, HIT is an uncommon cause of thrombocytopenia in the ICU.[2,17] HIT is a paradoxical condition in which modest thrombocytopenia may be associated with devastating thrombosis. Thus the entire health care team needs to be vigilant for the development of HIT in any patient receiving heparin. HIT has been associated with all types of heparin (unfractionated [UFH] and low–molecular-weight [LMWH]), at any dose, and by any route, including flushes and heparin-coated catheters.[1,18] The incidence of HIT has been estimated to be less than 1% of patients

in the ICU.[2,17,19] HIT occurs in three time intervals. Classic HIT occurs 5 to 15 days after the initiation of heparin. Rapid-onset HIT develops hours to 1 to 2 days after heparin therapy is started in individuals who have preformed circulating antibodies from a previous exposure to heparin, usually in the past 2 months. Classic and rapid-onset HIT may be manifested as thrombocytopenia with or without thrombosis. Delayed-onset HIT occurs an average of 12 days after the discontinuation of heparin and is manifested as isolated thrombosis. Rare cases of true autoimmune HIT without heparin exposure have been described. The thrombocytopenia of HIT is usually modest with an average platelet count of 50,000 to 60,000/μL.[20] Severe thrombocytopenia (<10,000/μL) should suggest an alternative diagnosis. HIT may be associated with a normal platelet count if there is a baseline thrombocytosis (e.g., postoperatively). HIT may be manifested as isolated thrombocytopenia or thrombocytopenia with potentially devastating thrombosis. Venous complications include deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral sinus thrombosis, infarctive adrenal hemorrhage, and skin necrosis at the heparin injection site. Arterial complications include iliofemoral artery thrombosis, digital ischemia, myocardial infarction, stroke, and mesenteric artery thrombosis.

• BOX 74.3 Clinical Situations to Suspect Heparin-Induced Thrombocytopenia

Current Use of Heparin or Heparin Exposure Within 40 Days and at Least One of the Following:

- Platelets <100,000/μL
- Platelets <50% of baseline or <50% of the maximum level if reactive thrombocytosis is present
- Platelets less than baseline 5 days after open heart surgery
- New arterial or venous thrombotic event
- Inflammation or necrosis at heparin injection sites
- Acute allergic or anaphylactic reaction to a heparin bolus

Recent Admission to a Hospital, Nursing, or Rehabilitation Facility Plus

- A new venous thromboembolic event
- A new arterial ischemic event

HIT is an immune-mediated process in which the heparin–platelet factor 4 complex becomes immunogenic. Antibodies are formed that activate platelets, causing the release of thrombogenic microparticles.[17,20,21] The antibodies can also activate monocytes and endothelial cells.

The diagnosis of HIT is clinicopathologic. HIT should be thought of in appropriate clinical situations (Box 74.3). The "4T" score has been used to predict the likelihood (pretest probability) of HIT (Table 74.1).[17,22] The HIT Expert Probability score, devised by an expert consensus panel, has also been validated.[23] Although the decision to initiate therapy should be based on the clinical likelihood of HIT, laboratory testing should be used for the retrospective confirmation of the pretest likelihood of HIT. The complexities of HIT antibody testing are reviewed elsewhere.[17,21,24,25] In general, a strongly positive HIT enzyme-linked immunosorbent assay (ELISA) and strongly positive serotonin release assay (SRA) with a high pretest probability confirm the diagnosis of HIT, whereas a negative ELISA and SRA make the diagnosis of HIT unlikely with a low pretest probability. In other situations, clinical judgment prevails in establishing or excluding a diagnosis of HIT, especially because ELISA and SRA testing from commercial laboratories has not been validated in clinical studies.[1,17,24]

Once the diagnosis of HIT is thought to be likely, all heparin should be discontinued. Heparin-coated pulmonary artery catheters should be replaced with noncoated catheters. Catheters for dialysis or apheresis should be locked with 4% citrate or tissue plasminogen activator. The patient's chart and bedside should be labeled *heparin allergy.* Platelet transfusions should be avoided except for life-threatening bleeding, given the anecdotal observations of acute thrombosis occurring after platelet transfusion. A patient with life- or limb-threatening arterial thrombosis should be evaluated for surgical intervention. Anticoagulation with a DTI should be initiated in all patients unless contraindicated. Fondaparinux is a factor Xa inhibitor, but unlike direct factor Xa inhibitors, it mediates its effects indirectly through antithrombin (AT) III, and unlike heparin, it is selective for factor Xa. Although not approved by the U.S. Food and Drug Administration (FDA) because of lower cost, fondaparinux has been used off-label in some centers.[25] LMWH is contraindicated in HIT caused by UFH. Bridging to warfarin can be considered after a minimum of 5 days of DTI therapy if the platelet count has returned to normal (suggesting that the

TABLE 74.1 Determining the Pretest Probability of Heparin-Induced Thrombocytopenia (HIT): The "4 Ts"

Points	Thrombocytopenia	Timing of Onset of Thrombocytopenia (or Other Serious Sequelae)[a]	Thrombosis or Other Sequelae	Other Causes of Thrombocytopenia
2	>50% decrease and nadir >20,000/μL	Day 5–10 or <1 day with recent heparin (past 30 days)	Proven new thrombosis, skin necrosis, or acute systemic reaction to heparin bolus	None evident
1	30%–50% decrease or nadir of 10,000–19,000/μL	>Day 10 or timing unclear or <1 day with recent heparin (past 31–100 days)	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (not proved)	Possible
0	<30% decrease or nadir of <10,000/μL	<Day 4 (no recent heparin)	None	Definite

Pretest probability score: 0–3 points = low (<5%); 4–5 points = intermediate (physician judgment); 6–8 points = high (>80%).

[a]First day of heparin exposure = day 0.

Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006:4:759–765.

process has cooled off and the patient is no longer hyperprothrombotic) and no future invasive procedures are planned. Simply discontinuing heparin therapy and not starting a DTI is inappropriate because occult thrombosis may have already developed.[26] Starting or continuing warfarin monotherapy is also contraindicated because of the risk of venous limb gangrene.[27] If warfarin has been given at the time HIT is diagnosed, vitamin K should be given to replenish proteins C and S. If invasive procedures are needed (e.g., tracheostomy, pacemaker), it is best to delay them, if medically safe, until the platelet count is normal to minimize the risk of developing thrombosis during the time that DTI therapy is withheld. Inferior vena cava (IVC) filters should be avoided because of the risk of vena cava thrombosis. Patients with active HIT may need percutaneous coronary intervention (PCI). Bivalirudin and argatroban have been approved by the Food and Drug Administration (FDA) for use during PCI in patients with HIT.[28,29] In a patient who has active HIT or persistent HIT antibodies and who needs open heart surgery, medical management is recommended until the antibody becomes negative. If urgent surgery is needed, bivalirudin is most commonly used.[30] For the patient with a past history of HIT who needs open heart surgery and is currently HIT ELISA and serotonin release assay antibody negative, heparin can be used during bypass and a DTI started as soon as it is surgically safe postoperatively.[30,31]

Thrombotic Microangiopathies

There are three thrombotic microangiopathies with overlapping clinical features: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and atypical hemolytic uremic syndrome.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a relatively rare disorder whose hallmarks are thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and neurologic dysfunction. The diagnosis of TTP should be considered in any patient with unexplained thrombocytopenia and MAHA.[32] TTP is the clinical manifestation of a heterogeneous group of underlying disorders driven by different pathophysiologic processes. Although most cases of TTP are idiopathic, TTP may be associated with exposure to drugs (e.g., quinine, proteasome inhibitors, oxaliplatin, gemcitabine, quetiapine, oxymorphone), pregnancy, and HIV infection.[33,34] The morphologic hallmark of TTP is hyaline thrombi in precapillary arterioles composed primarily of platelets. Classic TTP is due to an immune-mediated deficiency of the metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which cleaves ultralarge multimers of von Willebrand factor (vWF) into smaller forms that are less platelet reactive.[35] Deficiency of this enzyme allows ultralarge forms of vWF that are normally sequestered in the endothelium to bind platelets and form microthrombi in the circulation. ADAMTS13 activity is low in classic TTP. Conversely, ADAMTS13 activity is normal in TTP, associated with bone marrow transplantation and in the hemolytic-uremic syndrome (HUS).[33,35] Organ dysfunction is due to microvascular thrombosis. Commonly involved organs are the brain, kidneys, heart, and pancreas. It is critical to establish the diagnosis quickly because TTP can be rapidly fatal if not properly treated.

The core laboratory features of TTP are those of MAHA (more than two schistocytes per oil immersion field on a peripheral smear, increased lactate dehydrogenase, and very low haptoglobin). ADAMTS13 activity is less than 10%. The differential diagnosis includes classic and atypical HUS, disseminated intravascular coagulation (DIC), severe vasculitis, eclampsia, HELLP (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets) syndrome, malignant hypertension, sepsis, catastrophic antiphospholipid syndrome, and malignancy, particularly metastatic adenocarcinomas.

Once the diagnosis of TTP is thought to be likely, therapy should be initiated quickly because of the proclivity of the disease to progress rapidly. All patients should initially be treated in the ICU. Platelet transfusions should be avoided except for life-threatening bleeding because of anecdotal reports of acute decompensation after platelet transfusions. A large-bore catheter will need to be placed, even in the face of severe thrombocytopenia, because the mainstay and only evidence-based component of therapy for TTP is plasma exchange.[36,37] Most commonly, 1.5 plasma volumes of FFP are exchanged daily. A clue that TTP is the correct diagnosis is the color of the plasma removed from the first plasmapheresis. A red or brown color suggests free hemoglobin or methemoglobin from intravascular hemolysis. If plasma exchange cannot be initiated in a timely manner, infusion of 30 mL/kg of FFP daily can be a temporizing maneuver.[36] Corticosteroids (e.g., prednisone, 1 mg/kg per day) are commonly used as well.[37] The use of vincristine is controversial.[38] In patients who do not respond to initial therapy, rituximab is an attractive second-line therapy.[33,39,40]

Hemolytic-Uremic Syndrome

HUS, the triad of thrombocytopenia, MAHA, and acute kidney injury, is most commonly due to infection with Shiga toxin–producing *Escherichia coli* in children.[41] Adult atypical HUS (aHUS) is not Shiga toxin associated. It may be idiopathic or associated with medications (calcineurin inhibitors [cyclosporin, tacrolimus, sirolimus, gemcitabine bevacizumab, interferon]), stem cell transplantation, and cancer.[33,41] aHUS is a complement deposition disease. Mutations in complement regulator proteins are found in approximately 50% (complement factors H and I, membrane cofactor protein/CD46 [MCP], factor B [FB]) as well as in nonregulatory proteins (thrombomodulin [THBD], diacylglycerol kinase epsilon [DGKE]). Although not as efficacious as when used for TTP, plasma exchange should be initiated when aHUS is suspected until the diagnosis can be confirmed and the anti-C5 antibody eculizumab (Soliris), which has been FDA approved for the treatment of aHUS, has been obtained.[42,43] Plasma exchange may be continued if there appears to be a response. Supplemental eculizumab dosing is required after each plasma exchange.[44] Patients need to receive quadrivalent meningococcal vaccine and possibly meningococcal B vaccine before starting eculizumab.[45]

Disseminated Intravascular Coagulation

DIC is always a manifestation of a severe underlying pathologic process (Box 74.4). The final common pathway is the generation of thrombin, which produces microthrombi that can lead to organ dysfunction.[46] In the process, natural anticoagulants are consumed and fibrinolysis is activated. Circulating FDPs, along with the consumption of platelets and coagulation factors, lead to a bleeding diathesis. The balance between these competing processes results in the clinical manifestations in any particular individual.

The clinical manifestations of DIC are protean. Microvascular thromboses produce ischemia in many tissues, including the brain (delirium, coma), skin (digital gangrene, purpura fulminans), kidney, lungs (acute respiratory distress syndrome), gastrointestinal tract (mucosal ulceration), and blood (MAHA). The bleeding associated with DIC is due to the combination of depletion of coagulation

• BOX 74.4 Common Causes of Disseminated Intravascular Coagulation

Acute

Infection
- Bacteria
- Fungus
- Virus
- *Rickettsia*

Complications of pregnancy
- Abruptio placentae
- Amniotic fluid embolism

Tissue trauma
Tissue hypoperfusion
Acute hemolytic transfusion reaction

Chronic

Neoplasia
- Adenocarcinoma

Liver disease
Retained dead fetus

Localized

Aortic aneurysm
Cavernous hemangioma

factors, thrombocytopenia, inhibitory effects of FDPs on coagulation and platelet function, and tissue necrosis with ulceration. Common manifestations are intracerebral hemorrhage, global oozing at lines and venipuncture sites, hematuria, epistaxis, and gingival and gastrointestinal bleeding.

There are no strict evidence-based laboratory criteria for the diagnosis of DIC.[46] The diagnosis is based on identifying an underlying predisposition, the clinical features, and laboratory testing. The most common laboratory features of DIC are thrombocytopenia, elevated FDP or D-dimers, and decreased fibrinogen. The PT and aPTT may or may not be prolonged, depending on the sensitivity of the assay, degree of baseline elevation of coagulation factors as acute-phase reactants, the rate of consumption of coagulation factors, and the amount of FDPs released. An absolute decrease in fibrinogen is very suggestive of DIC. However, fibrinogen activity in the normal range may still be consistent with DIC because fibrinogen is an acute-phase reactant and its level may be inappropriately low for the underlying physiologic state.[47] Serial measurement of fibrinogen is often useful. Schistocytes are seen in half the cases. Although the natural anticoagulants AT (previously called AT-III) and proteins C and S are decreased, and thrombin-AT complexes are increased, their levels usually cannot be measured in real time and are of limited clinical value.

The International Society on Thrombosis and Haemostasis has developed a scoring system for the identification of overt DIC using four commonly available tests (platelets, PT, FDPs such as D-dimer or soluble fibrin monomer, and fibrinogen) that has been prospectively validated.[48,49] It is important to remember that all the laboratory abnormalities seen in DIC can be caused by other disease processes. Vitamin K deficiency,[50] a heparin-contaminated blood sample, or a lupus anticoagulant can cause a coagulopathy, whereas elevations in FDPs can be seen with metastatic cancer or can be found after surgery or trauma. Other microangiopathies cause thrombocytopenia and RBC fragmentation. Liver failure can produce a constellation of laboratory abnormalities indistinguishable from those observed in DIC.[51]

The most important principle in the management of DIC is to treat the underlying cause. If the driving process cannot be controlled, the DIC will progress unabated. Hypothermia and acidosis should be corrected because they interfere with the function of coagulation factors.

If the diagnosis is suspected only because of laboratory abnormalities, management should be conservative. Alternative, potentially correctable processes should be kept in mind, such as vitamin K deficiency and drug-induced thrombocytopenia.

If clinically significant bleeding becomes apparent, a patient with overt DIC should receive blood component therapy (cryoprecipitate if fibrinogen <100 mg/dL, FFP, and platelets). A realistic goal is to keep the fibrinogen level above 150 mg/dL and the platelet count greater than 50,000/μL. Heparin is not routinely used for the treatment of DIC. Heparin may be helpful for thrombotic or ischemic manifestations.[52] Other treatment modalities have been tried in DIC. The use of AT concentrates showed no significant decrease in mortality rate.[53] Activated protein C (drotrecogin alfa) used for the treatment of sepsis has been withdrawn from the U.S. market. Because of the intense fibrinolytic activity in DIC, antifibrinolytic agents (ε-aminocaproic acid and tranexamic acid) have been tried in an attempt to reduce bleeding. In general, failure rates have been quite high, and serious thromboses have occurred because the lysis of diffuse microthrombi was suppressed.[54]

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome is an uncommon disorder manifested as multiple-organ dysfunction secondary to microvascular thrombi. The diagnosis should be considered in patients with an acute onset of three or more of the following: respiratory failure, stroke or other neurologic impairment, abnormal liver function, renal impairment, skin infarction, and thrombocytopenia. Laboratory testing should show evidence of antiphospholipid antibodies. Although not evidence based, empiric therapy has centered around the combined use of high-dose corticosteroids, anticoagulation, and plasma exchange or IVIG.[52]

Disorders of Hemostasis

It has been estimated that 16% of ICU patients have bleeding caused by a coagulation defect and another 66% have abnormal coagulation test results.

Artifacts

A common cause of an unexplained prolongation of the aPTT is unsuspected heparin in the line from which the blood was drawn. A diagnostic clue is a prolonged TT with a normal fibrinogen. A heparin level (anti–factor Xa assay) will confirm the diagnosis. Although venous access is often an issue in the ICU, blood for coagulation studies should be drawn by venipuncture if possible.

Coagulation Factor Abnormalities

Acquired Deficiencies of Procoagulants

Vitamin K Deficiency

Vitamin K is essential for the posttranslational modification (γ-carboxylation) of factors II, VII, IX, and X and proteins C, S, and Z. The daily requirement of vitamin K is 50 μg. Normal daily

intake of vitamin K is 200 μg from the diet and 200 μg from intestinal flora. Thus vitamin K deficiency occurs commonly in the ICU in the patient who is not being fed and who is receiving antibiotics that alter the gut flora. Vitamin K stores last approximately 1 week.

Because factor VII has the shortest half-life (~4 hours), early vitamin K deficiency is manifested by an isolated prolongation of the PT. As factors II, IX, and X become depleted, the aPTT will become prolonged. Vitamin K deficiency is common in critically ill patients and may result in serious bleeding.[50] Treatment of vitamin K deficiency depends on the clinical situation. In a nonbleeding patient, vitamin K should be given enterally if the gut is working. Subcutaneous vitamin K should be avoided if the gut is working because of its erratic absorption, especially in face of impaired tissue perfusion, and because anaphylactic reactions have been reported with subcutaneous vitamin K.[55] In a bleeding patient, FFP will correct the coagulopathy most quickly. In critically ill patients with an urgent need for vitamin K replacement, phytonadione may be administered intravenously if the benefits are thought to outweigh the risk of anaphylaxis. Vitamin K should be given no faster than 1 mg/min with cardiorespiratory monitoring because anaphylactic reactions can occur even at this slow infusion rate.[55] One milligram of vitamin K twice a week can prevent vitamin K deficiency.

Liver Disease

The perturbation of hemostasis in liver disease is complex. All hemostatic factors except for vWF and plasminogen activator inhibitor-1 are synthesized in the liver. Loss of the ability to synthesize factor VII is disproportionately greater in patients with liver disease than in those receiving warfarin. Thus the bleeding risk of a prolonged international normalized ratio (INR) from liver disease is not as great as the same INR with warfarin therapy.[56] As outlined later, changes in factor VIII/vWF and decreased synthesis of natural anticoagulants and fibrinolytic proteins may help keep the patient with liver disease in hemostatic balance,[51] making the autoanticoagulation of liver disease promulgated among house staff a myth.

Although hepatic dysfunction is most commonly associated with bleeding, the risk of thrombosis has been underappreciated.[51] Synthesis of hemostatic proteins becomes impaired when the albumin falls below 2.5 g/dL. Similar to vitamin K deficiency, the earliest abnormality is a reduction in factor VII. In more severe liver disease, the other coagulation factors become deficient. Factor V and fibrinogen do not usually decrease significantly until the liver failure is severe. In contrast, the activities of factor VIII and vWF are normal or elevated. AT, proteins C and S, and plasminogen are decreased. Hepatic clearance of activated procoagulants and FDP is reduced. Thrombocytopenia may develop owing to decreased thrombopoietin production or splenic sequestration. Advanced liver disease may also be complicated by vitamin K deficiency from malnutrition and decreased vitamin K absorption owing to cholestasis.

A variety of approaches have been used to treat the coagulopathy of liver disease. If the patient is not bleeding, a trial of vitamin K can be given for 3 days to see if the coagulopathy corrects. Because all patients with liver disease have some degree of biliary obstruction and fat malabsorption, the subcutaneous route has been preferred over oral administration. Although the risk of anaphylaxis with IV and subcutaneous vitamin K is low, it is not generally recommended empirically in a patient with liver disease because of the low likelihood that vitamin K will completely correct the coagulopathy.[55] If bleeding is a problem, FFP should be administered. Because the relationship between the levels of coagulation factors and the PT/aPTT is nonlinear, the greater the prolongation of the PT and aPTT, the greater the chance of correction with FFP. However, it is difficult to normalize the PT.[57] On average, 1 unit of FFP increases all coagulation factors by 6% to 7%. A typical patient with the coagulopathy of liver disease may have approximately 10% to 15% of the normal level of coagulation factors. If a factor level of 50% of normal is needed for hemostasis, 6 units of FFP would be expected to correct the bleeding diathesis. The PT and aPTT may still be prolonged, however, depending on the sensitivities of PT and aPTT assays. The PT (and aPTT) should be checked immediately after the FFP is administered. Given the short half-life of factor VII, waiting until the next morning's routine blood draw will produce a prolongation of at least the PT and give the impression that the coagulopathy is uncorrectable.

Massive Transfusion

Massive volume replacement (>1 blood volume in <24 hours) may not give the liver sufficient time to replace coagulation factors. In a hemodynamically stable patient, coagulation studies should be followed serially and FFP infused when a coagulopathy develops. Conversely, exsanguinating patients should be managed with balanced transfusion of RBC:FFP:platelets in a ratio of 1:1:1 (either 1 unit of single donor or 6 units or random donor platelets).[58]

Acquired Circulating Inhibitors

Factor VIII Inhibitors

The clinical manifestations of factor VIII inhibitors can range from an unexplained prolongation of the aPTT to severe bleeding. The aPTT is markedly prolonged with a normal BT, PT, TT, and fibrinogen. The mixing study does not correct. Further evaluation includes factor VIII, IX, XI, and XII activities and a lupus anticoagulant panel. Hematomas should not be drained except in severe circumstances (e.g., compartment syndrome) because of the risk for bleeding, even with replacement therapy. Treatment options depend on the severity of the inhibitor. A low-titer inhibitor (<5 Bethesda units [BU]) may be treated with factor VIII infusion (200 U/kg every 8–12 hours). For a high-titer antibody (≥5 BU), the treatment options are recombinant human factor VIIa (rH-VIIa; NovoSeven) and virally inactivated concentrates containing activated coagulation factors (FEIBA [factor eight inhibitor bypass activity]). The dose of rH-VIIa is 90 μg/kg, which can be repeated every 2 hours until the bleeding stops. rH-VIIa carries a risk of thrombotic and ischemic events even in individuals with severe coagulopathy.[59] Coagulation studies are not used to adjust the dose. The PT always falls below the lower end of normal. The FEIBA dose is 50 to 100 U/kg, which is repeated every 6 to 12 hours (maximum daily dose 200 U/kg per day owing to thrombotic risk). A total of 500 units of heparin can be added to each bag to prevent infusion phlebitis. The response to FEIBA is monitored clinically. The choice of rH-VIIa versus FEIBA should be dictated by local practice.

Factor V Inhibitor

Topical thrombin (a.k.a. fibrin glue) is used to achieve hemostasis with many invasive procedures. Bovine thrombin is contaminated with factor V. Approximately 7 to 10 days after the use of fibrin glue, the PT and aPTT may prolong as a result of the development of antibodies against bovine factor V and rarely factor II. Bleeding

is uncommon because platelet factor V is protected from the antibody.

Inherited Deficiencies of Procoagulants

Management of critically ill patients with inherited coagulopathies requires specialized expertise. A hematologist or coagulationist should be consulted. Laboratory measurement of coagulation factor activity should be available on site.

von Willebrand Disease

von Willebrand disease (vWD) is the most common inherited coagulopathy. Synthesized in the vascular endothelium and megakaryocytes, vWF is the ligand that binds to the platelet GP Ib/IX/V complex and promotes platelet adhesion in vivo. vWF is a complex multimeric protein, with the largest molecular weight forms having the greatest platelet-binding capacity. Factor VIII procoagulant, which is synthesized by the liver, circulates bound to vWF.

vWD is inherited in an autosomal dominant manner with partial penetrance. The clinical features, diagnosis, and subclassification of vWD are reviewed elsewhere.[60]

Patients with vWD in the ICU most commonly have had major surgery, closed head trauma, major trauma, or life-threatening hemorrhage. The goal of therapy is to increase vWF activity and factor VIII activity to 100% of normal and to maintain them above 50%. Two virally inactivated factor VIII concentrates available in the United States (Humate-P and Alphanate) are rich enough in vWF to be of clinical use for treating vWD. The dose is 40 to 50 U/kg of vWF followed by 20 to 25 U/kg every 12 hours. Peak and trough levels of factor VIII (and vWF activity if available) should be obtained to help guide therapy. Doses should be rounded to the size of the nearest vial, if possible, so that these expensive factors are not wasted. The other brands of factor VIII concentrate do not contain enough vWF to be of clinical value in vWD. rH-VIII, used in hemophilia A, is of no benefit in vWD. In an emergency situation in a smaller facility that does not stock hemostatic factors on site, cryoprecipitate can be used at a dose of 2 bags per 5 kg followed by 1 bag per 5 kg every 12 hours until the patient can be transferred to a referral center. In mild cases of type I vWD, DDAVP may be adequate for promoting hemostasis in known DDAVP responders. Repeat doses may be given every 12 hours, although tachyphylaxis will likely develop as the result of exhaustion of vWF stores in the Weibel-Palade bodies of the endothelium. Patients should be monitored for hyponatremia, especially if large volumes of fluid are given.

Factor VIII Deficiency

Factor VIII deficiency (hemophilia A) is an X-linked recessive disorder that occurs in approximately 1 in 10,000 Caucasian males. Bleeding characteristically occurs in the joints, soft tissues, and gastrointestinal tract. Although the platelet count should be normal, individuals with hemophilia A complicated by hepatitis C or HIV infection (primarily from exposure to contaminated blood products before the era of viral inactivation) may have a concomitant immune thrombocytopenia.

For major surgery, closed head trauma, major trauma, or life-threatening hemorrhage, the factor VIII level should be raised to 100% and then maintained continuously above 50% for the first 5 to 7 days and above 40% for an additional 5 to 7 days. rH-factor VIII is the treatment of choice because it has no risk of viral infection. Infusing 1 unit of factor VIII per kilogram should raise the plasma factor VIII activity by 2%. Thus the initial dose is 50 U/kg followed by 25 U/kg every 8 hours. Peak and trough factor VIII levels should be obtained after the first dose and at least daily. In an emergency situation if rH-factor VIII is not available, virally inactivated factor VIII would be the treatment of choice. The dosing schema is similar to that of rH-factor VIII. In an emergency situation in a smaller facility that does not stock hemostatic factors on site, cryoprecipitate can be given every 8 hours until the patient can be transferred. Similar to vWD, DDAVP can be given for mild or moderate factor VIII deficiency in known DDAVP responders. As the hemophilia population ages, coronary artery disease is becoming an increasing problem. Individuals with hemophilia A should be supported through indicated cardiac procedures and surgery.[61]

Factor IX Deficiency

Except for the rate of spontaneous mutations, the clinical picture of factor IX deficiency (hemophilia B) is indistinguishable from that of hemophilia A. The laboratory features are similar except factor IX activity is decreased and factor VIII activity is normal. The treatment of choice is rH-factor IX. Because of differences in the volume of distribution compared with rH-factor VIII, the initial loading dose of rH-factor IX is 100 U/kg followed by half the dose every 12 hours. At least 30% of individuals require a higher dose. Thus it is not unreasonable to start with a dose of 125 U/kg, especially in a patient you do not want to underdose. Peak and trough levels should be monitored. If rH-IX is not available in an emergency situation, virally inactivated prothrombin complex concentrate (PCC) can be used. The initial dose is factor IX 100 U/kg followed by 50 U/kg every 12 hours. DDAVP and cryoprecipitate are not effective.

Factor XI Deficiency

Factor XI deficiency is an autosomal recessive disorder most commonly seen in Ashkenazi Jews. The bleeding history is variable, ranging from menorrhagia to bleeding with delivery or surgery. Therapy depends on the clinical situation and the patient's past bleeding history.[62] For severe deficiency, FFP (10–20 mL/kg followed by 3–6 mL/kg every 6 hours) is used. The goal is factor XI activity greater than 40% to 45%. Antifibrinolytic therapy may also be of value. Individuals with factor XI deficiency may be seen in the ICU because factor XI deficiency is not protective against coronary artery disease as was once thought.[63,64] These individuals may require emergency cardiac catheterization with PCI or coronary bypass.[63] Clopidogrel, prasugrel, and aspirin have been given safely.[63,64,65]

Venous Thromboembolism

Venous thromboembolism (VTE) is common in critically ill patients. Twenty-nine percent of medical ICU patients have been found to have asymptomatic lower extremity DVT, although 5.8% and 4.2% have symptomatic DVT and pulmonary emboli (PE), respectively.[66] Most patients admitted to the ICU have multiple risk factors, including recent surgery, trauma, sepsis, malignancy, immobilization, stroke, advanced age, heart or respiratory failure, previous VTE, and indwelling catheters.[66–68]

Deep Venous Thrombosis Prophylaxis

All patients admitted to the ICU should be evaluated for their perceived risk of thrombosis and bleeding.[66] The International Medical Prevention Registry on Venous Thromboembolism

(IMPROVE) score and Caprini score have been used for medical and surgical patients, respectively.[69,70] In medical patients, options for pharmacologic prophylaxis are LMWH and UFH, whereas mechanical prophylaxis is recommended for those with a high risk of bleeding.[66] Beyond the size limitations of this chapter, specific recommendations for DVT prophylaxis are available for trauma, abdominal/pelvic, thoracic, cardiac, and neurologic surgery.[71]

Therapy for Venous Thromboembolism

In the noncritical care setting, VTE is routinely treated with either (1) at least 5 days of UFH, LMWH, or fondaparinux, followed by warfarin or (2) a direct oral anticoagulant (DOAC).[72] In the ICU, IV UFH is the safest mode for immediate anticoagulation given its rapid reversibility for procedures or bleeding. LMWH has the disadvantages of a longer half-life and being only partially reversed with protamine. As discussed in the following section on anticoagulation, fondaparinux should not be used routinely in the ICU. ICU patients should not be transitioned to warfarin given their risk of bleeding and frequent need for invasive procedures. Warfarin is hard to regulate because of frequent drug interactions (especially with antibiotics) and erratic oral intake. Warfarin may stick to feeding tubes.[73] Warfarin is absorbed in the upper small bowel and may not be absorbed if given via J-tube.[74]

Inferior Vena Cava Filter

Approximately 80% of PE occur as a result of a lower extremity DVT. IVC filter placement is indicated in two situations: (1) acute DVT and a contraindication to anticoagulation (e.g., recent intracranial hemorrhage or stroke, recent neurologic or ophthalmologic surgery, active gastrointestinal hemorrhage, cerebral metastasis with a high risk of bleeding [e.g., melanoma, renal cell, seminoma][75]), and (2) recurrent PE despite therapeutic anticoagulation. Filters may have some benefit in face of PE causing hypotension.[72] IVC filters are not indicated for PE without DVT. IVC filters do not eliminate all risk of PE and their routine use does not decrease mortality rates.[72,76]

Anticoagulants

A variety of parenteral and oral anticoagulants acting through different mechanisms are commercially available with many more in development. The University of Washington Pharmacy Department Anticoagulation Service has an excellent reference website (http://depts.washington.edu/anticoag/home/).

Heparin, Heparin Derivatives, and Heparinoid

Heparin

Heparin is a glycosaminoglycan that anticoagulates blood by augmenting the activity of AT.[77] Complexes of heparin and AT inhibit thrombin, factor Xa, and other procoagulant proteases. The first five sugars of heparin bind to AT. The additional sugars determine the protein binding properties and pharmacokinetics of UFH and LMWH.[77]

Unfractionated Heparin

Binding of heparin to AT varies markedly between individuals, making monitoring a requirement. The anti–factor IIa property of heparin is measured by the aPTT. Because the anti-IIa and anti-Xa properties of UFH are equal, UFH may be monitored by the aPTT or by heparin (anti-Xa) level.

The goal of therapeutic heparin is to maintain the aPTT in a range that corresponds to a heparin level of 0.3 to 0.7 U/mL.[77] Given the marked variability in aPTT response to heparin because of differences in reagents and laboratory equipment, this range needs to be determined in each laboratory. An aPTT ratio of 1.5 to 2.5 times the control value correlates very poorly with the anti-Xa heparin assay and should not be used. The dose of heparin is weight based. No adjustments are needed for obesity, hepatic dysfunction, or renal impairment.[78,79] The hemoglobin and platelet count should be monitored daily as surveillance for occult bleeding and HIT. Overanticoagulation with heparin can usually be managed by simply interrupting the infusion. With serious bleeding, heparin can be reversed immediately with IV protamine sulfate.[77] One milligram of protamine will neutralize 100 units of heparin. If bleeding occurs during the constant infusion, the amount of heparin given during the previous 2 hours should be used for the calculation. Thus a patient who is bleeding after a 5000-unit heparin bolus will need 50 mg of protamine, whereas a patient receiving a 1250 U/h infusion will need only 25 mg of protamine. Protamine should be given slowly over 1 to 3 minutes to minimize the risk for hypotension and bradycardia. The risk for anaphylaxis is increased in those who have received protamine zinc insulin or who have had a vasectomy.

Low–Molecular-Weight Heparin

The properties of LMWH vary significantly from those of UFH.[77,78] The anti-Xa:anti-IIa ratio of LMWH is approximately 4:1. Thus LMWH does not significantly affect the aPTT. There is little protein binding, allowing for predictable renal excretion. The properties of the available LMWHs (enoxaparin, dalteparin, tinzaparin) are different.[78] Their kinetics and dosing are not interchangeable.[77] In a normal-sized adult (50–150 kg) with normal renal function, routine laboratory monitoring is not necessary. If monitoring is necessary (weight outside the usual range, impaired renal function), anti-Xa activity is measured 3.5 to 4.0 hours after an enoxaparin dose. The therapeutic range for enoxaparin (1 mg/kg every 12 hours) is 0.5 to 1.0 U/mL. LMWH is only 60% reversible by protamine.[77] If bleeding occurs within 8 hours of an LMWH injection, 1 mg of protamine per 100 anti-Xa units should be given. Because of the kinetics of LMWH, a second protamine dose of 0.5 mg per 100 anti-Xa units should be given if the bleeding persists.[77]

Pentasaccharide

Fondaparinux (Arixtra) is a synthetic analog of the first five sugars of heparin. Because of its small size, it is a pure factor Xa antagonist. Fondaparinux is FDA approved for treatment of DVT and PE and for DVT prophylaxis in orthopedic and abdominal surgery. Although not FDA approved, fondaparinux has been used off-label for the prophylaxis and treatment of heparin-induced thrombocytopenia and thrombosis (HITT).[17,52] As a result of its 18- to 21-hour half-life, its use in the ICU is limited because it is not rapidly cleared in a patient population that needs frequent procedures, that has a high risk of bleeding, and often has renal impairment (contraindicated with creatinine clearance [CrCl] <30 mL/min). It does not prolong the PT, aPTT, or TT. It can be measured in the anti-Xa assay calibrated for fondaparinux. It is not reversed by protamine. Bleeding owing to pentasaccharide should be supported by transfusion. rH-factor VIIa can also be tried.

Heparinoid

Danaparoid is a mixture of sulfated glycosoaminoglycans, distinct from heparin, that produces an anticoagulant effect primarily by enhancing the activity of AT. Danaparoid is primarily used in the setting of HIT. Dosing schema are available for most clinical situations.[79,80] If monitoring is necessary, such as during renal failure, anti-Xa activity must be determined. Although no longer available in the United States, danaparoid is available in Canada and Europe.

Direct Thrombin Inhibitors

As the name implies, DTIs directly bind to and inhibit the function of thrombin. Because of their expense, parenteral DTIs are generally reserved for the treatment of patients with HITT or true heparin allergy. Although none of them have an antidote, rH-VIIa has anecdotally been used off-label to stop life-threatening bleeding.

Argatroban is an arginine analog with a 40-minute half-life that is FDA approved for the treatment of HITT and for anticoagulation during PCI in face of HITT. It is metabolized in the liver, and its half-life increases to around 140 minutes with hepatic dysfunction. Because of its short half-life, an initial bolus is not needed. The standard dose is 2 μg/kg per minute as a continuous infusion, which should be decreased to 0.5 μg/kg per minute in individuals with significant liver disease or in the ICU (e.g., open heart surgery, congestive heart failure). Although argatroban is monitored by the aPTT, it has a significant effect on the PT.[81] Argatroban monotherapy will approximately double the INR and can markedly prolong the INR with concomitant warfarin therapy. As long as the aPTT is therapeutic, this exaggerated increase in INR does not increase the bleeding risk.

Hirudin is a family of recombinant proteins originally extracted from the salivary glands of leeches.[82]

Lepirudin is no longer commercially available worldwide.

Bivalirudin is a reversible synthetic analog of hirudin that is FDA approved for anticoagulation during PCI with HITT.[30] Bivalirudin has the advantage of a 25-minute half-life. Although it is cleared primarily by intravascular proteolysis, the dose must be reduced with renal dysfunction. Although not FDA approved, bivalirudin is used off-label in many centers for systemic anticoagulation for HITT.[83,84] It is also used off-label for cardiac bypass surgery in individuals with HIT.[30]

Dabigatran (Pradaxa) is the first FDA-approved oral DTI. It is approved for prevention of stroke and systemic embolization with nonvalvular atrial fibrillation and the treatment of VTE.[85,86] It binds free and clot-bound thrombin and is primarily cleared via the kidneys with a half-life of 12 to 17 hours.[87] The CrCl should be determined by the Cockcroft-Gault formula when using dabigatran. It should be used with extreme caution in the elderly, especially because of the risk of bleeding owing to overestimation of the CrCl and risk of trauma in the infirm. Recommendations for dosing with renal impairment are extrapolated from pharmacokinetic data because individuals with impaired renal function (CrCl <30 mL/min) were excluded form clinical trials.[88,89] Recommendations have included that it should not be used (1) with a CrCl 15–30 mL/min and concomitant use of a strong permeability glycoprotein (P-gp) inhibitor, with a CrCl <15 mL/min[90]; or (2) with a CrCl <30 mL/min.[88,91] P-gps are a family of xenobiotic efflux transporters found on the luminal side of enterocytes whose function is to prevent the absorption of potentially toxic substances.[90] Dabigatran is best absorbed in the stomach and duodenum, which have the lowest P-gp absorption compared with the distal small bowel. Gastric bypass surgery may impair the absorption of dabigatran.[92] Capsules should be given intact and not by nasogastric tube.[93]

Although dabigatran levels can be determined in reference laboratories, there is no standardized laboratory test to measure the dabigatran level in real time. Thus in a patient who is having bleeding or thrombotic events while taking dabigatran, there is no test to tell whether the event may be related to overanticoagulation or underanticoagulation. Ideally, a sample level should be sent to a reference laboratory. If possible, the sensitivity of the aPTT and TT to dabigatran should be predetermined in the local laboratory. As a screening test, given its sensitivity, a normal TT generally suggests that there is no dabigatran present. Although the blood concentration after fixed dosing is known, the therapeutic range for dabigatran has not been determined. How long dabigatran should be discontinued before procedures depends on the renal function and the bleeding risk of the procedure.[87,88]

Approaches to the reversal of dabigatran in a bleeding patient and before emergent surgery are shown in Figs. 74.2 and 74.3, respectively. In the bleeding patient, activated charcoal may be given if within 2 hours of ingestion. Idarucizumab (Praxbind) is an FDA-approved monoclonal antibody that rapidly reverses the anticoagulant effect of dabigatran and is the treatment of choice for the patient with severe or life-threatening bleeding. There is a risk of recurrent VTE during the period of dabigatran reversal. Because it is a humanized, mouse monoclonal antibody, idarucizumab may be immunogenic.[93] Whether it can be used on multiple occasions without causing allergic reactions or affecting idarucizumab excretion is not known.

Direct Oral Anticoagulants

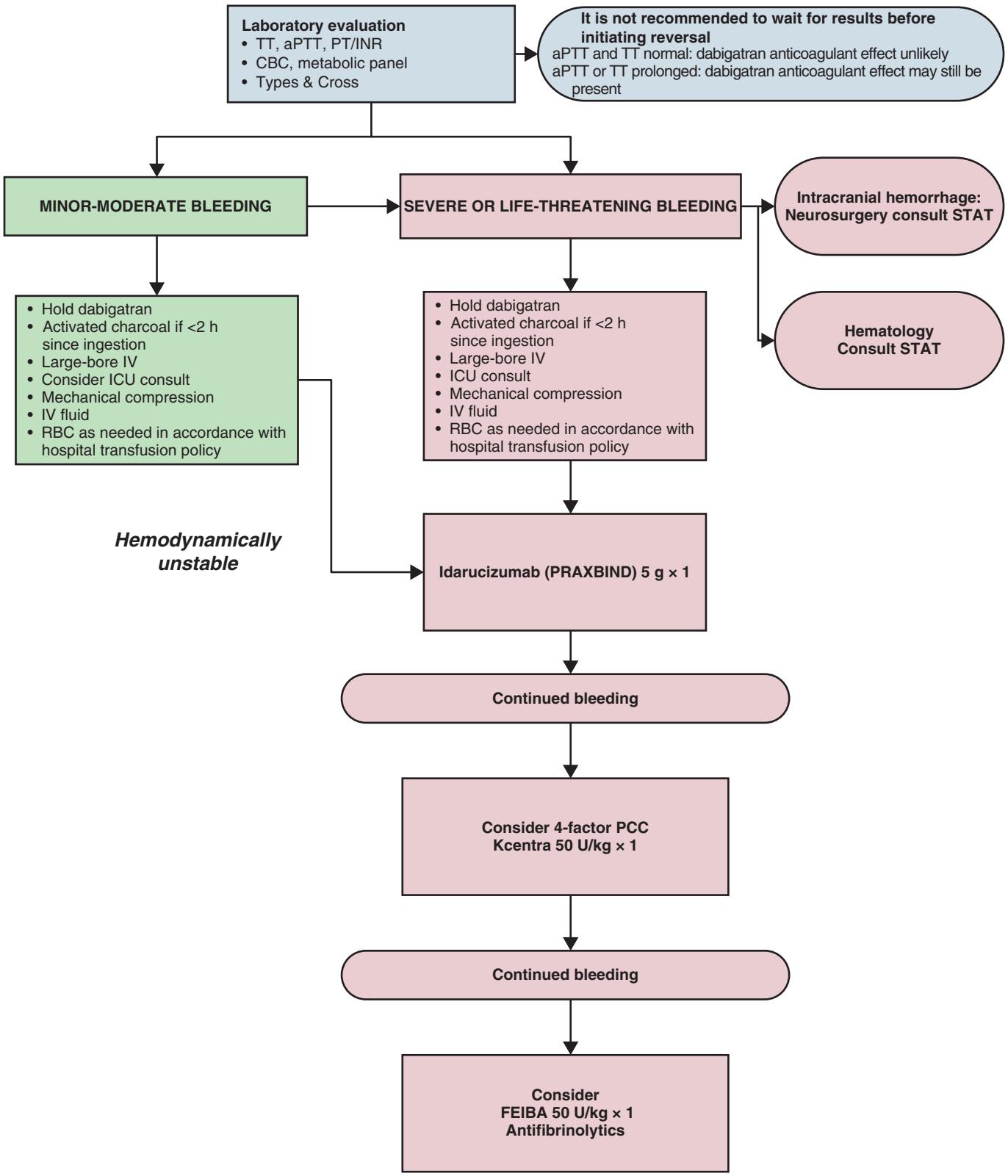
Direct oral anticoagulants (DOACs) to thrombin and factor Xa are commercially available.

Direct Oral Thrombin Inhibitors

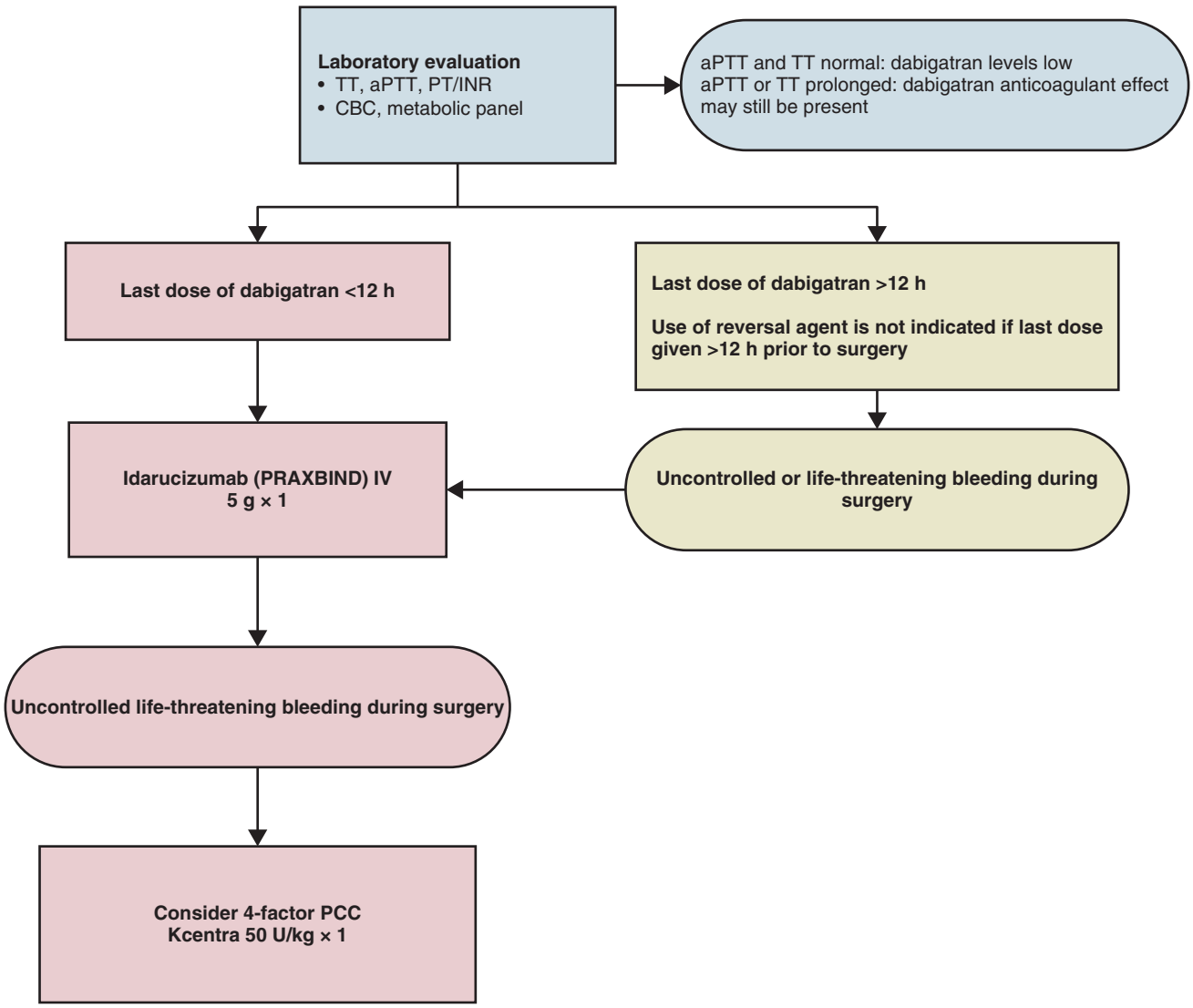
See the previous discussion of dabigatran.

Direct Oral Factor Xa Inhibitors

Three oral factor Xa inhibitors are currently FDA approved for stroke prevention in nonvalvular atrial fibrillation and treatment of VTE. They have distinct pharmacologic properties and are not interchangeable.[94] The CrCl should be determined by the Cockcroft-Gault formula when using any DOAC. Dosing in patients with end-stage renal disease and those using dialysis is not evidence based because individuals with CrCl below 25 to 30 mL/min were excluded from clinical trials.[88,91] All oral factor Xa inhibitors are substrates affected by inducers or inhibitors of P-gp.[88] Although levels of all three factor Xa inhibitors can be determined in reference laboratories, there is no standardized laboratory test to measure their levels in real time. Thus in a patient having bleeding or thrombotic events while taking any oral factor Xa inhibitor, there is no test to tell whether the event may be related to overanticoagulation or underanticoagulation. A blood level should be sent to a reference laboratory at the time of any event. Although not as accurate as using liquid chromatography/mass spectroscopy, the levels of all three factor Xa inhibitors can be measured by the anti-Xa assay used to monitor heparins. Unfortunately, standards to calibrate the assay are not available in the United States. A normal anti-Xa level calibrated either for UFH or LMWH will exclude the presence of a clinically relevant level of an oral factor Xa inhibitor. Although the blood concentration



• **Fig. 74.2** Approach to bleeding with dabigatran. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *FEIBA,* factor eight inhibitor bypassing activity; *ICU,* intensive care unit; *INR,* international normalized ratio; *IV,* intravenous; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time.

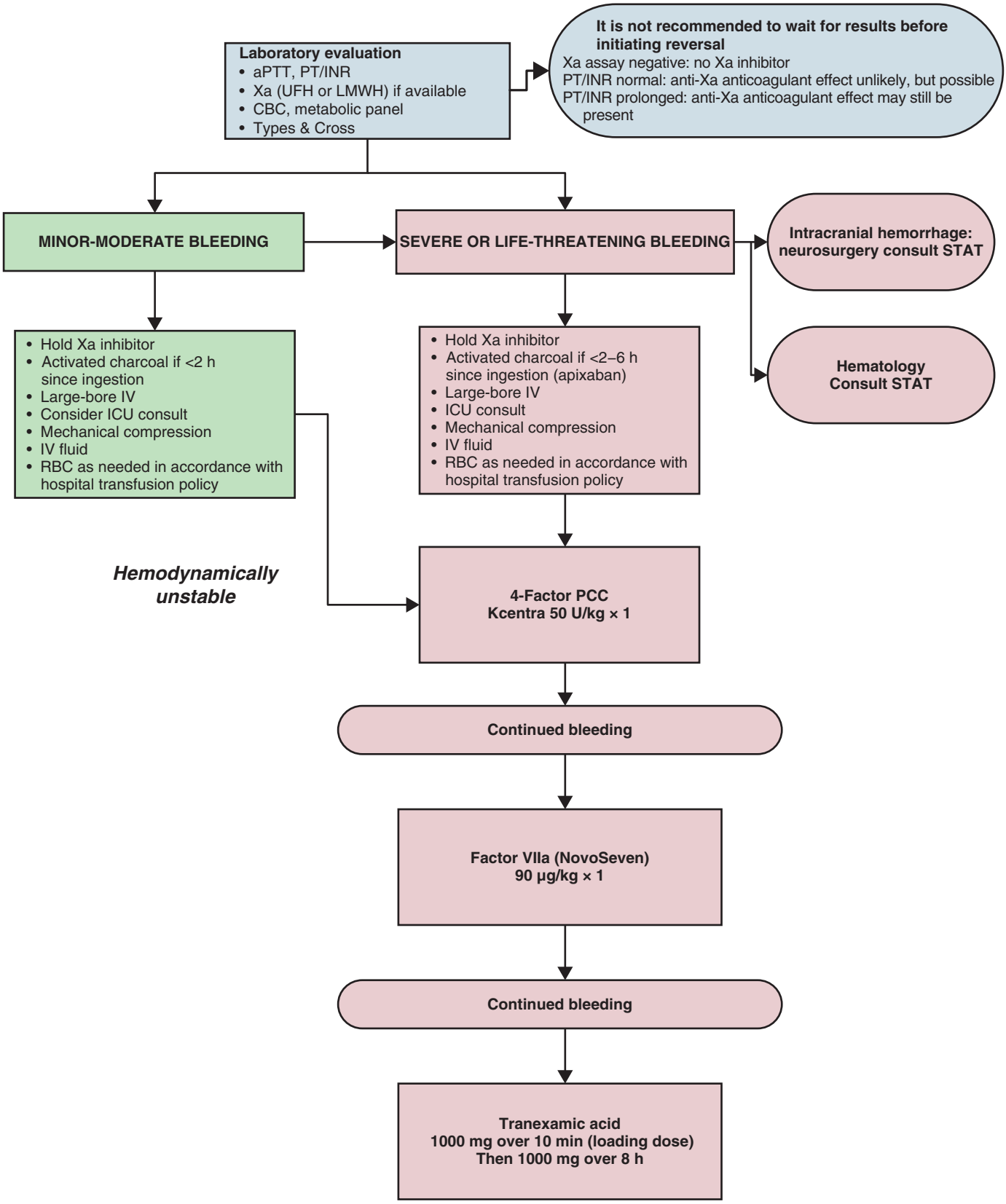


• **Fig. 74.3** Approach to emergency surgery with dabigatran. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *INR,* international normalized ratio; *IV,* intravenous; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *TT,* thrombin time.

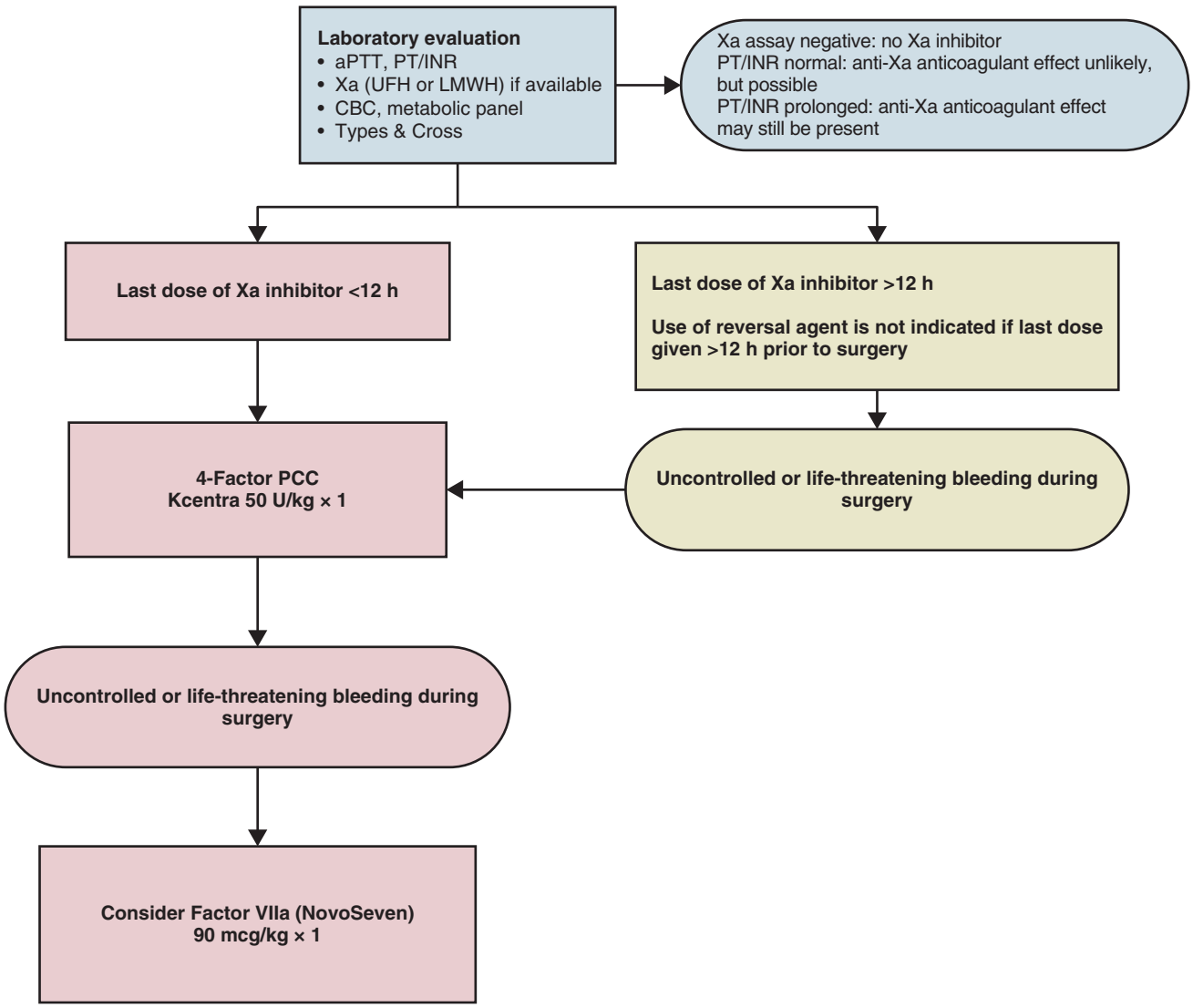
after fixed dosing is known, the therapeutic range for the oral factor Xa inhibitors has not been determined. How long these agents should be discontinued before procedures depends on the renal function and the bleeding risk of the procedure.[88,95] In general, oral factor Xa inhibitors should be withheld for 24 to 48 hours before standard risk and 48 to 72 hours for high-risk surgical procedures depending on renal function.[88] They should be held for at least 72 hours before neuroaxial procedures. Most commonly, individuals taking DOACs are admitted to the ICU for bleeding or need emergent procedures. Approaches to the reversal of oral factor Xa inhibitors in the bleeding patient and before emergent surgery are shown in Figs. 74.4 and 74.5, respectively. All factor Xa inhibitors have a relatively short half-life. Because their anticoagulant activity is significantly decreased after two half-lives, many individuals need just supportive care by the time they present with bleeding.[88] Although not yet FDA approved, andexanet alfa and ciraparantag are undergoing clinical trials for the reversal of the class of oral factor Xa inhibitors. Because there are no evidence-based data regarding the reversal of oral factor Xa inhibitors in the bleeding patient and given the ubiquity of renal dysfunction in the ICU, these agents should be used with caution, if at all, in the ICU.

Apixaban

Apixaban (Eliquis) is FDA approved for the prevention of stroke in atrial fibrillation and treatment of deep venous thrombosis and pulmonary embolus.[96] It has an 8- to 15-hour half-life, and its elimination is fecal and renal. P-gp inhibitors and strong cytochrome 450 (CYP) 3A4 inhibitors significantly increase its plasma concentration, whereas strong P-gp inducers may increase the risk of stroke.[90] When treating atrial fibrillation, the dose of apixaban should be reduced for any two of the following: age older than 80 years, weight 60 kg or less, or creatinine level of 1.5 mg/dL of less, Because of its relatively limited renal excretion compared with the other DOAC, it may be the safest DOAC to give to patients with renal insufficiency. However, there are no evidence-based data on



• **Fig. 74.4** Approach to bleeding with oral factor Xa inhibitors. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *ICU,* intensive care unit; *INR,* international normalized ratio; *IV,* intravenous; *LMWH,* low–molecular-weight heparin; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time; *UFH,* unfractionated heparin.



• **Fig. 74.5** Approach to emergency surgery with oral factor Xa inhibitors. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *INR,* international normalized ratio; *LMWH,* low–molecular-weight heparin; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time; *UFH,* unfractionated heparin.

its efficacy and safety in individuals with end-stage renal disease or those using dialysis who are receiving chronic apixaban.[88,91,95] It may be crushed and given immediately via nasogastric tube.

Rivaroxaban

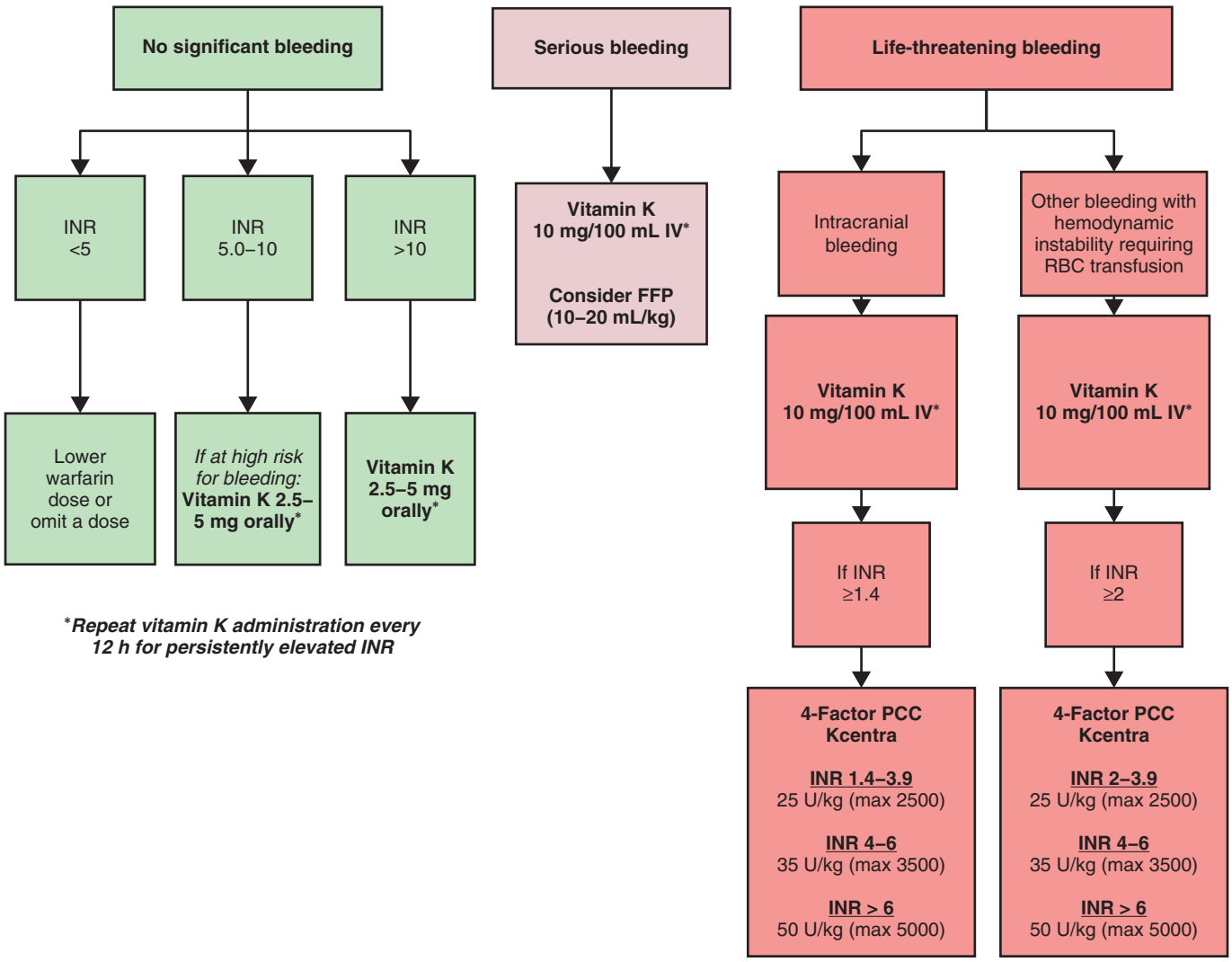
Rivaroxaban (Xarelto) is FDA approved for the prevention of stroke in atrial fibrillation and, treatment of deep venous thrombosis and pulmonary embolus.[97,98] It has a 5- to 9-hour half-life (9–13 hours in the elderly) and is metabolized primarily via the cytochrome system. Combined strong P-gp and strong CYP 3A4 inhibitors may significantly increase the plasma concentration of rivaroxaban, whereas strong P-gp inducers may increase the risk of recurrent VTE.[88,90] It should be avoided in the face of significant hepatic dysfunction. Dosing recommendations have included dose reduction for atrial fibrillation and a CrCl of 15 to 50 mL/min versus not using it with a CrCl less than 30 mL/min.[89] It should not be used for treatment of VTE with a CrCl less than 30 mL/min.[78,88] It should not be administered via feeding tube distal to the stomach.

Edoxaban

Edoxaban (Savaysa) has a 10- to 14-hour half-life and is excreted primarily as unchanged drug in the urine. The dose should be reduced in the face of cardiac medications that are strong P-gp inhibitors.[90] Recommendations have included dose reduction for CrCl 15 to 50 mL/min versus withholding it for a CrCl less than 30 mL/min.[88] It is contraindicated for a CrCl greater than 95 mL/min owing to increased clearance and an increased risk of stroke. There are no data on crushing tablets or giving edoxaban via feeding tube.

Warfarin

The vitamin K antagonist warfarin decreases the activities of factors II, VII, IX, and X and proteins C, S, and Z. Although prolongation of the PT is often seen within the first 24 to 48 hours after initiation of warfarin as result of the decrease in factor VII, 4 to



• **Fig. 74.6** Approach to the reversal of warfarin. *FFP,* Fresh frozen plasma; *INR,* international normalized ratio; *IV,* intravenous; PCC, prothrombin complex concentrate; *RBC,* red blood cell count. (Adapted from Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 suppl):e44S–e88S.)

5 days are required for factors II and X to drop to antithrombotic levels.

The response to warfarin is variable and is affected by many factors common in the ICU, such as poor nutrition (vitamin K deficiency), liver dysfunction, and coadministration of medications that affect warfarin pharmacokinetics. It is not uncommon for patients to become overanticoagulated with warfarin. An approach to warfarin reversal is shown in Fig. 74.6.[99,100] Specific therapy (4-factor PCC [Kcentra]), if available, is recommended over FFP.[101,102] Kcentra contains heparin and is contraindicated in individuals with a history of HIT or true heparin allergy.

Key Points

- Hemorrhagic and thrombotic complications in a critically ill patient can usually be anticipated and avoided by careful history taking and physical examination. Routine laboratory tests (platelet count, PT, aPTT, TT, fibrinogen) are helpful in evaluating hemorrhagic disorders but not thrombotic disorders.
- Vitamin K deficiency is a relatively common coagulopathy in critically ill patients, and it is easily treated if recognized.
- von Willebrand disease, the most common inherited coagulopathy, varies highly in clinical severity. Humate-P and Alphanate are the only "factor VIII" concentrates that are therapeutic.
- The bleeding diathesis of uremia can improve with several different treatments, including dialysis, DDAVP, IV administration of estrogens, and cryoprecipitate.

- Idiopathic thrombocytopenic purpura in adults is usually chronic. If life threatening, several modalities are available for urgent elevation of the platelet count.
- DIC is always a secondary disease process. Treatment must be focused on the underlying cause. If bleeding occurs, blood components should be given. Heparin is generally reserved for clinically evident thrombosis.
- TTP is a clinical diagnosis associated with multiple inciting events. It is often fatal unless recognized early and treated with plasma exchange.
- HIT with thrombosis may be life threatening. It should be looked for in any patient with thrombocytopenia who has been exposed to heparin. It can be managed with DTIs.
- Deep venous thrombosis is common in critically ill patients. Prophylactic treatment should be considered for every patient in the ICU. IV UFH is often the safest treatment of established DVT in the critical care setting.
- Direct DOACs (thrombin and factor Xa inhibitors) are being used with increasing frequency. They do not need routine monitoring. They should be used with caution in the face of renal dysfunction because of an increased risk of bleeding.

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Review Questions/Answers

1. A 70-year-old-male has end stage renal disease and is being treated with hemodialysis. He develops a pulmonary embolus that requires anticoagulation. Which of the following would be the *best* option for initial anticoagulation?
a. Weight-based unfractionated heparin
b. Argatroban 2 μg/kg/min constant infusion
c. Fondaparinux with a 50% dose reduction
d. Full-dose rivaroxaban
e. Full-dose apixaban
Answer: a. Weight-based unfractionated heparin dosing is not affected by renal function. Although argatroban is metabolized by the liver and does not need dose reduction for renal disease, its cost limits its use to individuals with heparin-induced thrombocytopenia or true heparin allergy. Fondaparinux has an 18-hour half-life in normal individuals and is excreted through the kidneys. It is contraindicated with a creatinine clearance (CrCl) less than 30 mL/min. None of the trials with rivaroxaban or apixaban have included individuals with a CrCl less than 25 to 30 mL/min. Rivaroxaban should not be used with a CrCl less than 15 to 25 mL/min. Apixaban is an intriguing option because it has the least renal clearance of the direct oral anticoagulants (DOACs). Although there was no difference in apixaban level in individuals on dialysis who were given a single dose of apixaban compared to normal individuals, there are no efficacy and safety data on the use of apixaban when given chronically to individuals using dialysis.

2. A 68-year-old male with a history of hypertension, diabetes, and atrial fibrillation presents with altered mental status who was initially "found down," unconscious. Per his daughter, the patient takes metformin, aspirin, lisinopril, and dabigatran. He took these medications 1 hour ago. Vital signs are normal. His complete metabolic panel (CMP) and complete blood cell count (CBC) are within normal limits. International normalized ratio (INR) is 1.1 (normal <1.2) and activated partial thromboplastin time (aPTT) is 27 seconds (normal 22–29 seconds). A computed tomography (CT) head shows a subdural hemorrhage with no mass effect. What is the *best* treatment modality?
a. Vitamin K
b. Prothrombin complex concentrate
c. Idarucizumab
d. Protamine
e. No intervention needed because his prothrombin time (PT) and aPTT are normal
Answer: c. Idarucizumab is a humanized mouse monoclonal antibody that binds to dabigatran with high affinity, reversing its anticoagulant effects and concentrations in serum. This was illustrated in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE-AD) trial. Vitamin K is a reversal agent for warfarin. Prothrombin concentration (PCC) has mainly been used in vitro studies and animal models, but no strong clinical evidence in humans. Although the patient is taking dabigatran, the PT and aPTT may be normal depending on the sensitivity of the assays and how long after the dose was taken that the blood is obtained.

3. A 28-year-old female with no significant past medical history is admitted to the intensive care unit with a saddle pulmonary embolus. Her INR is 1.0 (normal <1.2) with an aPTT of 41.4 seconds (normal 22–29 seconds). Results of a CBC and a CMP are normal. There is no history of bleeding in the patient or any family members. Which of the following is the *best* diagnostic test?
a. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) level
b. von Willebrand profile
c. Factor X level
d. Mixing studies
e. Complement factor H
Answer: d. Mixing studies will determine whether the prolonged aPTT is due to factor deficiency or the presence of a circulating inhibitor. Mixing studies are tests performed on *blood plasma* and used to distinguish factor deficiencies from *factor inhibitors* (such as *lupus anticoagulant*). Mixing studies take advantage of the fact that factor levels that are 50% of normal should give a normal PT or *partial thromboplastin time* (PTT) result. Mixing studies are a useful tool for the assessment of a coagulopathy. ADAMTS13 is deficient in thrombotic thrombocytopenic purpura and would not be helpful with a normal CBC. Although most patients with von Willebrand disease have an elevated aPTT, she has no history of bleeding, thus making this unlikely. Factor X deficiency causes elevation of INR and APTT because it resides in the common pathway. Abnormalities in complement protein H may predispose to adult atypical hemolytic-uremic syndrome, which is not in the differential diagnosis with a normal CBC and normal renal function.

75

Use of Blood Components in the Intensive Care Unit

FAISAL ZAHIRUDDIN AND JANICE L. ZIMMERMAN

CHAPTER OUTLINE

Blood Components and Indications for Transfusion
- Whole Blood and Red Blood Cells
- Platelets
- Plasma-Derived Components

Adverse Effects of Blood Component Transfusion
- Acute Transfusion Reactions
- Delayed Hemolytic Transfusion Reactions
- Transfusion-Associated Circulatory Overload
- Transfusion-Related Acute Lung Injury
- Transfusion-Associated Graft-Versus-Host Disease
- Transfusion-Related Immunomodulation
- Transfusion-Transmitted Infectious Diseases

Special Transfusion Situations in the Critical Care Setting
- Massive Transfusion
- Autoimmune Hemolytic Anemia
- Necessary Transfusion of Incompatible Blood

Alternatives to Transfusion of Blood Components
- Blood Substitutes
- Desmopressin
- Antifibrinolytic Agents
- Vitamin K
- Hematopoietic Growth Factors
- Cell Salvage Technology

Legal Issues in Transfusion Medicine

Transfusion of blood components is a frequent intervention in hospitalized patients, particularly in critically ill patients. An estimated 20,933,000 units of red blood cells (RBCs), platelets, plasma, and cryoprecipitate were transfused in 2011 in the United States.[1] RBC transfusion is often used to optimize oxygen-carrying capacity and tissue perfusion that may be due to blood loss, inadequate marrow function, and RBC destruction. Additionally, hemostatic disorders may necessitate the administration of other blood components such as plasma, platelet concentrates, or cryoprecipitate.

Blood components should be considered therapeutic agents with potential benefits as well as adverse effects. Unlike pharmaceutical agents, however, blood components have fewer objective indications for use and no therapeutic index relating dose to safety. Although infectious risks of blood component transfusion have diminished, recognition of risks such as immunomodulation and transfusion-related acute lung injury (TRALI) has increased. Programs of blood conservation management are proposed to determine appropriate evidence-based use of blood components and to minimize use of blood products.[2] Although more quality evidence has become available to guide clinical decisions in transfusion, more questions remain to be explored through clinical trials, particularly in critically ill patients.

Blood Components and Indications for Transfusion

Blood component therapy is used to optimize management of the blood supply. The basic principle of blood component therapy is to use the specific blood product that meets the patient's need. Up to four components (RBCs, plasma, platelets, cryoprecipitate) can be derived from a single whole blood (WB) donation and then distributed to several recipients with differing physiologic needs. Component therapy thus meets the clinical requirements of increased safety, efficacy, and conservation of limited resources. As the variety of available blood product components increases, however, the complexity of transfusion medicine also increases. A WB donation is typically separated into RBCs, a platelet concentrate, and fresh frozen plasma (FFP). The plasma may be further processed into cryoprecipitate and supernatant (cryopoor) plasma. The characteristics of more commonly transfused blood products are described in Table 75.1.

Whole Blood and Red Blood Cells

Unseparated venous donor blood with a preservative solution constitutes a WB unit. It contains all blood components, but after less than 24 hours of refrigerated storage, platelet and leukocyte function is lost. With further storage, levels of the labile coagulation factors V and VIII markedly decrease.[3] The growing need for specialized blood components has resulted in processing the majority of blood donations into components, thus limiting the availability of WB.

RBCs, commonly known as *packed red blood cells* (PRBCs), are the blood component most commonly transfused to increase RBC mass. PRBCs are derived from the centrifugation or sedimentation of WB and removal of most of the plasma/anticoagulant solution.

TABLE 75.1 Characteristics of Blood Components

Blood Component	Content	Volume (mL)	Plasma (mL)	Shelf Life
Red Cell Products				
Whole blood	RBCs (Hct 40%–45%), WBCs, plasma, platelets (nonviable)	500–515	~300	21–35 days at 1°C–6°C (depending on anticoagulant) 24 h if unrefrigerated
Packed RBCs	RBCs (Hct 60%–80%), WBCs, plasma, platelets (nonviable)	250–300	~25–50 mL	21–42 days at 1°C–6°C (depending on anticoagulant)
Leukocyte-reduced RBCs (filtered)	RBCs (Hct 90%), minimal plasma	200	Minimal	21–42 days at 1°C–6°C (depending on anticoagulant)
Washed RBC	RBCs (Hct 60%), some WBCs	340	0	24 h
Frozen RBCs	RBCs (Hct 90%, minimal WBC and platelets (nonviable)	170–190	0	10 years at –80°C
Platelets				
	Platelets, some WBCs, some RBCs, plasma			Open, 24 h at 20°C–24°C with continuous agitation Closed, 5 days at 20°C–24°C with continuous agitation
Single-donor (apheresis)	$\geq 3 \times 10^{11}$ platelets/unit	~300 (200–400)	~250	
Random donor	$\geq 5.5 \times 10^{10}$ platelets/unit	50	50	
Plasma-Derived Products				
Fresh frozen plasma (frozen within 6–8 h of phlebotomy)	Plasma with all coagulation factors and inhibitors, complement, fibrinogen, albumin, globulins	*Whole blood donor:* 200–250 *Apheresis donor:* 400–600	200–250 400–600	1 year at –18°C; 24 h at 1°C–6°C once thawed
Plasma frozen within 24 h (separated from whole blood stored at 4°C–6°C within 24 h of collection)	Plasma with all coagulation factors and inhibitors but with lower levels of V and VIII; complement, fibrinogen, albumin, globulins	200–250	200–250	1 year at –18°C 24 h at 1°C–6°C once thawed
Cryoprecipitate-reduced plasma (fresh frozen plasma with cold-induced precipitate removed)	Similar to fresh frozen plasma but deficient in XIII, VIII, fibrinogen, and von Willebrand factor	200–225	200–225	1 year at –18°C 24 h at 1°C–6°C once thawed
Cryoprecipitate	Factor VIII (minimum 80 IU), XIII, fibrinogen (minimum 150 mg), von Willebrand factor, plasma, fibronectin	5–20	5–20	1 year at –18°C 4–6 h at room temperature once thawed

Hct, Hematocrit, *RBCs,* red blood cells; *WBCs,* white blood cells.

PRBCs may be further modified to meet the specific needs of patients or blood bank regulations. Leukocyte-reduced PRBCs are the most commonly transfused modified RBC product. Transfusion of blood components containing leukocytes may lead to nonhemolytic febrile transfusion reactions, a greater propensity for platelet alloimmunization, and transmission of pathogens carried by leukocytes, such as cytomegalovirus (CMV). Leukocyte reduction requires filtration of the blood component by a special filter at the time of blood donation and processing or later at the time of transfusion ("bedside filtration"). Leukocyte-reduced RBC units must contain less than 5.0×10^6 leukocytes. Filtration before storage conveys the benefit of removing white blood cells (WBCs) before they can deteriorate and elaborate cytokines and other unwanted substances during storage.[4] Because of proven and theoretical benefits of leukocyte reduction of blood components (discussed later in the section covering the adverse effects of transfusion), many European countries and Canada require that all PRBCs be leukocyte reduced, a process called *universal leukoreduction*. Some institutions in the United States have also made that decision, but either method of leukocyte reduction adds significantly to the cost of each transfusion, and the benefits of this measure when applied globally are still debated.[5] Almost 85% of transfused PRBCs are leukoreduced in the United States.[1]

Washing PRBCs involves recentrifuging in normal saline solution to remove the plasma/preservative solution from the unit. Washing removes 99% of the plasma proteins and 85% of leukocytes. Washing may take an hour or more, limits subsequent storage time to 24 hours, and causes loss of RBCs (10%–20%). Washing

is not an effective method of leukoreduction. Washed PRBCs may be indicated for patients with febrile transfusion reactions not prevented by leukoreduction, immunoglobulin (Ig) A deficiency with documented antibodies to IgA, and history of a previous anaphylactic reaction to blood transfusion.

PRBCs can also be modified by irradiation to inactivate lymphocytes. Transfusion of irradiated blood is indicated in severely immunocompromised patients at risk of graft-versus-host disease (GVHD), such as transplant recipients, those with aggressively treated malignancies, and those with congenital immunodeficiencies. The transfusion of irradiated PRBCs in the United States is increasing and accounted for 13.4% of blood transfusions in 2011.[1] Irradiation of RBCs reduces RBC viability and increases release of intracellular potassium.

PRBCs can be frozen in cryoprotective solution and stored for extended periods. Frozen RBCs are generally limited to units of special value, such as those with a rare RBC antigen profile or autologous blood donations that need to be stored for future use. A rare-donor registry of frozen PRBCs exists in most countries to assist in providing blood to patients with complex or multiple alloantibodies to RBC antigens. Significant advance planning is necessary to acquire and thaw frozen PRBCs for transfusion, thus limiting their use in acute situations.

RBC components incur some cell loss during storage. The current technology with preservative solutions attempts to optimize cell quality and quantity by using strict criteria to determine the allowable storage time. Nonetheless, as RBC metabolism decreases progressively, a "storage lesion" results, with accumulation of a variety of undesirable substances and loss of cellular function.[6] During storage, a slow rise in the concentration of potassium, lactate, aspartate aminotransferase, lactate dehydrogenase, ammonia, phosphate, and free hemoglobin and a slow decrease in pH and bicarbonate concentration occur. Cytokines and inflammatory mediators such as interleukin (IL) 1, IL-6, and tumor necrosis factor also accumulate. The pH of freshly stored blood in citrate solution is 7.16, which declines to approximately 6.73 at the end of the unit's shelf life. As potassium leaks from RBCs during storage, levels as high as 25 mEq/L may result. However, each unit transfused supplies at most 7 mEq of potassium, which is usually well tolerated.

During the storage period there is also a progressive decrease in RBC-associated 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate.[6] A decrease in 2,3-DPG increases the affinity of hemoglobin for oxygen, which shifts the oxyhemoglobin dissociation curve to the left and decreases oxygen delivery to tissues. There is little evidence, however, that this transient increase in oxygen affinity has clinical importance. After infusion, 2,3-DPG gradually increases as the transfused RBCs circulate, with 25% recovery in 8 hours and full replacement by 24 hours.[7] Decreased adenosine triphosphate during storage diminishes the viability of RBCs after transfusion and is one of the chief factors limiting storage time. The majority of blood transfusions are in the form of PRBCs, the component indicated for normovolemic patients or those for whom intravascular volume constraints are necessary. Resuscitation in patients requiring increased oxygen-carrying capacity and volume is effectively achieved with the use of PRBCs and crystalloid or colloid solutions. Each unit of PRBCs is expected to raise the hemoglobin concentration by approximately 1 g/dL and the hematocrit by 3% in stable, nonbleeding, average-sized adults.

Indications for RBC Transfusion

Despite a long tradition of transfusion of RBCs in critically ill patients, the precise indications and hemoglobin threshold for transfusion remain a source of debate, and transfusion practices may vary widely among clinicians, intensive care units (ICUs), institutions, and geographic regions. Multiple observational studies document transfusion rates in ICU patients that vary from 17% to 53%,[8–12] and the rate of transfusion increases with longer ICU length of stay.[8,13] There has been a trend over time for use of a lower transfusion threshold in critically ill and hospitalized patients.[14,15]

RBCs should be transfused to enhance tissue oxygen delivery, but the underlying physiology of anemia, the complex adaptations to anemia, and the potential advantages and disadvantages to particular groups of patients are not as well understood. Determining when an anemic patient would truly benefit from increased oxygen-carrying capacity remains an imprecise task. In addition, evidence argues that transfusions may result in donor-recipient interactions deleterious to the critically ill patient, including the disruption of compensatory physiology, the immunomodulation caused by the presence of foreign cells, and the introduction of unintended plasma contents.

Compensatory mechanisms for acute and chronic anemia are complex and work in concert to maintain oxygenation within the microcirculation.[16,17] Cardiovascular adjustments leading to increased cardiac output include decreased afterload and increased preload resulting from changes in vascular tone, increased myocardial contractility, and elevated heart rate. Lowered blood viscosity permits improved flow of RBCs within capillaries. Blood flow is redistributed to favor critical organs with higher oxygen extraction such as the heart and brain. Pulmonary mechanisms, though contributing relatively little to short-term oxygenation demands, exert potent effects on related metabolic variables. Finally, the hemoglobin molecule can undergo biochemical and conformational changes to enhance the unloading of oxygen at the capillary level. Increased synthesis of RBC 2,3-DPG in anemia results in a rightward shift of the oxyhemoglobin dissociation curve and facilitates the release of oxygen to tissues. A rightward shift of the oxyhemoglobin curve can also occur with a decrease in pH (Bohr effect) but the clinical significance is small.[16] All these mechanisms contribute to an oxygen reserve capacity that exceeds baseline requirements by approximately fourfold. Unfortunately, acute illness and chronic morbidities may limit these compensatory mechanisms in critically ill patients. Reports in patients refusing transfusion indicate that an extremely low hematocrit is tolerated if tissue perfusion is adequate.[17,18]

Although RBC transfusion can increase oxygen-carrying capacity and thus oxygen delivery, it may not improve tissue oxygen consumption. Multiple case series evaluating the effects of RBC transfusion in critically ill patients have failed to document increased oxygen consumption or improvement in lactate level.[19,20–22] Hypotheses to explain this discrepancy include an increase in blood viscosity limiting microvascular flow and impaired tissue and cellular oxygen utilization.

In practice, the hemoglobin concentration is most often used to determine the need for blood transfusion. The relevant issue for clinicians is determining the most appropriate hemoglobin threshold that should trigger RBC transfusion. Although anemia has been associated with increased mortality in critically ill patients,[23–25] results of multiple randomized clinical trials in different patient populations suggest that restrictive transfusion strategies are equivalent to liberal transfusion strategies for most patients. The first multicenter randomized trial of RBC transfusion strategies in the critically ill (Transfusion Requirement in Critical Care [TRICC]) compared a liberal (transfusion threshold, hemoglobin 10 g/dL) with a restrictive (transfusion threshold, hemoglobin 7 g/dL)

RBC transfusion policy in 838 euvolemic patients.[26] The primary outcome measure of 30-day all-cause mortality rate was not statistically different between the restrictive strategy and the liberal strategy groups ($P = 0.11$). A secondary outcome measure of overall hospital mortality rate was significantly lower in the restrictive strategy group ($P = 0.05$). The restrictive strategy was superior for subgroups of patients younger than 55 years and patients with lower (<20) APACHE (Acute Physiology, Age, and Chronic Health Evaluation) II scores. In addition, liberal transfusion was not associated with shorter ICU or hospital stays or less organ failure; longer mechanical ventilation times and cardiac events were more frequent in the liberal strategy group. The number of transfusions was reduced by 54% with the restrictive strategy.

The results of the TRICC study were replicated in a study of transfusion strategy in critically ill pediatric patients.[27] A liberal transfusion threshold of 9.5 g/dL was compared with a restrictive transfusion threshold of 7.0 g/dL. The primary outcomes of death and new or progressive multiple organ dysfunction as well as adverse events were similar in both treatment groups, but 54% of patients in the restrictive group did not receive transfusion compared with only 2% in the liberal group. Additional prospective randomized trials have validated the use of a restrictive transfusion strategy in other adult patient populations.[28–35] The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) transfusion trial enrolled 2016 high-risk elderly patients who had a history of or risk factors for cardiovascular disease who underwent surgery for hip fracture. The liberal transfusion strategy used a hemoglobin threshold of 10 g/dL and the restrictive strategy used a hemoglobin threshold of 8 g/dL. Mortality and functional recovery were similar in both groups.[28] The multicenter Transfusion Requirements in Septic Shock (TRISS) trial in 998 patients compared transfusion thresholds of 7 g/dL and 9 g/dL and found similar mortality and fewer transfusions in the restrictive group.[29] A liberal transfusion strategy (threshold hemoglobin 10 g/dL) did not result in improved neurologic outcomes compared to a restrictive strategy (threshold hemoglobin 7 g/dL) in patients with closed head injury.[30] A restrictive transfusion strategy has also been tested in patients with acute severe upper gastrointestinal bleeding including patients with cirrhosis.[31] The single-center study found that a restrictive strategy using a hemoglobin threshold of 7 g/dL compared with a threshold of 9 g/dL resulted in improved mortality and decreased rate of further bleeding. A multicenter, cluster randomized trial is planned to further assess these transfusion strategies in acute upper gastrointestinal bleeding.[32]

Transfusion strategies in patients with cardiovascular disease continue to be debated and clinical trial results have been variable.[33,34] The single-center Transfusion Requirements After Cardiac Surgery (TRACS) study compared transfusion thresholds of hematocrit less than 30% (hemoglobin ~10 g/dL) with hematocrit less than 24% (hemoglobin ~8 g/dL) from the start of surgery through the ICU stay.[33] There was no difference in the composite outcome of 30-day all-cause mortality rate and severe morbidity between the liberal and restrictive strategies, and fewer blood products were administered in the restrictive group. A multicenter study in cardiovascular surgery patients assessed slightly different transfusion thresholds (hemoglobin 7.5 g/dL and hemoglobin 9 g/dL) in the postoperative period.[34] No difference was found between groups in the primary outcome of serious infection or ischemic events within 3 months. However, a secondary outcome analysis of all-cause mortality at 3 months found more deaths in the restrictive threshold group (4.2% vs. 2.6%). Transfusion studies in patients undergoing elective cardiac surgery do not answer the question of whether patients with acute coronary syndromes (current or recent ischemia) would benefit from a liberal transfusion strategy. Results from retrospective and prospective observational studies of anemia and transfusion in patients with acute coronary syndrome have yielded conflicting results.[36–40] A prospective, randomized pilot study of 45 patients with acute myocardial infarction (MI) and hematocrit 30% or less compared a transfusion threshold of hematocrit less than 24% with hematocrit less than 30%.[41] The composite safety endpoint of in-hospital death, new MI, or new or worsening heart failure occurred in 38% of the liberal strategy patients versus 13% in the conservative strategy patients ($P = 0.046$). Another pilot study in 110 patients with acute coronary syndrome or stable angina compared a similar protocol with a liberal threshold of 10 g/dL and restrictive threshold of 8 g/dL.[42] A composite outcome of death, MI, or unscheduled revascularization within 30 days trended in favor of the liberal group with more frequent events in the restrictive group (25.5% vs. 10.9%, $P = 0.054$). Larger studies in the future should help determine whether a restrictive transfusion strategy should be adopted in patients with acute coronary syndromes.

Prior guidelines for transfusion of RBCs did not specifically address critically ill patients and were primarily based on consensus rather than evidence. Current guidelines of the American Association of Blood Banks,[43] American Red Cross,[44] National Institute for Health and Care Excellence,[45] British Committee for Standards in Haematology,[46] American Society of Anesthesiologists,[47] and the National Blood Authority of Australia[48] provide an evaluation of clinical evidence and recommendations for transfusion that are applicable to the critically ill. A summary of the guideline recommendations is presented in Box 75.1. A Cochrane review of transfusion thresholds concluded that a restrictive strategy (hemoglobin threshold of 7 to 8 g/dL) reduces exposure to transfusion and does not have an impact on mortality of morbidity.[49] There was insufficient evidence to determine the safety of transfusion strategies in certain subgroups of patients, such as those with acute coronary syndrome, neurologic injury, and malignancy. Transfusion of single units of RBCs is recommended by several guidelines,[44,45,47,48] and most clinical trials of transfusion strategies use protocols with single-unit transfusions. The threshold for administration of RBCs should also be considered as part of a comprehensive, multidisciplinary patient blood management program to detect and treat anemia, reduce surgical blood loss, and optimize hemostasis.[2]

Because of concerns regarding RBC storage lesion, the use of "fresh" rather than older RBC units has been considered to avoid any negative impact on critically ill patients.[50–52] Clinical trials in adult and pediatric populations have provided evidence that the age of RBC units does not affect mortality.[53–56] Some transfusion guidelines contain recommendations regarding use of fresher blood (see Box 75.1).[43,46]

Platelets

Platelet components are available as random donor units or single-donor apheresis units. Because of the limited storage time and the increasing demand for this component, platelets are often subject to supply shortages. A random donor platelet concentrate is obtained by centrifugation from a unit of WB. This type of platelet concentrate contains up to 50% of the leukocytes from the WB unit. The average transfused dose of random donor platelets has been decreasing over time and is now 5 units in the United States.[1] If bags are entered for pooling before transfusion, the platelets must

• BOX 75.1 Guideline Recommendations for Transfusion of Red Blood Cells

American Association of Blood Banks[43] (2016)

- Recommend a restrictive strategy in hospitalized, hemodynamically stable patients including critically ill patients (*strong recommendation*).
  - Transfuse when hemoglobin ≤7 g/dL.
- Recommend restrictive strategy in patients undergoing orthopedic or cardiac surgery or those with cardiovascular disease *(strong recommendation).*
  - Transfuse when hemoglobin ≤8 g/dL.
- Adhere to a restrictive strategy in hospitalized, hemodynamically stable patients with preexisting cardiovascular disease (*weak recommendation*).
  - Consider transfusion when hemoglobin ≤8 g/dL.
- There is insufficient evidence to recommend a specific transfusion strategy in patients with acute coronary syndrome, severe thrombocytopenia, and chronic transfusion-dependent anemia.
- Recommend that patients receive RBC units at any point within their licensed dating period (standard issue) rather than limiting to transfusion of only fresh (<10 days storage) RBC units *(strong recommendation).*

American Society of Anesthesiology Task Force on Perioperative Blood Management[47] (2015)

- A restrictive RBC transfusion strategy (hemoglobin <8 g/dL) may be used to reduce transfusion requirements.
  - RBCs should be administered unit by unit, when possible, with interval reevaluation.

National Blood Authority, Australia[48] (2012)

- A restrictive transfusion strategy should be used in critically ill patients.
  - RBC transfusion is likely to be appropriate with hemoglobin <7 g/dL.
  - The decision to transfuse with hemoglobin 7 to 9 g/dL should be based on clinical signs and symptoms of anemia.
  - RBC transfusion is likely to be appropriate for patients with acute coronary syndrome with hemoglobin <8 g/dL.
- Transfusion of a single RBC unit is appropriate followed by reassessment to determine the need for further transfusion.

British Committee for Standards in Haematology[46] (2013)

- A transfusion threshold of ≤7 g/dL should be the default for all critically ill patients, unless specific comorbidities or illness-related factors modify decision making *(strong recommendation).*
- There is insufficient evidence to support the routine administration of fresher blood to critically ill patients.

RBCs, *Red blood cells.*

be administered within 4 hours. A single-donor apheresis platelet unit contains the equivalent of 4 to 6 units of random donor platelet concentrates. This type of platelet concentrate is considered to be leukoreduced and no additional filtration is needed. Single-donor platelets offer the benefit of reducing the risk of multiple-donor exposure to the recipient, and may also be the only available alternative for recipients who have been alloimmunized by previous platelet transfusions.

Platelets are stored at room temperature to avoid loss of function from refrigeration and are constantly agitated to maximize gas exchange. Some loss of viability and platelet numbers occurs during storage, but 5-day-old platelets still effect hemostasis. The plasma contained in platelet concentrates is a good source of stable coagulation factors and contains diminished but still potentially beneficial amounts of factors V and VIII. Platelet components may be modified by leukocyte reduction, irradiation, and washing similar to that for RBCs. Transfusion of ABO-compatible platelets is desirable but not essential. When ABO-mismatched platelets are given, removal of some of the incompatible plasma can be carried out before transfusion. Single-donor apheresis platelets may be matched to an alloimmunized recipient for human leukocyte antigens (HLA) or platelet antigens. There is no contraindication to the use of Rh-positive platelets in Rh-negative patients. However, if Rh-positive random donor platelets are administered to Rh-negative women with childbearing potential, Rh immune globulin should be used prophylactically owing to the small risk of Rh alloimmunization from RBCs that may be contained in the platelet concentrate. In similar circumstances, Rh immune globulin is not indicated if single-donor apheresis platelets are transfused because they contain few RBCs.

Each unit of random donor platelets is expected to increase the platelet count by 10×10^9/L (sometimes expressed as $10^3/\mu L$) in a typical 70-kg adult. A 1-hour posttransfusion platelet count should be obtained to determine the adequacy of response. The following equation, which relates platelet number and body size to the posttransfusion increment, can be used to assess the effectiveness of the transfusion:

$$\text{Corrected count increment (CCI)} = \frac{\text{Observed rise in platelet count} \times \text{Body surface area } (m^2)}{\text{Number of platelet units transfused}}$$

A CCI of 10×10^9/L or higher can be considered a good response, whereas a CCI of 5×10^9/L or lower indicates a poor response to transfusion.[57] The increment in platelet count is higher with single-donor apheresis units, ABO-identical platelets, and platelets stored no longer than 3 days.[58–60] However, there is no advantage of these platelet characteristics on prevention of clinical bleeding.[58]

Indications for Platelet Transfusion

Although the prevalence of thrombocytopenia in the critically ill varies with the definition used and clinical setting, thrombocytopenia is associated with platelet transfusions and increased mortality rate in ICU patients.[61,62] Guidelines for transfusion of platelets are derived from consensus opinion and clinical studies primarily in patients with chemotherapy-induced thrombocytopenia rather than critically ill patients.[44,45,63–67] Extrapolation of these guidelines to critically ill patients is problematic because the cause, risks, and consequences of thrombocytopenia may be different. General indications for platelet transfusions include active bleeding as the result of thrombocytopenia or functional platelet defects (therapeutic transfusion) or prevention of bleeding at specified low platelet counts (prophylactic transfusion). The majority of platelet transfusions in the ICU are performed for prophylactic indications.[68] Suggested guideline recommendations for platelet transfusion are summarized in Table 75.2.[44,45,63–67] Most medical or surgical patients with active bleeding and platelet counts of 50×10^9/L or above will not benefit from transfusion of platelets if thrombocytopenia is the only abnormality. The threshold for transfusing platelets is higher in bleeding patients in whom the consequences of continued bleeding pose significant risk to survival or functional ability such as neurosurgical bleeding. Recommendations for platelet transfusion in trauma with massive transfusion have varied.

In nonbleeding patients, previous debate centered on whether to transfuse platelets prophylactically or to transfuse therapeutically when bleeding occurred. A clinical trial comparing a no-prophylaxis strategy for platelet transfusion with a prophylactic strategy when

TABLE 75.2 Indications for Platelet Transfusion

Clinical Situation	Transfusion Trigger: Platelet Count $\times 10^9$/L
Therapeutic	
Active bleeding	≤50
Major bleeding and massive transfusion	≤50–100
Active bleeding with central nervous system/spinal/ocular surgery	≤100
Prophylactic	
High risk of spontaneous bleeding	≤10
High risk of spontaneous bleeding with concomitant coagulation abnormality, anticoagulant therapy, sepsis, fever, concurrent antibiotic use, rapidly decreasing count, or planned minor invasive procedure (central venous catheter)	≤20
Invasive procedure with high risk of bleeding or life-threatening hemorrhage (nonneuroaxial surgery, neuroaxial anesthesia, lumbar puncture)	≤50
Neuroaxial or ocular surgery	≤100
Platelet Dysfunction	
Bleeding, invasive procedure or surgery with abnormal platelet function test, use of antiplatelet drugs, or severe uremia	No specific trigger

the platelet count was less than 10×10^9/L in patients with hematologic cancers found more bleeding in the no-prophylaxis group.[69] It is often assumed that a prophylactic platelet transfusion strategy will have similar benefits in the critically ill.

Prophylactic platelet transfusions are administered to prevent spontaneous bleeding or bleeding with invasive procedures. Patients who have platelet counts of 5×10^9/L or lower are at increased risk for significant spontaneous bleeding, and guidelines propose prophylactic platelet transfusion to prevent hemorrhage at a threshold of 10×10^9/L or less.[44,45,63–67] The recommendations are based on clinical trials in patients with hematologic malignancies and chemotherapy-induced hypoproliferative thrombocytopenia.[70] A prospective study of a more conservative platelet transfusion protocol found that major bleeding episodes occurred on 1.9% of days with counts of less than 10×10^9/L and on only 0.07% of days with counts of 10 to 20×10^9/L.[71] Additional studies have confirmed the safety of using 10×10^9/L or less as a prophylactic platelet transfusion threshold in patients with hematologic malignancies or stem cell transplants.[72–74] The trigger for prophylactic platelet transfusion threshold of 10×10^9/L or less, however, applies primarily to a specific population of thrombocytopenic patients in stable condition. Factors such as fever, use of anticoagulant or antiplatelet drugs, and invasive procedures must be considered when generating a treatment plan for individual patients. Patients experiencing rapid drops in platelet count may be at greater risk than those at steady state and thus may benefit from transfusion at higher counts. Prospective studies in critically ill patients have not been reported. Benefits to the patient of more conservative use of platelet transfusion include decreased donor exposure, which lessens the risk of transfusion-transmitted disease; fewer febrile and allergic reactions that may complicate the hospital course; and the potential delay or prevention of alloimmunization to HLA and platelet antigens.

The threshold for platelet transfusion before invasive procedures should take into account the type of procedure, bleeding risks associated with the procedure, consequences of bleeding, and concomitant factors affecting hemostasis. For critical invasive procedures in which even a small amount of bleeding could lead to loss of vital organ function or death, maintaining the platelet count greater than 50×10^9/L is typically preferred. The presence of factors that affect platelet function, such as certain drugs, foreign intravascular devices (e.g., intraaortic balloon pump or membrane oxygenator), infection, or uremia, alter this requirement upward. Patients at risk for small but strategically important hemorrhage, such as neurosurgical patients, may need to be maintained at platelet counts of 100×10^9/L.

The most appropriate platelet count for procedures that may be performed in critically ill patients, such as placement of central venous catheters and arterial catheters, thoracentesis, and paracentesis, has not been definitively established. Most ICU procedures carry a low risk of bleeding but coagulopathy or thrombocytopenia may increase that risk.[75] A retrospective study suggests that central venous catheters can be placed safely when the platelet count is 20×10^9/L or higher.[76] However, there are no randomized clinical trials to suggest that platelet transfusion is necessary before central line insertion or the optimum platelet count.[77] Likewise, there is no evidence to determine the correct platelet transfusion threshold for lumbar puncture.[78]

Patients undergoing cardiac bypass surgery experience a drop in platelet count and often acquire a transient platelet functional defect from damage associated with the bypass equipment.[79] Most patients do not experience platelet-associated bleeding, however, and prophylactic transfusion in the absence of bleeding is not warranted. In a patient who continues to bleed postoperatively, more likely causes are a localized, surgically correctable lesion or failure to reverse the effects of heparin. If these conditions are excluded or platelet function testing results are abnormal, empiric transfusion of platelets may be justified.

Patients who are thrombocytopenic by virtue of immunologic destructive processes such as idiopathic thrombocytopenic purpura may receive little benefit from platelet transfusions because transfused platelets are rapidly removed from the circulation. In the event of life-threatening hemorrhage or an extensive surgical procedure, transfusion may prove beneficial for its short-term effect but may require higher doses of platelets or increased frequency of transfusion. Platelet transfusion may be more effective when high-dose immunoglobulin or high-dose anti-D antiserum are administered.[80,81] Platelet transfusion is usually not recommended in thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome, and heparin-induced thrombocytopenia.[44,45,65,67] Cautious administration of platelets may be considered in cases of life-threatening thrombocytopenic bleeding.

Platelets are less commonly transfused for platelet dysfunction, but prophylactic and therapeutic transfusion of platelets has increased in patients receiving antiplatelet drugs. Some in vitro studies show that platelet dysfunction related to antiplatelet drugs can be reversed with platelet transfusion, and limited clinical studies suggest improved platelet function after platelet transfusion in intracranial hemorrhage.[82,83] However, improved platelet function may not translate into better outcomes.[84,85] A randomized clinical

trial of platelet transfusion in intracerebral hemorrhage associated with antiplatelet drugs found worse outcomes for death or dependence at 3 months for the group receiving platelet transfusion.[86] Currently platelet transfusion guidelines provide either no recommendation or weak recommendations regarding platelet transfusion in the setting of bleeding or prophylaxis associated with antiplatelet drugs owing to the lack of high-quality evidence.[44,46,63,65,87]

The development of refractoriness to platelet transfusions as the result of alloimmunization is a serious event. Poor response to platelet transfusions owing to increased platelet consumption also occurs with splenomegaly, fever, trauma and crush injury, burns, disseminated intravascular coagulation (DIC), concomitant drugs, and transfusion of platelets of substandard quality.[88] These factors should be identified and corrected if possible. Alloimmunization is characterized by the development of anti-HLA or platelet-specific antibodies, with resultant immune platelet destruction. Leukocyte depletion of transfused components can prevent or delay this phenomenon, but it is important to use leukoreduced components early in the course of transfusion therapy.[88,89] When patients fail to achieve expected increments after platelet transfusion, provision of single-donor ABO-specific platelet concentrates that are less than 48 hours old may improve the response. If no improvement is seen, the patient should be screened for HLA antibodies or be HLA typed and provided with HLA-compatible single-donor platelets. Alternatively, platelet cross-matching with the patient's serum can be carried out. There is no advantage to unmatched single-donor platelets in this situation.

Plasma-Derived Components

Plasma

Standard FFP is prepared by centrifugation of WB or single-donor apheresis and is frozen within 8 hours of blood donation. Standard FFP contains all coagulation factors (including the labile factors V and VIII) and inhibitors, approximately 400 mg fibrinogen, complement, albumin, and globulins. By convention, the coagulation factors are present in concentrations of 1 units/mL. Plasma that is separated and frozen from refrigerated WB more than 8 hours but within 24 hours of phlebotomy is referred to as PF24. PF24 differs from standard FFP by having lower levels (~15%–25% reduction) of factors V and VIII, but the decrease in labile factor levels is not considered clinically significant. The processing technique for PF24 allows for clinical utilization of plasma collected at distant sites and increases the plasma supply. Cryoprecipitate-reduced plasma (also called *cryopoor plasma*) refers to FFP with the cold-induced precipitate removed. Cryopoor plasma is thus deficient in factors VIII and XIII, fibrinogen, and von Willebrand factor. The most common method of thawing FFP requires about 30 to 45 minutes in a 37°C water bath. Cross-matching to the recipient is not performed, but FFP must be ABO compatible. Standard FFP is as likely to transmit hepatitis, HIV, and most other transfusion-related infections as cellular components. A pathogen-reduced solvent-/detergent-treated pooled plasma product is available in the United States and other countries. The following types of other pathogen-reduced plasma products may be available in some countries outside the United States: methylene blue–treated plasma, psoralen- and ultraviolet light–treated plasma, and riboflavin- and ultraviolet light–treated plasma.[90]

Indications for Fresh Frozen Plasma

FFP is frequently transfused inappropriately in critically ill patients who are not bleeding or in whom the international normalized ratio (INR) is less than 1.5.[91,92] Guidelines for transfusion of FFP have been primarily based on expert opinion rather than any clinical evidence (Box 75.2).[44,93–95] A summary of practice recommendations for specific clinical circumstances based on a systematic review is presented in Box 75.3. The review emphasized the lack of high-quality evidence on plasma infusion and the need for well-designed trials to address relevant knowledge gaps.[96] The use of prothrombin complex concentrate is often recommended as initial therapy instead of FFP for significant warfarin-related bleeding owing to more rapid correction of the INR.[44]

FFP should be administered only to provide coagulation factors or plasma proteins that cannot be obtained from safer sources. FFP is commonly used to treat bleeding patients with acquired deficiency of multiple coagulation factors, as in liver disease, DIC, or dilutional coagulopathy as the result of massive transfusion. However, changes in INR after FFP transfusion are usually minimal and not clinically significant when the pretransfusion INR is less than 2.0.[92,97] FFP may be indicated for the provision of protein C or S in patients who are deficient and have acute thrombosis. FFP should be administered as boluses as rapidly as feasible so that the resulting factor levels achieve hemostasis. The use of continuous FFP infusions is not helpful. Variable doses of FFP have been recommended including 2 units initially (probably

• BOX 75.2 Guideline Recommendations for Transfusion of Fresh Frozen Plasma

Deficiency of coagulation factors with abnormal coagulation tests AND
  Active bleeding
  OR
  Planned surgery or invasive procedure
Immediate reversal of warfarin effect with active bleeding or planned procedure
Thrombotic thrombocytopenic purpura
Congenital factor deficiency with bleeding or need for prophylaxis and no alternative therapy
Rare protein deficiencies (protein C or S)

• BOX 75.3 Recommendations Regarding Fresh Frozen Plasma Transfusion in Specific Conditions[a]

1. Suggest that FFP be transfused to trauma patients requiring massive transfusion.
2. Cannot recommend for or against of FFP transfusion at a plasma-to-RBC ratio of 1:3 or more in trauma patients with massive transfusion.
3. Cannot recommend for or against FFP transfusion in patients undergoing surgery in the absence of massive transfusion.
4. Suggest FFP be transfused in patients with warfarin-related intracranial hemorrhage.
5. Cannot recommend for or against FFP transfusion to reverse warfarin in patients without intracranial hemorrhage.
6. Suggest against FFP transfusion in other groups of patients (in the absence of massive transfusion, surgery, bleeding, or overanticoagulation).

[a]*Based on a systematic review.*
FFP, *Fresh frozen plasma;* RBC, *red blood cell.*
Adapted from Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. Transfusion. *2010;50:1227–1239.*

underdosage) up to 10 to 20 mL/kg. However, some studies suggest that doses as high as 30 mL/kg may be needed to achieve adequate factor levels.[98] FFP is frequently incorporated into massive transfusion protocols in a ratio of 1 unit for every 1 to 2 units of RBCs transfused.[99,100] Because of the short half-life of factor VII, FFP should be infused every 6 to 8 hours if bleeding continues. FFP should not be used for volume expansion or as a nutritional source of protein. Anticoagulation induced by heparin, direct thrombin inhibitors (e.g., dabigatran), or direct factor Xa inhibitors (e.g., rivaroxaban) is not reversed by FFP.

Patients do not usually bleed as a result of coagulation factor deficiency when the INR is less than about 2.0, and even then the results are not always predictable.[101] The partial thromboplastin time is also not useful in predicting procedural bleeding risk.[102] Prophylactic administration of FFP does not improve patient outcome in the setting of cardiac surgery unless there is bleeding with an associated documented coagulation abnormality.[103,104] FFP is often requested prophylactically before an invasive procedure when the patient exhibits mild prolongation in coagulation studies. Most of these procedures may be carried out safely without transfusing FFP.[101,105] A randomized trial of FFP versus no FFP in critically ill nonbleeding patients with INR between 1.5 and 3.0 scheduled to undergo central venous catheter placement, thoracentesis, percutaneous tracheostomy, or drainage of abscess or fluid found no differences in bleeding complications.[106]

Coagulation factors are normally present in the blood far in excess of the minimum levels required for hemostasis. As little as 10% to 30% of the normal plasma concentration of several factors will effect hemostasis. Conversely, FFP treatment of acquired multiple deficiencies, as in hepatic failure, is often ineffective because many patients cannot tolerate the infusion volumes required to achieve hemostatic levels of coagulation factors, even transiently.[107] The plasma half-life of transfused factor VII is only 2 to 6 hours. It may be impossible to administer sufficient FFP every few hours without encountering intravascular volume overload. Finally, in some instances, transfusion of seemingly adequate volumes may still fail to correct the coagulopathy.[108] Careful documentation of both the need for FFP and the adequacy and outcomes of therapy is essential.[109]

Transfusion of FFP is associated with significant adverse effects. It may be implicated in the development of TRALI. Because of the large volumes that may be transfused, FFP administration is a risk factor for transfusion-associated circulatory overload (TACO). Allergic reactions to FFP are usually mild with the exception of anaphylactic reactions to IgA proteins that can occur when plasma is transfused in IgA-deficient patients.

Cryoprecipitate

A total of 1.1 million units of cryoprecipitate was transfused in 2011 in the United States.[1] Cryoprecipitate is prepared by thawing and centrifuging FFP below 6°C and resuspending the precipitated proteins in a small volume of supernatant plasma. Each unit is a concentrated source of factor VIII (≥80 IU), von Willebrand factor (50% of original plasma content), fibrinogen (≥150 mg), factor XIII (30% of original plasma content), and fibronectin. It is considered to be leukoreduced without additional filtration. Cryoprecipitate offers the advantage of transfusing more specific protein and less total volume than an equivalent dose of FFP. Cryoprecipitate does not require cross-matching, but ABO compatibility with the recipient is preferred. Cryoprecipitate must be transfused within 4 to 6 hours of thawing with the shorter time required for units exposed to an open process.

Indications for Cryoprecipitate Transfusion

In the past, cryoprecipitate was used to treat patients with inherited coagulopathies, such as hemophilia A, von Willebrand disease, and factor XIII deficiency. However, the availability of safer specific factor concentrates makes use of cryoprecipitate unwarranted for these conditions unless factor concentrates are unavailable. In the critical care setting, cryoprecipitate is most commonly used to replenish fibrinogen, especially in bleeding patients with hypofibrinogenemia caused by dilutional or consumptive coagulopathy. Transfusion of cryoprecipitate is usually recommended when fibrinogen levels are less than 100 to 150 mg/dL in the setting of bleeding or need for an invasive procedure.[44,95,110] Cryoprecipitate also reportedly improves hemostasis in uremic patients, presumably by reversing the functional platelet defect,[111] but desmopressin or dialysis should be used preferentially to avoid potential transfusion-related complications. Similar to other blood components, cryoprecipitate is often transfused inappropriately.[112]

The usual dose of cryoprecipitate to treat hypofibrinogenemia is 10 units to start, then 6 to 10 units every 8 hours or as necessary to keep the fibrinogen level above 100 mg/dL. The fibrinogen response will depend on the patient's plasma volume (varies with gender and weight), initial fibrinogen level, and consumption of fibrinogen. Although several formulas are available to calculate the fibrinogen requirement, most dosing is empiric with reassessment of fibrinogen levels.[44] Each unit of cryoprecipitate carries a risk of disease transmission equivalent to that of 1 unit of blood.

Adverse Effects of Blood Component Transfusion

The decision to transfuse blood components must be made with full awareness of the potential risk to the recipient, as well as the expected benefits. For some patients, the benefit from transfusion of a blood product is so obvious that the associated risks are not significant compared to the consequences of withholding transfusion. However, the clinician's knowledge of the incidence and management of the adverse effects to transfusion is vital, not only to ensure the best patient care but also to provide appropriate patient education and true informed consent.

The nature of adverse reactions associated with blood product transfusion ranges from those that are common but clinically unimportant to those that may cause significant morbidity or death. The U.S. Food and Drug Administration reported 41 transfusion-related or potentially transfusion-related deaths in 2015, compared with 58 in 2011.[113] From 2011 through 2015, TRALI accounted for 38% of fatalities followed by TACO in 24%.

Why blood component transfusions may be harmful in critical care patients is not well understood. With the modern techniques in screening, storing, and matching RBCs, the mortality rate directly attributable to transfusions is extremely low; however, retrospective data often link increased numbers of transfusions to increased mortality or adverse outcomes.[8,9,12,40,114] It is difficult to distinguish whether this trend is a function of anemia as a signal for increased severity of illness versus an actual consequence of the transfusion. Nevertheless, the relationship between transfusions and increased mortality rates is concerning, and a better understanding would help both clinicians and patients understand the risks involved with transfusions, as well as to aid investigators to develop new methods of safer transfusions. Potential mechanisms of recipient harm include risk of infections or multiorgan failure via immunomodulatory effects from the introduction during transfusion of

unintended lipid breakdown products, cell-signaling factors, and donor-recipient antigen-antibody interactions.

Acute Transfusion Reactions

The signs and symptoms of severe, life-threatening transfusion reactions are frequently indistinguishable from those of less significant reactions. However, every transfused patient who experiences a significant change in condition, such as an elevation in temperature, change in pulse or blood pressure, dyspnea, or pain, must be promptly and fully evaluated to identify the cause of the reaction and to institute treatment when necessary.[115] The basic approach to all acute reactions should be to maintain a high index of suspicion for acute hemolytic reactions (with RBC components) by stopping the transfusion immediately, maintaining venous access with intravenous fluids, and informing the blood bank laboratory immediately so that the appropriate transfusion reaction protocol can be instituted and posttransfusion specimens obtained. Early recognition of severe transfusion reactions may be lifesaving.

Acute Hemolytic Transfusion Reaction

Acute hemolytic transfusion reactions (AHTRs) are caused by the recipient's existing complement-fixing antibodies attaching to donor RBC antigens with resultant intravascular RBC lysis. Non-ABO incompatibility is now more commonly implicated than ABO incompatibility in these incidents.[113] In addition to hemolysis, complement activation stimulates the release of inflammatory mediators and cytokines and can lead to hypotension and vascular collapse. Activation of the coagulation system may result in DIC and bleeding. Acute renal failure may also occur, presumably on the basis of immune complex interactions. Morbidity and mortality rates are directly related to the quantity of incompatible blood transfused, which is why prompt recognition and cessation of transfusion are imperative. Misidentification of the patient, or clerical error, at any time beginning with acquisition of the donor specimen through release of the unit and initiation of infusion is the major cause of AHTRs.[116] It is preferable to transfuse non–cross-matched group O RBCs than to chance ABO incompatibility caused by improper patient and specimen identification procedures.

The most common clinical sign of an AHTR is sudden onset of fever, with or without chills.[115] Other common signs and symptoms include back or flank pain, anxiety, nausea, light-headedness, dyspnea, and hemodynamic instability. In a comatose or anesthetized patient, these symptoms may not be evident; therefore signs such as hypotension, hemoglobinuria, and diffuse oozing from puncture sites or incisions may be the only notable features.

Immediate management of suspected AHTRs includes cessation of the transfusion; the remainder of care is supportive. Rapid verification of patient and unit identification must be made, not only to confirm the suspected reaction but also to prevent a second patient from receiving a reciprocally incompatible unit if a clerical error has been made. Steroids, heparin, or other pharmacologic interventions have no role in treatment.

Febrile Nonhemolytic Transfusion Reactions

Febrile nonhemolytic transfusion reactions (FNHTRs) are the most commonly occurring acute reaction to RBC and platelet transfusions. These reactions can cause significant discomfort and must be investigated because they share manifestations with AHTRs and bacterially contaminated blood. Although a temperature increase of 1°C is often used to define an FNHTR, fever may be absent in patients pretreated with antipyretics. Additional clinical signs include chills or rigors usually beginning 1 to 2 hours after the start of the transfusion but occasionally delayed up to 4 to 6 hours. Associated manifestations may include nausea, vomiting, and dyspnea. FNHTRs occur in approximately 1.0% of transfusion episodes but are more common with platelet transfusions (4%–31%).[117,118] The cause of FNHTRs varies with the transfused product, but the release or presence of cytokines and pyrogens results in the clinical manifestations. This reaction to RBC transfusion is usually initiated by the interaction of recipient antibodies to donor leukocytes. Nonhemolytic transfusion reactions (NHTRs) with platelet products are most commonly initiated by leukocyte- or platelet-derived cytokines or other biologic response modifiers.[118] Management of NHTRs includes discontinuation of transfusion and initiation of the appropriate transfusion reaction evaluation. Antipyretics such as acetaminophen may be administered. Antihistamines are neither preventive nor therapeutic. Once acute hemolysis is excluded, transfusion of a new unit may be instituted. If repeated NHTRs become problematic, leukocyte-depleted blood components should be supplied. The implementation of universal leukocyte reduction results in a reduction in the frequency of all fever seen after transfusion by about 12%.[119] Pretreatment with antipyretics or corticosteroids may also minimize FHTRs.

Anaphylaxis

Anaphylactic reactions to blood transfusions are rare but may be life-threatening. The usual cause is recipient antibody to a component of plasma that the patient lacks, most commonly antibody to IgA in IgA-deficient individuals. However, antibodies to other proteins (antihaptoglobin) have been demonstrated and activated platelet membranes may also play a role.[120,121] The highest rate of anaphylaxis occurs with platelets followed by FFP and RBCs. Signs and symptoms usually begin within minutes after transfusion is initiated and include severe anxiety, flushing, dizziness, dyspnea, bronchospasm, abdominal pain, vomiting, diarrhea, hypotension, and eventually shock. Fever and hemolysis do not occur. Management includes immediate cessation of transfusion and standard therapy for anaphylaxis. If anti-IgA antibodies are determined to be the cause of this reaction, the patient must receive blood components donated by IgA-deficient individuals or, if unavailable, specially prepared washed RBCs and platelet concentrates. Plasma-derived preparations, such as albumin, and immunoglobulins contain varying amounts of IgA and pose a substantial risk in these patients.

Allergic and Urticarial Reactions

Hives and pruritus are relatively common cutaneous adverse effects of transfusion and may occur with transfusion of RBCs, platelets, and FFP.[117] They are a hypersensitivity reaction localized to the skin, and their cause is unknown but may include both donor and recipient characteristics. These reactions consist of localized or generalized urticaria beginning shortly after the start of transfusion without fever or signs or symptoms of anaphylaxis or hemolysis. The transfusion should be temporarily interrupted, and antihistamines administered. If the hives resolve in a short time, the same unit of blood may be cautiously restarted. If repeated urticarial reactions occur, premedication with antihistamines may be effective.

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions (DHTRs) are an uncommon but probably underrecognized reaction to RBC transfusion

that result from the stimulation of a primary or secondary (anamnestic) recipient antibody response to foreign RBC antigens. These antibodies are below the limit of detection at the time of transfusion but increase after transfusion. DHTRs typically occur 3 to 14 days after transfusion but may not be recognized because of the lack of a clear temporal association with transfusion. DHTRs are more likely in patients requiring frequent RBC transfusion such as those with sickle cell disease.[115,117] Patients may be asymptomatic or experience fever, chills, and an unexplained decline in hematocrit.[115] Transient elevation in unconjugated bilirubin and lactate dehydrogenase may also occur. The diagnosis is established by a positive direct antiglobulin (Coombs) test resulting from recipient antibody coating donor RBCs. The specificity of the antibody is often against such RBC antigens as the Rh family, Kidd, Duffy, or Kell systems. Hemolysis may not occur, but if it does, it is likely to be extravascular and only rarely causes renal failure or DIC.

Prevention of these reactions is difficult. Alloimmunization to foreign RBC antigens occurs in approximately 1% of transfusions. Detection of delayed antibodies is the purpose for requiring a new blood bank specimen every 72 hours if the patient has recently been transfused. Permanent transfusion records should record the occurrence of delayed antibodies, even though they may not be apparent at a later cross-match.

Transfusion-Associated Circulatory Overload

TACO has been associated with increased mortality and hospital length of stay and accounted for 24% of transfusion-related fatalities in the United States between 2011 and 2015.[113,122,123] It is more likely to occur with RBC or FFP transfusion because of the higher volumes of these blood components.[121] Aside from the inherent volume of the blood components, the concurrently administered normal saline solution adds to the volume load. Risk factors for TACO include older age, critical care patients, cardiac and renal dysfunction, chronic anemia, positive fluid balance, increased volume of blood products, and rapid rate of transfusion.[115,122,123] Clinical manifestations of TACO include dyspnea, orthopnea, cough, and worsening oxygenation owing to hydrostatic pulmonary edema. Management options include slowing the rate of transfusion and administration of diuretics. Careful attention to transfusion requirements and use of the smallest volumes necessary can help minimize volume overload in most instances. TACO may be difficult to distinguish clinically from TRALI, but TACO is less likely to be associated with fever and hypotension and more likely to be associated with a significantly elevated brain natriuretic peptide and hypertension.

Transfusion-Related Acute Lung Injury

TRALI is the leading cause of transfusion-related deaths in the United States.[113] Products containing plasma (e.g., FFP and platelets) seemed to have a higher risk before current risk mitigation interventions, but the reaction can be seen with all types of blood components. Transfusion of plasma from female donors increases the risk of TRALI.[124,125] TRALI is defined as the development of acute lung injury (hypoxia and bilateral infiltrates of noncardiac cause) within 6 hours of transfusion in the absence of another more likely cause.[125,126]

In patients without prior respiratory compromise, TRALI manifests as acute hypoxia with the development of rales and diffuse infiltrates on chest radiograph.[127] It may also be accompanied by tachycardia, fever or hypothermia, and hypotension or hypertension. Recognition of TRALI may be difficult in critically ill patients who may have other reasons for dyspnea or may already require mechanical ventilation. In addition, TRALI and TACO may be difficult to distinguish. Clinical features that favor TRALI over TACO include the presence of fever and leukopenia.

Unlike other forms of acute lung injury (ALI), TRALI is usually self-limiting and resolves within 1 to 4 days. However, reactions can be severe and may necessitate mechanical ventilation. Treatment consists of supportive care, including the prompt management of hypoxia. If mechanical ventilation is required, lung-protective ventilation and a restrictive fluid strategy should be implemented. Because the inciting factor is derived from the donor product rather than the patient, additional blood products can still be transfused if necessary with low risk of redevelopment.

Studies have suggested several mechanisms in the development of TRALI. The presence of leukocyte antibodies in the donor blood has been consistently linked to many cases, although other triggers such as lipids and biologic response modifiers (cytokines) have also been implicated.[125,128,129] When exposed to donor antibodies, neutrophils that are already recruited to the pulmonary vascular endothelium release inflammatory products, leading to injury of the endothelial cells and increased vascular permeability. Recipient factors are also involved, as blood products from the same donor do not consistently cause TRALI in different recipients. Critically ill patients may be more susceptible to TRALI owing to increased localization of neutrophils in the pulmonary vasculature.

To reduce the risk of TRALI, blood agencies have adopted a risk mitigation strategy of using male-predominant plasma transfusion to reduce exposure to donor leukocyte antibodies.[130] The number of fatalities related to plasma have been decreasing in the United States and elsewhere, most likely owing to reduced plasma transfusion from female donors.[113]

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated GVHD (TA-GVHD) is a rare and usually fatal immunologic complication of blood component transfusion.[117] Immunocompromised patients infused with blood components containing viable donor lymphocytes are at risk for engraftment of the allogeneic lymphocytes and ensuing rejection of recipient (host) tissues. Transfusion recipients who are at highest risk include bone marrow and organ transplant recipients, patients with leukemia and lymphoma, and recipients of blood donated by relatives. TA-GVHD has been reported in patients after cardiac surgery who received designated donor blood from relatives; presumably, the HLA antigenic differences between donor and recipient were insufficient to stimulate a recipient immune response but sufficient to elicit a donor immune response.[131] The onset of TA-GVHD is usually within 8 to 30 days after transfusion, and it is manifested as fever and skin rash, followed by diarrhea and evidence of liver dysfunction and bone marrow suppression. TA-GVHD differs from that seen in bone marrow transplantation by its involvement of the marrow and far greater mortality risk. Treatment is largely ineffective, and mortality rate exceeds 90%.

Irradiation of blood components at 25 Gy prevents TA-GVHD by eliminating the donor lymphocyte mitogenic response. All cellular blood components should be irradiated before transfusion to high-risk patients. The functions of the cellular components of blood are unaffected, although damage to RBC membranes limits the duration of postirradiation storage of PRBCs to 28 days. Blood

donated by a relative for any patient should be irradiated, as should HLA-matched or cross-matched platelet products.

Transfusion-Related Immunomodulation

Transfusion-related immunomodulation (TRIM) may potentially have significant adverse effects that affect patient outcome. Allogeneic RBC transfusion has been shown to suppress the recipient's immune response, an effect first noted with kidney transplantation that resulted in increased survival of the transplanted kidney.[132] However, immunosuppression is generally undesirable in critically ill patients, even though the clinical impact of blood component transfusion is not well defined. As noted in previous sections, immunomodulation likely contributes to AHTRs, NHTRs, anaphylaxis, and TRALI. The major clinical issues regarding TRIM center around the association between blood product transfusion and the increased risk of infection and increased and more rapid rates of tumor recurrence in surgical oncology patients. The largest prospective trial of colorectal cancer resection, for example, had negative findings,[133] but a meta-analysis of existing data suggests that an adverse effect on recurrence does exist.[134] Significant heterogeneity exists in the reported studies and makes definitive conclusions difficult.[135] Most retrospective and prospective trials of postoperative or critical care unit infections suggest an adverse effect of blood component transfusion.[136–138]

The precise mechanism of the immunomodulation induced by transfusion has not yet been delineated, and several mechanisms may be involved. Allogeneic plasma, leukocytes, and substances that accumulate in stored blood components may contribute to TRIM. Alterations identified in laboratory and clinical transfusion recipients have included depression of the T-helper/T-suppressor lymphocyte ratio, decreased natural killer cell activity, diminished IL-2 generation, formation of anti-idiotype antibodies, impairment of phagocytic cell function, and chronic persistence of donor lymphocytes (microchimerism), suggestive of low-level GVHD. Difficulties in analysis of human data arise because patients requiring blood component transfusions have conditions that may induce immune changes. Well-designed prospective trials are needed to more clearly elucidate the impact of any immunomodulatory effects of transfusing blood products.

Transfusion-Transmitted Infectious Diseases

Transfusion-associated AIDS has done more to revolutionize transfusion practice than any other transfusion risk by resulting in more conservative blood use, more stringent donor selection criteria, and improved screening tests. The result is that viral transmission rates are now difficult to measure, and the risk of transfusion-related infectious diseases is lower than ever.[139] Bacterial infection has become the most common infectious risk.

Microbial and Endotoxin Contamination

Several fatalities are reported yearly from the transfusion of blood components contaminated with viable bacteria, with or without the accumulation of endotoxin.[113,140] Platelet concentrates stored at room temperature are particularly prone to bacterial growth, with a reported incidence of 1.13 in 10,000 components with apheresis units having the highest contamination rate.[141] Organisms isolated from platelets and implicated in fatal transfusion reactions include *Staphylococcus* and *Streptococcus* species and gram-negative bacilli. Fatalities resulting from bacterial contamination of refrigerated RBCs have occurred as well and more often involve cryophilic bacteria. RBC transfusions contaminated by *Yersinia enterocolitica* have been consistently reported.[142] Transfusion reactions caused by bacterial or endotoxin contamination are fortunately quite rare, but the mortality rate may exceed 60%.

Signs and symptoms of reactions caused by microbial contamination overlap those of hemolytic transfusion reactions and consist primarily of fever and hypotension, along with other signs of septic shock. A Gram stain of the implicated unit can be prepared immediately and, if positive, appropriate antibiotic and supportive therapy instituted. Autologous blood components may also be contaminated at the time of collection; therefore reactions occurring in patients who are receiving their own blood should be evaluated as fully as though they were receiving allogeneic blood.

Hepatitis

The success of viral screening measures is most clearly illustrated by the fall in the risk for posttransfusion hepatitis over the past several decades. The elimination of paid donors in 1972 and the introduction of nucleic acid tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) have resulted in a steady reduction in the rates of posttransfusion hepatitis. The estimated residual risk for hepatitis B surface antigen is 1 per 300,000 donations.[143] Although about 30% to 40% of HBV transmissions result in acute hepatitis, chronic HBV infection develops in less than 10% of such patients. In contrast, the risk for chronic HCV infection after transfusion is higher, nearly 50%.[144] The risk of HCV transmission is even lower than HBV with a residual risk estimate of 8.7 per 10 million transfused blood components.[145] The clinical course of hepatitis A is generally milder, and the lack of a chronic carrier state means that with donor screening for symptoms of the acute illness, the risk of transmission is rare.

Retroviruses

Retroviruses known to be capable of transmission by transfusion are human immunodeficiency virus (HIV-1, HIV-2) and human T-cell leukemia/lymphoma virus (HTLV I and II). The screening enzyme-linked immunosorbent assay to detect antibody to HIV-1 was incorporated into the blood-screening process in 1985. Improved confidential donor screening also decreased the risk of infectious units appearing in the donor pool.[146] The discovery that heat treatment decreased transmission resulted in a reduction in transmission by plasma products, especially to persons with hemophilia. Removal of donor units with seropositivity by enzyme-linked immunosorbent assay was insufficient to prevent transmission of HIV-1. Subsequent development of an assay for the p24 antigen and nucleic acid testing have lowered the risk of transfusion-associated HIV-1 infection to an estimated 1 in 1,467,000 transfused blood components.[145] Despite donor screening and sensitive assays, an extremely small but finite risk of HIV-1 transmission by screened blood transfusions remains. This risk is largely due to the interval between infection and development of detectable concentrations of HIV ribonucleic acid in plasma in newly infected donors.

A second retrovirus, HIV-2, first described in residents of countries in West Africa and subsequently detected in migrants to western Europe, causes an immunodeficiency syndrome similar to that caused by HIV-1. Although very few cases of HIV-2 have been reported in donors in the United States, experience with other retroviruses suggests that screening may prevent the majority of potential transmissions. Therefore donated blood is now screened for the presence of HIV-2.

The retrovirus HTLV-I is the causative agent of adult T-cell leukemia (ATL) and is strongly implicated in the chronic, progressive

neurologic disorder termed *tropical spastic paraparesis* or *HTLV-I–associated myelopathy* (TSP/HAM). HTLV-II has been linked to hairy cell leukemia, but no transfusion-transmitted cases have been reported. The virus exhibits strong serologic cross-reactivity with HTLV-I such that screening assays fail to distinguish between the two viruses. Transfusion-transmitted HTLV-I has been demonstrated.[147] The prevalence of HTLV-I in first time donors in the United States is 5.1 per 10^5 and 14.7 per 10^5 for HTLV-II.[147] Donated blood is currently screened for antibodies to HTLV-I and HTLV-II.

Cytomegalovirus

CMV is a human herpesvirus that establishes latent infection in the host's tissues, particularly leukocytes, and is transmitted by all cellular blood components. Seropositivity, or the presence of antibody, denotes previous exposure to the virus but does not confer protective immunity. Secondary reinfection or reactivation of latent infection can occur. Antibodies to CMV persist for life and serve as a marker indicating the potential for transmission of live virus.

Immunocompetent recipients of transfused CMV-positive blood experience minimal morbidity and mortality risks. The majority of cases are asymptomatic, whereas a heterophile-negative mononucleosis syndrome may develop in a few patients. Immunocompromised patients, however, may incur life-threatening manifestations such as severe interstitial pneumonitis, gastroenteritis, hepatitis, or disseminated disease. Several groups of patients are at particular risk (Box 75.4),[148] and these patients should receive blood incapable of transmitting the virus. Screening of donated blood for CMV is not routine but can be performed quickly if necessary. Because the prevalence of donor seropositivity is quite high, CMV-seronegative blood may not be readily available. Leukocyte-depleted blood may be as effective as seronegative blood in the prevention of CMV transmission. However, a recent systematic review found that data were of poor quality and insufficient to propose any specific guideline regarding CMV-seronegative blood versus leukocyte-depleted blood for preventing CMV transmission by transfusion.[149] Pathogen inactivation techniques available for FFP and platelets may be effective in preventing CMV transmission but are not available for blood.

Parasites

Many blood-borne parasites may be transmitted by transfusion, although this is a rare occurrence in the United States because of donor screening questions and the low endemicity of implicated agents. Changing immigration patterns and global travel, however, make transfusion-transmitted parasites an increasing concern.

On a worldwide basis, malaria is the most important transfusion-transmitted infective parasite, although only a few cases are reported in the United States each year.[150] Such infections are manifested by delayed fever, chills, diaphoresis, and hemolysis, often masked by underlying medical conditions. Fatalities have occurred. Babesiosis, a tick-borne disease caused by *Babesia microti*, is endemic in regions of the northeastern United States. Transfusion-transmitted cases have been reported, with asplenic, elderly, or immunocompromised patients being particularly susceptible.[151] Babesiosis was the second leading cause of infectious transfusion-related fatality in the United States from 2011 to 2015 (after *Staphylococcus aureus*). Although there are no licensed tests for screening donor blood, an investigational product recently resulted in a decrease in the risk of transfusion-transmitted babesiosis.[152] With increases in the number of Central and South American immigrants to North America, Chagas disease, transmitted by the protozoan parasite *Trypanosoma cruzi,* has emerged as a potential transfusion-transmissible infection.[153] Other parasitic diseases that have been transmitted by transfusion include toxoplasmosis, leishmaniasis, and Lyme disease.

• BOX 75.4 Patients for Whom Cytomegalovirus-Safe Blood Components Are Strongly Recommended

Seronegative pregnant women
Seronegative premature infants weighing <1200 g
Seronegative allogeneic or autologous bone marrow transplant recipients
Seronegative transplant recipients of seronegative organs

Emerging Infections in Transfusion Medicine

Human parvovirus B19 has been recognized as a pathogen capable of transmission by transfusion, with typical clinical findings and the potential for aplastic anemia. Epstein-Barr virus infection with a typical mononucleosis-like illness has been reported after transfusion. West Nile and dengue virus can also be transmitted by transfusion. Transmission of Zika virus infection by platelet transfusion has been reported.[154,155] H2N1 influenza, severe acute respiratory syndrome, and other new viral infections should be capable of transmission by transfusion, although cases have not been reported and the prevalence of asymptomatic disease is unknown. A rising concern is the transmission of prion disease, either Creutzfeldt-Jakob disease or bovine spongiform encephalopathy. Donor referral criteria were implemented in 1987 for these diseases, and transfusion transmission of bovine spongiform encephalopathy has been reported in the United Kingdom.

Special Transfusion Situations in the Critical Care Setting

Massive Transfusion

Massive transfusion is commonly defined as the administration of blood components in excess of one blood volume or greater than or equal to 10 units PRBCs within a 24-hour period.[156] Massive transfusion may cause complications not generally seen in usual transfusion practice: accumulation of undesirable substances present within stored blood, electrolyte abnormalities, hypothermia, and dilutional depletion of normal blood constituents that are lacking in stored units. Trauma victims, surgical patients undergoing complex or emergent procedures, and patients with vascular or coagulation disorders may require massive transfusion in the critical care setting. The first priority in such patients is to stop the bleeding but transfusion of blood products occurs simultaneously to maintain hemostasis and ensure oxygen-carrying capacity. Survival is determined more by the nature and degree of the patient's injuries or medical conditions than by the transfusions, but the presence of adverse effects of massive transfusion can complicate a patient's course in the ICU.

Blood preservative solutions contain citrate, which anticoagulates stored blood by binding ionized calcium. PRBCs and FFP contain approximately 3 g of citrate. Patients with normal liver function can metabolize this amount of citrate in 5 minutes, but hepatic

impairment may extend removal time. Toxicity may result when citrate is administered in excess of the metabolic capacity, thereby causing a decrease in ionized calcium levels.[157] Although paresthesias, cramps, and myoclonus can result from citrate excess, the principal danger of hypocalcemia is depression of myocardial contractility and potential prolongation of the QT interval. Because the effects of citrate are transient and the use of PRBCs containing little residual citrated plasma is far more common than massive transfusion with WB, routine administration of calcium is not indicated. Ionized calcium levels should be monitored and calcium administration used to maintain levels in the normal range. Hypomagnesemia is common in patients with massive transfusion, and it is often associated with hypocalcemia.[158] Citrate binds magnesium as well as calcium and may play a role in the development of hypomagnesemia.[156] Hypomagnesemia does not appear to affect outcomes in patients receiving massive transfusions.

Potassium leaks from RBCs during storage and up to 7 mEq of extracellular potassium may accumulate in each unit. Irradiation of RBCs increases extracellular potassium. However, dangerous levels of potassium rarely develop from transfused blood in adults; the potassium level is more likely to be determined by the patient's acid-base status and underlying renal function.[159] Studies of patients who receive massive transfusions have demonstrated a wide range of potassium levels, with hypokalemia seen as frequently as hyperkalemia. Because of the complexity of physiologic changes during resuscitation, it is impossible to predict the net effect of massive transfusion on serum potassium levels. Potassium levels need to be monitored closely in patients receiving large amounts of PRBCs.

The pH of stored blood drops during storage, from 7.16 at the time of collection to as low as 6.73 after several weeks of storage. The administration of large quantities of acidic blood, together with the metabolic acidosis common in these patients before resuscitation, would lead one to expect worsening acidosis as the outcome of massive transfusion. However, patients are more likely to exhibit metabolic alkalosis at the end of the transfusion episode,[159,160] partly because of improved tissue perfusion and the metabolism of citrate and lactate to bicarbonate. Patients in renal failure may be unable to handle the bicarbonate load and require dialysis. Acidosis persisting after transfusion suggests inadequate tissue perfusion.[157] Empiric administration of bicarbonate to counter the acid load is not warranted.

RBC components are stored at approximately 4°C and require 30 to 45 minutes to warm to room temperature. Elective transfusions at standard flow rates are tolerated without the need to warm the blood; however, core body temperature, measured by esophageal probe, can fall to 30°C or lower with the administration of large volumes of cold blood over a period of 1 to 2 hours.[161] Adverse effects of hypothermia include a decreased heart rate and myocardial contractility, cardiac arrhythmias, vasoconstriction, increased affinity of hemoglobin for oxygen resulting in decreased tissue oxygen delivery, coagulopathy, and impaired ability to metabolize the citrate load of stored blood. Both blood warmers and patient warming may be instituted during massive transfusion, and patient core temperature should be monitored during resuscitative efforts.

Massive transfusion might precipitate acute respiratory distress syndrome (ARDS) because all cellular transfusions contain damaged or activated WBCs, cell membranes, aggregated platelets, and microthrombi, all of which are capable of lodging in and damaging pulmonary capillaries. Despite this possibility, neither microfiltration of transfusions nor routine leukocyte depletion has shown a significant impact on the incidence of ARDS in patients receiving massive transfusions.[162] Certainly, other causes of ARDS exist in patients who undergo massive transfusion, and the possibility of TACO and TRALI should be considered in the evaluation of patients with hypoxia and diffuse pulmonary infiltrates after massive transfusion.

Autoimmune Hemolytic Anemia

Patients with autoimmune hemolytic anemia have an autoantibody, usually of broad specificity, that fixes itself to their RBCs and triggers extravascular immune-mediated destruction. Patients with autoimmune hemolytic anemia have a positive result on direct antiglobulin testing (commonly known as the Coombs test)[163] and varying degrees of hemolysis, and their autoantibodies cause agglutination of RBCs from all donors during cross-matching. If the hemolysis is brisk, patients may require RBC transfusion to support oxygen needs before medical management is effective. Hence, transfusion is difficult because agglutination during cross-matching interferes with proper definition of compatible units of RBCs and because the transfused RBCs are themselves subject to the same immune hemolysis as the host RBCs. Many blood banks have methods for depletion of autoantibodies from the recipient's plasma and elution of antibodies from RBCs to arrive at a proper cross-match.[164] Although such cross-matches are time consuming and not generally available on an emergency basis, they can be lifesaving. Criteria for transfusion should remain the same as for other recipients.

Necessary Transfusion of Incompatible Blood

RBCs are cross-matched for RBC antigens in the ABO and Rh_0(D) groups and for other RBC antigens when antibodies are present. However, there are several hundred other RBC antigens in the human family and recipients with repeated transfusion may become alloimmunized to other antigens. Generally, alloimmunization occurs in approximately 1% of transfusions, but the prevalence of alloantibodies is higher in chronically transfused, relatively immunocompetent patients, especially African Americans, whose distribution of RBC antigens has significant variation from the white population. Alloimmunization may present difficulties in cross-matching of blood to the point that compatible blood must be obtained from rare-donor registries, if at all. In some patients the alloantibody is never precisely identified, yet the majority of blood available for transfusion is incompatible. The delay engendered by working with multiple or unidentified antibodies may be unacceptable in some critical care situations in which the need for oxygen-carrying capacity leaves no choice but to transfuse incompatible blood. The behavior of these antibodies in the laboratory may assist in predicting the clinical outcome of the incompatible transfusion.[165] Special procedures such as clearance studies, flow cytometry, and in vivo cross-matching (cautious administration of a small aliquot of blood, with subsequent observation of serum and urine for evidence of hemolysis) are useful if time permits.

Emergency transfusion of type O, Rh-negative non–cross-matched blood is generally reserved for the resuscitation of trauma patients, for whom the delay in cross-matching may be life-threatening. The risks of alloimmunization to non-ABO antigens are generally accepted as low, and one study found antigen-incompatible RBCs were transfused in 2.6% of patients who required emergency blood release.[166] Even Rh-positive type O RBCs may be used because rates of alloimmunization to Rh_0(D) are low under the circumstances of emergency transfusion.

Alternatives to Transfusion of Blood Components

The safest transfusion is one that is not given. Therefore alternatives to blood component therapy continue to be sought. It may be possible to limit blood component exposure by the appropriate use of pharmacologic agents that promote hemostasis and the administration of recombinant hematopoietic growth factors to stimulate marrow hematopoiesis.

Blood Substitutes

Two types of alternative oxygen carriers have been evaluated for clinical use, but no oxygen-carrying blood substitute is currently approved for use in the United States.[167,168] Perfluorocarbons are hydrophobic molecules with high oxygen-carrying capacity that have to be administered as an emulsion to be soluble in plasma. The perfluorocarbon solutions have failed to demonstrate any utility as intravascular oxygen carriers because of their unfavorable P-50 (oxygen half-saturation pressure) and oxygen off-loading characteristics. The other type of preparation that has been explored in clinical trials is cell-free hemoglobin solutions cross-linked or polymerized by chemical manipulation to prevent rapid clearance from the circulation. Known as hemoglobin-based oxygen carriers, they are intended to provide short-term oxygen-carrying capacity for acutely ill patients and have the advantage of not requiring cross-matching and no risk of infection. Although these proposed products may have a longer shelf life and are easier to transport, they have many drawbacks. Most have a circulatory half-life of only about 24 hours. The oxygen dissociation curve for these substitutes is also frequently not favorable: either a high fraction of inspired oxygen (FIO_2) is required to "load" these molecules or they are less likely to deliver oxygen efficiently at lower partial pressure of oxygen (PO_2) levels. Main concerns for hemoglobin-based oxygen carriers have been unfavorable side effects, including hypertension, increased cardiovascular mortality risk, and renal dysfunction. Because the hemoglobin source is reclaimed bovine or human RBCs, it is unlikely that patients who do not accept blood components because of their religious beliefs (Jehovah's Witnesses) will accept these types of hemoglobin solutions.

Desmopressin

The synthetic vasopressin analog, desmopressin (DDAVP), increases plasma factor VIII:c and promotes the release of von Willebrand factor from endothelial stores.[169] DDAVP has provided effective hemostasis in bleeding patients with mild hemophilia A and type I von Willebrand disease and has been used as prophylaxis for patients undergoing surgery. DDAVP reportedly improves platelet function in some patients with qualitative platelet disorders associated with uremia, cirrhosis, and aspirin ingestion. Studies of its efficacy in cardiopulmonary bypass procedures are conflicting, but a subset of these patients may benefit. The chief drawback to its use is tachyphylaxis, which develops in essentially all cases after short-term repeated administration.

Antifibrinolytic Agents

The lysine analogs ε-aminocaproic acid and tranexamic acid inhibit fibrinolysis by blocking the binding of plasminogen and plasmin to fibrin. These antifibrinolytic agents may decrease bleeding and thus the need for blood components in patients with hemophilia, thrombocytopenia, and systemic fibrinolysis. A novel and effective use of tranexamic acid involves administration as a mouthwash in preparation for oral surgery in patients with hemophilia or those receiving oral anticoagulant therapy. Tranexamic acid has also been demonstrated to effectively decrease mortality rates in high-risk trauma patients when given within 3 hours of presentation.[170] Use may also be promising in decreasing blood transfusion requirements in high-risk surgical procedures, such as radical prostatectomy.[171] The most serious side effect of these agents when systemically administered is thrombosis; thus it is important to use them appropriately and monitor the patient carefully during their use.

Aprotinin is a naturally occurring bovine serine protease inhibitor that acts on plasma serine proteases such as plasmin, kallikrein, trypsin, and some coagulation proteins. Aprotinin was previously shown to reduce blood loss in patients undergoing cardiopulmonary bypass surgery by inhibiting fibrinolysis and preventing platelet damage.[172] However, an observational study and a large multicenter randomized trial in cardiovascular surgery patients found that use of aprotinin was associated with an increased mortality rate, and therefore should not be used routinely.[173,174]

Vitamin K

When time permits, vitamin K is the preferred agent to reverse the coagulopathy induced by warfarin. Normalization of the prothrombin time (PT) can be seen in as few as 6 to 12 hours. Additionally, selected patients with cirrhosis may exhibit improvement in the PT when treated with therapeutic doses of vitamin K. Many patients in critical care units exhibit a prolonged PT, especially if dietary supplements are limited and broad-spectrum antibiotic therapy is given. Vitamin K is a safe and effective agent for reversing this effect. Intravenous administration of vitamin K is associated with a small risk of anaphylaxis, and oral replacement is preferred over subcutaneous administration for more consistent absorption.

Hematopoietic Growth Factors

Recombinant erythropoietin (EPO) has dramatically reduced the RBC transfusion requirements of patients with chronic renal failure, in which decreased renal EPO production accounts for the anemia. Studies of EPO efficacy in reducing perioperative RBC transfusion requirements by increasing the yield of predeposited autologous blood or stimulating bone marrow synthesis after surgery have shown benefit in reducing blood transfusion, although preoperative planning and autologous deposits are required.[175] Despite initial promising results, use of EPO in critically ill patients lacked efficacy in decreasing RBC transfusions and increased the risk for thrombotic vascular events.[176] Consideration for EPO administration may be appropriate in select patients who are unable to receive blood transfusions after risks and benefits are addressed.

Cell Salvage Technology

Cell salvage equipment has been in clinical use for several decades, and although cell salvage is clearly capable of rescuing otherwise "lost" RBCs, its full impact on transfusions has been poorly documented. Cell salvage generally consists of collection of shed blood from a clean, uncontaminated operating field, followed by removal of the cellular elements and retransfusion into the patient. Cell

salvage has been used both intraoperatively and postoperatively, especially in cardiac surgery. Although clinical studies of cell salvage have many methodologic flaws, it does reduce the need for blood transfusion in adult elective cardiac and orthopedic surgery.[177] Risks include bacterial contamination, febrile reactions, triggering of DIC, and coagulopathy as a result of dilution. When combined with acute intraoperative hemodilution, this technology is also potentially cost saving.[178]

Legal Issues in Transfusion Medicine

Most states regulate blood banking and medical practice, but blood products are regarded as a service, not as a commodity, so standard product liability does not pertain to blood components.[179] However, negligence in the course of preparing, testing, transferring, cross-matching, and administering blood products is still a potential cause for legal action. Every clinician who orders transfusions must be aware that blood components, like drugs, are approved for specific uses and that the indications should be clearly documented in the medical record.

The informed consent of the patient is an important area of potential liability. The Joint Commission has required written patient consent for blood transfusions since 1996. What constitutes adequate informed consent and who is responsible for advising the patient are still debated. Elements of informed consent include an understanding of the need for transfusion, its risks and benefits, and the alternatives, including the risk of not undergoing transfusion, as well as the opportunity to ask questions. Whether the clinician documents informed consent with an individual progress note in the patient record or with a standardized form is generally established as institutional policy. Similarly, institutions vary with respect to policies for consenting adults who are temporarily incompetent, such as sedated patients in the ICU.

A competent adult patient may refuse blood transfusion, and Jehovah's Witnesses commonly do so for religious reasons. Case law is clear in upholding this right of the patient,[180] which extends to care given at such time as the patient may become incompetent (i.e., comatose) after such refusal was expressed before becoming incompetent. Courts will usually order a lifesaving transfusion for minors. Exceptions have been made in the case of some "emancipated minors" who are at the age of reason. Most states have evoked a "special interest" in the welfare of a fetus in ordering transfusions to pregnant women.

The advent of sentinel event reviews and other quality management procedures for patient safety has had an impact on transfusion practice as well. Procedures for patient identification before surgical procedures, including devices such as bar code readers, have also been applied to transfusion practice.

Key Points

- Blood components should be prescribed like therapeutic agents as part of a blood management program.
- RBC transfusion can be considered when the hemoglobin is 7 g/dL or lower for the majority of hemodynamically stable ICU patients. A transfusion threshold of less than 8 g/dL may be appropriate for patients with symptomatic cardiovascular disease and postoperative surgical patients.
- Platelet transfusions are indicated for patients who have active bleeding as the result of thrombocytopenia or functional platelet defects and for the prevention of bleeding related to thrombocytopenia.
- FFP is indicated for the repletion of coagulation factors in bleeding patients deficient in those factors or to provide specific plasma proteins that cannot be obtained from safer sources.
- Cryoprecipitate is a concentrated source of fibrinogen and selected coagulation factors. Cryoprecipitate may be more helpful than FFP in correcting the hypofibrinogenemia of dilutional or consumptive coagulopathy.
- Adverse reactions to blood components occur in 1% to 2% of transfusion episodes. Adherence to routine protocols for the evaluation of transfusion reactions may save lives.
- Transmission of infectious agents by transfusion has been markedly reduced, and bacterial infection is now the most common infectious complication of transfusion.
- Informed consent for blood transfusion is a standard of practice. A competent adult has the legal right to refuse blood transfusion.

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Review Questions

1. A 48-year-old man with a history of multiple myeloma has undergone bone marrow transplantation. He is admitted to the intensive care unit (ICU) because of minor bleeding with profound thrombocytopenia (platelet count 4000/mm^3). Five units of random donor platelets are transfused with a post-transfusion platelet count of 10,000/mm^3. He still experiences minor bleeding. Which one of the following is the *best* next treatment decision?

a. Screen for human leukocyte antigen (HLA) antibodies and transfuse HLA-compatible, single-donor platelets.
b. Transfuse ABO-specific platelet concentrates that are less than 48 hours old.
c. No further transfusion is necessary; monitor platelet count in 8 hours.
d. Administer a 2-week course of prednisone.

Answer: a. Transfusion of ABO-specific platelet concentrates that are less than 48 hours old is optimal in this case. Poor response to platelet transfusion can be seen with splenomegaly, fever, disseminated intravascular coagulation (DIC), substandard-quality platelets, and similar to this patient, bone marrow transplantation. When patients do not achieve expected increments in platelet counts after platelet transfusion, ABO-specific platelet concentrates less than 48 hours old may improve the response. If no incremental improvement is seen in a patient with no risk factors for poor response to platelet transfusion, the patient should be screened for HLA antibodies and transfused with HLA-compatible, single-donor platelets. This patient is still symptomatic after platelet transfusion and will need additional platelet concentrates. Prednisone will not improve the response to platelet transfusion.

2. A 78-year-old woman was hospitalized 10 days ago because of anemia from gastrointestinal (GI) bleeding. During the hospitalization, she required transfusion of 4 units of packed red blood cells. She now arrives at the emergency department with fever, chills, a hematocrit of 18%, and no evidence of active GI bleeding. Her total bilirubin is 5.0 mg/dL, and her lactate dehydrogenase (LDH) level is 1400 U/L. Which one of the following laboratory tests will establish the diagnosis?

a. This is a clinical diagnosis, no laboratory tests are recommended.
b. Peripheral blood smear
c. Indirect antiglobulin test
d. Direct antiglobulin test (Coombs test)

Answer: d. The direct antiglobulin test (Coombs test) will establish the diagnosis. This patient is showing a classic delayed transfusion reaction, delayed hemolytic reaction, and serologic reaction. These reactions typically occur 3 to 14 days after transfusion but are unrecognized because of the lack of temporal association. Patients present with fevers, chills, and an unexplained drop in hematocrit. A transient elevation in LDH and bilirubin levels may also be present. The diagnosis is established by a direct antiglobulin test (Coombs test) resulting from recipient antibody coating of donor red blood cells (RBCs). The disease is recognized by the clinical scenario but can be established with Coombs testing. Detection of delayed antibodies is the reason that a new blood specimen is required every 72 hours if the patient has had a transfusion recently. Peripheral blood smear may show evidence of hemolysis but will not delineate between a delayed hemolytic reaction and other hemolytic processes. In addition, the direct antiglobulin test will detect recipient antibody coating of donor RBCs, but the indirect antiglobulin test will not.

3. Which of the following is the most common infectious etiology of transfusion-related fatality?

a. Bacterial
b. Viral
c. Fungal
d. Parasitic

Answer: a. Bacterial contamination is the leading cause of infection-related transfusion deaths in the United States and apheresis platelets are the most commonly contaminated blood product. *Staphylococcus aureus* is the most common organism followed by *Babesia microti* for the period from 2011 to 2015.

4. Which one of the following is most responsible for a decrease in the incidence of transfusion-related acute lung injury (TRALI)?

a. Leukocyte reduction of RBC products
b. ABO matching of platelets
c. Use of male donor fresh frozen plasma
d. Use of RBC products less than 14 days old

Answer 4: c. The frequency of TRALI has been decreasing since blood banks adopted a strategy of male-predominant plasma transfusion. This approach decreases exposure of recipients to donor leukocytes antibodies believed to be important in precipitating TRALI. Leukocyte reduction, ABO cross-matched platelets, and fresh blood have not been associated with a decrease in TRALI.

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Intensive Care of the Cancer Patient

REZA SAMAD AND STEPHEN M. PASTORES

CHAPTER OUTLINE

Reasons for ICU Admission
- Pulmonary Complications in Patients With Cancer
- Infectious Complications
- Cardiovascular Complications
- Metabolic and Endocrine Complications
- Neurologic Complications
- Hematologic Complications
- Renal Complications
- Complications of Novel Biologic Therapies
- Delivery of Antineoplastic Therapy in the ICU
- Complications of Hematopoietic Stem Cell Transplantation

Triage of Cancer Patients for ICU Care

Palliative, Ethics, and End-of-Life Care Issues

Summary

Despite a 25% decline in the overall cancer mortality rate between 1991 and 2014, and a 1.5% annual decline among men and women from 2005 to 2014, cancer remains the second leading cause of death in the United States.[1] Cancer is the leading cause of death, however, among certain demographic groups, including men and women 40 to 59 years of age, men and women 60 to 79 years of age, and Hispanic and Asian Americans.[2–4] Although the mortality rates for female breast, prostate, colorectal, and lung cancers have declined, mortality rates for liver cancer and uterine cancer increased from 2010 to 2014.[1]

The overall cancer incidence between 2004 and 2013 has been stable for U.S. women and declined by nearly 2% annually in U.S. men.[1] Over the past 2 decades, notable advances in the diagnosis and management of cancer patients, including the use of high-dose chemotherapy, stem cell transplantation, targeted therapies, and immunotherapy, have translated to an increasing number of people living with cancer. From 2006 to 2012, nearly 67% of patients diagnosed with cancer survived 5 years or more after their diagnosis. An estimated 14.1 million people were living with cancer in the United States in 2013, and this is expected to reach 19 million by 2024.[5]

Worldwide the global cancer burden continues to increase, accounting for an estimated 14.1 million new cancer cases and 8.2 million cancer deaths in 2012.[1,6] Cancer may soon become the leading cause of death in many developed countries. If rates remain unchanged, the global cancer burden is expected to increase to 23.9 million cases and 14.6 million deaths by 2035.[6]

Patients with malignancy have been reported to account for 10% to 15% of all intensive care unit (ICU) admissions.[7,8] As the prevalence of patients living with cancer increases, it can also be anticipated that there will be more patients who require ICU admission.

Critical care of the cancer patient is a complex and expanding field as the mechanisms underlying cancer biology continue to be elucidated and novel therapeutics are developed. This chapter reviews select oncologic clinical syndromes and cancer treatment toxicities seen among patients with cancer who require ICU management. The multidisciplinary care of the patient with cancer requires consideration of these unique complications, in addition to pathologic conditions seen among patients without cancer. The triage of patients with cancer for ICU care is discussed, as well as the ethical, palliative, and end-of-life care aspects of treating cancer patients in the ICU setting.

Reasons for ICU Admission

Patients with cancer may require ICU admission because of the malignancy itself or the result of complications of cancer therapy (Box 76.1). The most frequent indications for ICU admission include acute respiratory failure from infectious and noninfectious causes; neutropenic sepsis; oncologic emergencies, such as tumor lysis syndrome and hypercalcemia; and postoperative management of complications from high-risk cancer surgery. Acute kidney injury (AKI), cardiovascular disease, and neurologic complications are other common reasons. ICU admission may also be offered for the administration of high-risk antineoplastic therapies in noncritically ill patients, adverse drug reactions, or the administration of medications not routinely offered on medical wards.

Pulmonary Complications in Patients With Cancer

Acute Respiratory Failure

Acute respiratory failure (ARF) is the leading cause for ICU admission in cancer patients and is usually associated with high mortality rates, especially in those requiring mechanical ventilation. The incidence of ARF is about 5% in the patients with solid tumors and up to 50% in those with hematologic malignancies. ARF accounts for up to 80% of hematopoietic stem cell transplant (HSCT) recipients hospitalized for respiratory complications, with an overall survival rate of approximately only 15% in those receiving mechanical ventilation.

The most common causes of ARF in cancer patients include infections, cardiogenic and noncardiogenic pulmonary edema (acute

• BOX 76.1 Common Reasons for ICU Admission of Patients With Cancer

- Infection
  - Infectious pneumonia
  - Sepsis
- Noninfectious Respiratory Failure
  - Pneumonitis
  - Cardiogenic pulmonary edema
  - Noncardiogenic pulmonary edema
  - Pulmonary hemorrhage
  - Malignant infiltration
  - Pulmonary thromboembolism
  - Malignant airway obstruction
  - Bronchospasm/anaphylaxis
- Oncologic Emergencies
  - Cardiac tamponade
  - Superior vena cava syndrome
  - Tumor lysis syndrome
  - Hypercalcemia
  - Malignant cord compression
  - Leukostasis
- Adverse Drug Reactions
  - Cytokine release syndrome
  - Thrombotic microangiopathy
- Neurologic Complications
  - Seizures
  - Encephalopathy
- Gastrointestinal Hemorrhage
- Postsurgical Care
  - Thoracic
  - Head and neck
  - Hepatobiliary/pancreas
  - Gynecologic
  - Colorectal

• BOX 76.2 Noninvasive Diagnostic Testing for Acute Respiratory Failure in Cancer Patients

- Imaging
  - Chest radiography
  - High-resolution computed tomography
  - Ultrasonography (cardiac, pulmonary, venous)
- Culture
  - Bacterial/fungal Culture (blood, sputum)
  - Acid-fast *Bacillus* culture (blood, sputum)
  - Methicillin-resistant *Staphylococcus aureus* (nasal swab)
- Antigen
  - Legionella antigen (urine)
  - *Streptococcus pneumoniae* antigen (urine)
  - Fungal cell antigen (blood)
    - (1-3)-β-D-glucan, *Aspergillus galactomannan,* cryptococcal antigen
- Polymerase Chain Reaction
  - Community-acquired pneumonia (nasal swab)
    - *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Bordetella pertussis*
    - *Pneumocystis jiroveci* (sputum)
    - *Mycoplasma tuberculosis* (sputum)
  - Community respiratory viruses (nasal swab)
    - Adenovirus, coronavirus, human rhinovirus/enterovirus, human metapneumovirus, influenza, parainfluenza, respiratory syncytial virus
  - Opportunistic viruses (blood)
    - Adenovirus, CMV, EBV, HHV-6, HSV
- Serum Biologic Markers
  - Brain natriuretic peptide (BNP) or pro-BNP
  - C-reactive protein
  - Procalcitonin
  - Cytokine assays
  - Autoimmune serology (e.g. ANA, RF, anti-dsDNA, anti-SSA, anti-SSB, anti–Jo-1 antibodies)
  - Paraneoplastic serology (e.g. anti-acetylcholine receptor)
- Cytology
  - Flow cytometry

ANA, *Antinuclear antibody;* CMV, *cytomegalovirus;* dsDNA, *double-stranded DNA;* EBV, *Epstein-Barr virus;* HHV-6, *human herpesvirus 6;* HSV, *herpes simplex virus;* RF, *rheumatoid factor;* SSA, *Sjögren's syndrome-related antigen A;* SSB, *Sjögren's syndrome type B.*

respiratory distress syndrome [ARDS]), antineoplastic (chemotherapy or immunotherapy, radiation) therapy-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.

Diagnostic Strategy and Management of ARF in Patients With Cancer

A detailed clinical history and thorough physical examination are the first steps to identifying the cause of ARF in patients with cancer. Making a diagnosis on clinical grounds is often difficult, however, as the physical examination and radiographic findings for a number of causes in this patient population overlap. A diagnostic algorithm to determine the etiology of ARF in patients with malignancy has been proposed and is based on factors encapsulated by the mnemonic DIRECT (*d*elay since malignancy onset or HSCT, since symptom onset, or since implementation of antibiotics/prophylaxis; pattern of *i*mmune deficiency; *r*adiographic appearance; clinical *e*xperience and knowledge of the literature; *c*linical picture; and findings on high-resolution computed tomography).[9,10] Further diagnostic investigations and empiric therapy as well as other life support measures can be selected based on the suspected diagnosis.

In particular, the appearance of acute or subacute pulmonary infiltrates with severe hypoxemia in the initial phase of malignancy, especially hematologic, may suggest infectious pneumonia or malignancy-related lung infiltration. Progressive, subacute lung infiltrates that occur late after the presentation of malignancy may suggest infiltrative disease, toxicity to antineoplastic therapy, or the occurrence of a second malignancy. Infectious etiologies and cardiogenic pulmonary edema should be excluded in all cases of ARF. A follow-up cohort analysis assessed the performance of the DIRECT approach and associated bacterial pneumonia with solid tumors, multiple myeloma, neutropenia, shock, less than 3 days since symptom onset, unilateral pulmonary crackles, and a unilateral radiographic pattern.[10] Use of steroids, lymphoproliferative disorders, and HSCT were associated with opportunistic infections, and acute leukemia was associated with noninfectious causes of ARF.

Fiberoptic bronchoscopy with bronchoalveolar lavage (FB-BAL) is the diagnostic strategy of choice for cancer patients whose respiratory symptoms are not severe enough to warrant ICU admission because their respiratory reserve will allow them to tolerate the procedure. Among patients with ARF, however, FB-BAL has been associated with respiratory deterioration and the need for mechanical ventilation.[11] Advances in noninvasive diagnostic testing (Box 76.2) have warranted reassessment of the role of semi-invasive or invasive tests such as FB-BAL and lung biopsy. In a randomized controlled trial comparing early FB-BAL plus a

standardized panel of noninvasive tests to noninvasive tests alone, noninvasive testing was not inferior to the combined strategy in diagnosing the etiology of ARF and was not associated with an increase in mortality rate.[12] In addition, noninvasive testing identified the cause of ARF more frequently and more rapidly than FB-BAL. FB-BAL added diagnostic information to noninvasive testing in only 18% of patients. Although no significant difference was found in the rate of intubation between both strategies, 25% of those patients who were not intubated at the time of early FB-BAL experienced respiratory decline induced by the procedure. All patients in the noninvasive strategy who had an undetermined diagnosis by day 3 underwent FB-BAL and required intubation afterward. Overall, even though early FB-BAL is safe in oncologic patients with ARF, it may be of little benefit and may risk respiratory deterioration earlier than a noninvasive strategy. Among patients who do not have a diagnosis after noninvasive testing, FB-BAL may yield additional diagnostic information; however, intubation before bronchoscopy should be considered.

Despite advances in the comprehensive noninvasive diagnostic workup and the use of empiric therapy, failure to determine an etiology of ARF and to make therapeutic modifications based on the diagnosis is associated with increased mortality, particularly among patients with hematologic malignancy.[13,14] The addition of invasive testing, including transbronchial lung biopsy and surgical lung biopsy, to noninvasive testing and FB-BAL in patients with ARF and diffuse pulmonary infiltrates may further increase the diagnostic yield and increase the opportunity for therapeutic modification.[14,15] In select patients, invasive testing does not risk additional procedure-related death or compromise overall outcomes compared to patients with complications from FB-BAL. The decision whether or not to pursue lung biopsy in cancer patients with ARF should be made after carefully weighing the risks and benefits of the procedure; factors such as thrombocytopenia, coagulopathy, severe hypoxemia, and multiple organ dysfunction may increase the risk of complications.

Basic management principles in patients with ARF include supplemental oxygen to correct hypoxemia, early initiation of appropriate empiric antimicrobial therapy in patients with suspected pneumonia, diuretics to decrease pulmonary congestion, and ventilator support including early use of noninvasive positive-pressure ventilation (NIPPV) as well as invasive mechanical ventilation, if necessary.[16] Previous observational studies have demonstrated that NIPPV is effective in improving gas exchange, reducing the need for mechanical ventilation, and is associated with improved outcomes compared with first-line invasive mechanical ventilation (IMV). However, NIPPV failure is associated with a high mortality that exceeds that of patients who received IMV, suggesting that the application of NIPPV or delay in intubation may have additional adverse effects in some patients.[17] Factors associated with NIPPV failure include infectious causes of respiratory failure, the concurrent need for vasopressors or RRT, ARDS, and a high respiratory rate under NIPPV. Alternatively, patients with risk factors for NIPPV failure on presentation of ARF should be considered for early IMV. Contemporary studies suggest there may be no benefit of early NIPPV compared to standard oxygen among patients with hematologic malignancies and isolated hypoxemic respiratory failure.[18,19]

High-flow nasal cannula (HFNC) oxygen therapy was recently shown to improve the survival rate among unselected patients with hypoxemic ARF, even though there was no difference in intubation rate observed with HFNC compared with standard oxygen therapy or NIPPV.[20] Similarly, Mokart et al. reported significant improvement in 28-day mortality in cancer patients with ARF treated with HFNC.[21]

Pulmonary Toxicity of Antineoplastic Therapy

Toxicity to antineoplastic therapy can occur at any time after treatment initiation; however, toxicity to a specific agent should be considered only after the exclusion of other causes and careful consideration of known clinical and radiographic presentations, associated dose regimens and exposure to additional antineoplastic therapy, and the reported frequency of toxicity. Treatment of toxicity to antineoplastic therapy may include any combination of supportive care, dose reduction or cessation of the suspected agent, or glucocorticoids. The decision to halt a particular antineoplastic therapy must take into account the severity of toxicity, the loss of benefit with regard to treatment of the underlying malignancy, and the availability and efficacy of other treatment options. Examples of antineoplastic therapy associated with ARF are provided (Table 76.1). The literature describing complications of antineoplastic therapy is abundant and beyond the scope of this chapter.

Pulmonary Tumor Embolism and Lymphangitic Carcinomatosis

Pulmonary tumor emboli result from the accumulation of circulating tumor cells within the pulmonary microvasculature, causing obstruction to circulation without changes in vessel architecture. Pulmonary tumor thrombotic microangiopathy is a related condition resulting in nonocclusive small vessel injury, with activation of local coagulation and inflammatory cascades ultimately leading to increased pulmonary vascular resistance and pulmonary hypertension. Tumor cells can also become embedded within pulmonary lymphatics causing lymphangitic carcinomatosis. Rather than distinct entities, these syndromes may represent a spectrum of embolic disease, with varying degrees of overlap seen clinically. The incidence of these syndromes is unknown; however, in autopsy series up to 26% of patients with solid tumors have evidence of tumor emboli, although this may overestimate clinical morbidity. Pulmonary embolization syndromes can complicate any malignancy; however, the risk appears to be highest in renal cell and hepatocellular carcinoma, as well as adenocarcinomas of breast, colon, stomach and lung.

Patients present with nonspecific subacute and progressive dyspnea. Imaging techniques are often nondiagnostic, whereas findings are variable depending on syndrome.[22] The presentation resembles thromboembolic disease, which must be excluded. Pulmonary tumor emboli are associated with an absence of pulmonary parenchymal disease, although case reports have identified dilated and beaded peripheral pulmonary arteries, and tree-in-bud opacities. Ventilation-perfusion scanning may demonstrate multiple symmetric peripheral defects producing a beaded appearance, sometimes with a segmental contour pattern. Pulmonary angiography also has poor sensitivity and specificity for pulmonary tumor thrombotic microangiopathy. The presence of tumor cells in bronchoalveolar lavage or aspiration of blood from the pulmonary capillary bed can confirm the presence of malignant disease. Lymphangitic carcinomatosis may present with thickening of the bronchovascular bundles and interstitial septae and pleural effusion on chest imaging. Transbronchial lung biopsy or surgical biopsy demonstrating tumor cells in the pulmonary vasculature or lymphatic is diagnostic. The prognosis is poor, although reports suggest combination therapy, including pulmonary vasodilators, anticoagulation, and chemotherapy, may extend survival.

TABLE 76.1 Selected Organ System Complications of Antineoplastic Therapies

Organ System	Antineoplastic Agent
Respiratory	
Acute pneumonitis	Bleomycin, bortezomib, cyclophosphamide, methotrexate, paclitaxel
NCPE	Cytarabine, interleukin 2, gemcitabine, mitomycin, IT, methotrexate
Pulmonary hemorrhage	Bevacizumab
Bronchospasm	Mitomycin, rituximab, vinblastine, cetuximab
Cardiac	
Heart failure	Bortezomib, cyclophosphamide, doxorubicin, trastuzumab
Myocardial ischemia	Fluorouracil, vinca alkaloids
Pulmonary hypertension	Dasatinib, mitomycin
Bradycardia	Crizotinib, paclitaxel
Atrial fibrillation	Ibrutinib
Hypertension	Bevacizumab
QTc prolongation	Arsenic trioxide
Neurologic	
Encephalopathy	Capecitabine, cisplatin, ifosfamide, methotrexate
Seizures	Busulfan, cisplatin, fluorouracil, ifosfamide
PRES	Cisplatin, methotrexate, cytarabine, carboplatin, gemcitabine
Central demyelination syndrome	Levamisole, fluorouracil
Renal and Metabolic	
SIADH	Cisplatin, cyclophosphamide, vinca alkaloids
TMA	Bevacizumab, gemcitabine, mitomycin, sirolimus
Renal tubular injury	Cisplatin, ifosfamide, pemetrexed, ipilimumab
Hypocalcemia	Mithramycin
Hypomagnesemia	Cisplatin, cetuximab
Hypophosphatemia	Imatinib
Hyperglycemia	Everolimus

IT, Intrathecal; *NCPE,* noncardiogenic pulmonary edema; *PRES,* posterior reversible encephalopathy syndrome; *SIADH,* syndrome of inappropriate antidiuretic hormone; *TMA,* thrombotic microangiopathy.

Infectious Complications

Febrile Neutropenia

Febrile neutropenia (FN) is a common complication of many chemotherapy regimens, although the incidence varies by cancer type and myelosuppressive regimen used.[23] It is associated with mortality rates of up to 20% among patients who are hospitalized for FN and more than 40% among critically ill patients.[23,24]

Identifying the cause of fever in patients with FN can be challenging, as the inflammatory response to infection may be muted. A careful physical examination, with attention to skin and mucosal surfaces including the oral cavity and perianal region, and inspection of intravenous (IV) catheters, is important to localize the site of infection. The diagnostic workup for FN should include cultures from a central venous catheter if present. Early use of fungal cell antigen tests such as (1-3)-β-D-glucan and *Aspergillus* galactomannan may be useful for early diagnosis of fungal infections. Additional imaging studies are guided by the clinical picture; however, chest radiographs may appear normal in neutropenic patients with lung infection. The evaluation should also consider noninfectious causes of fever that are common in this patient population, including drug fever, venous thromboembolism, or reaction to blood product transfusion. An unrevealing diagnostic workup for FN is common. Procalcitonin (PCT) does not appear to be helpful in distinguishing bacterial from nonbacterial inflammation in neutropenic patients with sepsis.[25] Furthermore, PCT levels should be assessed only in the context of a physical examination and when appropriate microbiological testing is performed.

Patients with FN should be risk stratified based on degree and anticipated length of neutropenia, symptom burden, and the presence of significant comorbidities. The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a well-validated tool for predicting patients at low risk for serious complications. However, the MASCC score does not perform as well in patients with hematologic malignancy.[26] Additional PCT testing may be useful in predicting adverse outcomes even in patients with a low-risk MASCC score.[27] High-risk MASCC scores, as well as comorbidities including thrombocytopenia, hypoproteinemia, renal failure, and elevated inflammatory markers, are associated with unfavorable outcomes in patients with FN.[27–29] Among critically ill cancer patients with neutropenia and severe sepsis or septic shock, older age, vasopressor use, and neurologic, respiratory or hepatic dysfunction are associated with higher mortality, as is the presence of an acute concurrent noninfectious condition.[24]

The microbial pathogens that infect neutropenic patients have changed over time. Recent epidemiologic data demonstrate that gram-positive and gram-negative bacteria account for 55% and 45%, respectively, of bacteremia in cancer patients.[30] The incidence of multidrug-resistant bacteria remains substantial.

Patients at high risk for severe or complicated infection should be hospitalized to receive empiric treatment with IV broad-spectrum antibacterial agents for coverage of gram-positive and gram-negative pathogens as soon as possible. The selection of agent should be guided by clinical presentation, recent antibiotic use and culture data, and risk factors for resistant bacteria, such as patient colonization or previous infection with a multidrug-resistant pathogen, and local epidemiology. Antibiotic therapy should be initiated promptly after blood cultures have been obtained. Initial monotherapy with an antipseudomonal β-lactam antimicrobial agent is recommended. Vancomycin is not recommended as standard therapy but should be considered for suspected skin or soft tissue infections, catheter-related infections, or hemodynamic instability. Anaerobic coverage can be considered in cases of suspected anaerobic infection, such as necrotizing mucositis, sinusitis, neutropenic enterocolitis, and pelvic infection. Modifications to the initial empiric regimen may be considered for patients who are at risk for antibiotic-resistant organisms, clinically unstable, or who have blood cultures suspicious for resistant bacteria. Antibiotic de-escalation from a regimen targeting resistant bacteria should be considered if resistant pathogens are not isolated, with no apparent increased risk of mortality.[31]

Antibiotic combinations such as a β-lactam with a fluoroquinolone or an aminoglycoside as empiric therapy for FN is controversial, as such combinations do not appear to be superior to monotherapy and may risk toxicity. The addition of aminoglycosides, for example, does not appear to improve outcomes but may increase the risk of kidney injury.[32] Such combinations may be considered in the subset of patients with septic shock.[24]

Empiric antifungal agents should be considered in high-risk patients who have persistent fever without an apparent cause after 4 to 7 days and are expected to have a prolonged duration of neutropenia, or earlier in patients in unstable condition or those who have a suspected fungal infection. The choice of empiric antifungal agent should be based on clinical suspicion for infection, comorbidities, and previous exposure to antifungal agents

Source control remains an important part of sepsis management in the neutropenic cancer patient, and central venous catheter removal should be considered among those in septic shock without an obvious source of infection, or with evidence of site infection, endocarditis, septic thrombosis, or with persistent culture positivity. Early catheter removal in neutropenic patients with severe sepsis or septic shock without an obvious source of infection may improve survival.[24] Catheter-related sepsis should also be considered when an infection is caused by certain microorganisms, including *S. aureus*, *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus*, *Acinetobacter* spp., or *Candida*.

Although the addition of colony-stimulating factors (CSFs), such as granulocyte-CSF or granulocyte-macrophage CSF to antibiotics for chemotherapy-induced FN, hastens neutrophil recovery, it does not appear to improve infection-related mortality.[33]

Cardiovascular Complications

Pericardial Disease and Cardiac Tamponade

Malignant involvement of the pericardium can manifest as pericarditis, pericardial effusion, cardiac tamponade, or constrictive pericarditis. Among cancer patients admitted to the ICU, the most frequent causes of cardiac tamponade are metastatic tumors of the breast, lung, and esophagus, and melanoma, and leukemias and lymphomas. The median time from cancer diagnosis to the onset of tamponade varies with cancer diagnosis, and the appearance of cardiac tamponade appears to be a marker for poor 1-year survival despite drainage, especially among patients with lung and gastric or esophageal cancers. Although a pericardial effusion in a patient with cancer usually represents pericardial disease, a negative cytology result does not exclude the diagnosis of malignancy and other etiologies should be considered including radiation- or treatment-induced pericarditis with pericardial effusion, or infectious or autoimmune pericardial effusions. Pericardiocentesis for relief of tamponade is indicated emergently when clinical evidence of hemodynamic compromise is present.

Pericardiocentesis may be complicated by paradoxical hemodynamic instability (PHI), or low cardiac output syndrome, the occurrence of unexpected hemodynamic compromise after pericardial fluid drainage. This has been reported in cancer patients with cardiac tamponade, and the presence of malignant cells in pericardial fluid increases the risk of PHI. The pathophysiology of PHI is not clear; however, it may be due to delayed recovery of myocardial function after relief of tamponade physiology. Drainage of pericardial fluid may also expose underlying constrictive physiology among patients with previous radiation exposure.

Therapies for durable prevention of pericardial fluid accumulation may be tailored according to etiology and include use of intrapericardial chemotherapy, corticosteroids, or sclerosing agents; extended catheter drainage; or creation of a pericardial window. Extended catheter drainage, pericardial sclerosis, and balloon pericardiotomy offer similarly low rates of recurrence compared with isolated pericardiocentesis.

Superior Vena Cava Syndrome

Obstruction of the superior vena cava (SVC) can be caused by invasion or external compression from pathologic processes involving adjacent structures, or by thrombosis within the SVC. Malignancy, particularly lung cancer and lymphoma, is the most common cause of SVC syndrome, although thrombosis on intravascular devices and postradiation vascular fibrosis can also occur during oncologic care. Duplex ultrasound can exclude thrombus in central upper extremity veins, and dampening of waveforms with loss of venous pulsatility and respiratory variation may suggest SVC obstruction. Contrast-enhanced computed tomography of the chest can identify obstruction as well as the underlying cause. In its most severe presentation, the resulting upper extremity venous congestion can result in central airway obstruction or laryngeal edema, or coma from cerebral edema. In these situations, immediate radiotherapy or endovascular stent placement should be pursued. In other cases, therapy depends on the underlying cause and may include chemotherapy, corticosteroids, and radiation therapy for susceptible malignancies. Thrombolysis is effective in catheter-associated SVC syndrome.

Cardiac Arrest

The outcomes of patients with cancer who undergo cardiopulmonary resuscitation (CPR) appears to be improving.[34] Among patients admitted to an ICU for out-of-hospital cardiac arrest or in-hospital cardiac arrest, 18% of patients survived to hospital discharge, and the majority had good neurologic outcome, and 14% survived to at least 6 months.[35] Survival did not differ significantly by malignancy type or status. Moreover, survival was not significantly different among matched controls with no malignancy. Among patients who underwent CPR in an ICU, however, mortality was worse, with 7.8% surviving to ICU discharge and only 5.8% surviving to hospital discharge.[36] CPR duration appears to be the only factor associated with outcome, with a 10% increase in mortality per minute of resuscitation time. Improved CPR outcomes reflect not only improved care of cardiac arrest patients, but also careful patient selection after treatment-limiting decisions.

Metabolic and Endocrine Complications

Hypercalcemia

Hypercalcemia is common among patients with malignancy, occurring in 10% to 20% of patients with solid tumors, particularly among those with multiple myeloma, breast, lung, kidney, and head and neck cancer. Increased mobilization of calcium from bone and decreased renal tubular calcium excretion are driven by tumor production of bone-resorbing hormones and cytokines such as parathyroid hormone-related peptide (PTHrP), as well as local osteolysis at metastatic sites. Increased production of calcitriol has been observed in cases of Hodgkin and non-Hodgkin lymphoma. Primary hyperparathyroidism should be excluded, as the incidence appears to be elevated in patients with cancer. Hypercalcemia of malignancy can be distinguished from other causes of hypercalcemia by high and more rapid increases in serum calcium, with greater symptomatology. A low serum parathyroid hormone level with an elevated PTHrP level is diagnostic of hypercalcemia of malignancy.

Bisphosphonates are potent osteoclast inhibitors and are essential in the treatment of hypercalcemia of malignancy, in addition to IV hydration and the short-term use of calcitonin. The maximum effect of bisphosphonates occurs in 2 to 4 days and is prolonged

over the course of weeks. Patients with high levels of PTH-rP may have an inferior response to bisphosphonates and may require higher doses. Bisphosphonates have potential nephrotoxicity and should be used with caution in patients with underlying kidney disease after careful consideration of specific agents associated with less risk.

Denosumab, a monoclonal antibody for receptor activator of nuclear factor κB ligand, an essential mediator of osteoclast formation and function, has demonstrated efficacy in a number of case series for the treatment of hypercalcemia of malignancy and should be considered for patients with bisphosphonate-resistant hypercalcemia. Denosumab is not cleared by the kidneys and thus may be used in patients with chronic kidney disease.

Additional alternatives to treat hypercalcemia include calcium-sensitizing calcimimetic agents to suppress parathyroid hormone secretion in patients with severe hypercalcemia owing to parathyroid carcinoma, and glucocorticoids in lymphoma patients with increased calcitriol production. Renal replacement therapy (RRT) may be necessary for severe AKI or in patients with underlying heart failure or AKI in whom hydration cannot be safely administered.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) describes the release of large amounts of intracellular potassium, phosphate, and nucleic acids into the systemic circulation resulting from massive tumor cell breakdown that may lead to life-threatening AKI, arrhythmias, and neurologic complications. TLS is typically associated with highly proliferative, chemosensitive hematologic malignancies, but it has also been rarely reported in solid tumors. It usually occurs after the initiation of antineoplastic therapies, although it can occur spontaneously.

AKI in TLS is likely multifactorial and involves the deposition of uric acid, phosphate, and xanthine within the renal tubules. Prevention and treatment of TLS involves aggressive fluid resuscitation to augment renal perfusion, glomerular filtration, and maintenance of a high urine output. Additional hypouricemic agents are used to reduce the risk of uric acid nephropathy. Allopurinol is a hypoxanthine analog and competitive inhibitor of xanthine oxidase, preventing the formation of additional uric acid. Caution is advised in its use among East Asian populations who may have severe cutaneous adverse events with allopurinol. Febuxostat is a selective inhibitor of xanthine oxidase that may be a reasonable alternative to allopurinol in the prevention of TLS; however, its use may be limited owing to concerns for drug-induced hepatoxicity. Neither allopurinol nor febuxostat addresses the accumulation of the uric acid precursor xanthine, and this may contribute to xanthine nephropathy. Rasburicase is a recombinant urate oxidase that catalyzes the oxidation of uric acid to allantoin, which is more soluble and readily excreted. The reduction in plasma uric acid levels is profound and rapid; however, severe adverse reactions including anaphylaxis, methemoglobinemia, and hemolytic anemia among those with glucose-6-phosphate dehydrogenase deficiency may occur.

Routine use of diuretics is not recommended unless there is evidence of volume overload. Urinary alkalinization is controversial and may increase the risk of phosphate and xanthine crystallization. RRT should be considered for those who have persistent metabolic abnormalities or renal failure despite fluid replacement. Continuous RRT may be preferred for ongoing TLS; however, intermittent hemodialysis should be considered in life-threatening hyperkalemia.

Hyponatremia

Moderate to severe hyponatremia (<130 mmol/L) occurs in nearly 4% of hospitalized cancer patients. Multiple etiologies contribute to this hyponatremia including volume status and concomitant medications. Of particular concern is the syndrome of inappropriate antidiuretic hormone (SIADH), which may be caused by tumors and antineoplastic therapies. SIADH is associated with carcinoid tumors, myeloma, lymphoma, and carcinomas originating in the lung, prostate, esophagus, head and neck, adrenal gland, and pancreas. Cerebral metastasis from any tumor can also give rise to SIADH. SIADH has also been reported as a complication of a number of antineoplastic agents (see Table 76.1) and commonly used palliative medications, including opioids, antidepressants, and antiemetics.

Salt-wasting nephropathy is another cause of hyponatremia in cancer patients and may be due to adrenal insufficiency, cerebral salt wasting after subarachnoid hemorrhage or intracranial surgery, or certain antineoplastic agents (e.g., cisplatin).

Hypoglycemia

Tumor-induced hypoglycemia is uncommon but can result in serious consequences. Several different mechanisms can give rise to hypoglycemia. Autonomous insulin production is most commonly associated with islet cell tumors, whereas production of insulin-like growth factors (IGF-1 or IGF-2) is seen with non–islet cell tumors. Slow-growing mesenchymal tumors such as leiomyosarcoma, mesothelioma, and fibrosarcoma are the most common non–islet cell tumors to produce insulin-like products; however, this is seen in other tumor types including hematomas and neuroblastomas. Hypoglycemia may also be the result of excessive glucose consumption by large tumors that exceed hepatic production or from hepatic or pituitary failure. A poor response on glucagon stimulation testing may be helpful in identifying hypoglycemia owing to poor hepatic reserve or function.

Primary treatment of tumor-related hypoglycemia involves control of the tumor. Supportive therapy involves dietary modification, glucose infusions, and corticosteroids. Insulinomas may respond to diazoxide, an inhibitor of insulin secretion. Continuous glucagon infusions may be appropriate for those who show a glycemic response to glucagon.

Adrenal Failure

More than 90% of adrenal tissue must be destroyed before clinical manifestations of adrenal insufficiency, such as weakness, weight loss, hyperpigmentation, hypotension, hyponatremia, hyperkalemia, and hypoglycemia, appear. Adrenal failure should also be considered in patients with hypotension refractory to fluid resuscitation and vasopressor agents. Primary adrenal insufficiency may be suspected in patients with metastatic cancer, particularly of tumors of lung, breast, kidney, stomach, pancreas, and melanoma origin, and evidence of metastases on imaging. Chronic corticosteroid therapy can mask adrenal failure or precipitate it after withdrawal. More often, however, adrenal insufficiency is iatrogenic in origin, following adrenalectomy or hypophysectomy, or treatment with medications including mitotane, aminoglutethimide, megestrol acetate, or chronic corticosteroids. Adrenal failure has also been reported in patients who developed T-cell–mediated hypophysitis after treatment of advanced melanoma with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors. The diagnosis of adrenal failure depends on measurement of inappropriately low serum cortisol, with concurrent measurement of adrenocorticotropic hormone to differentiate among primary, secondary, or tertiary failure. Alternatively, a normal cortisol response to a short adrenocorticotropic hormone stimulation test excludes primary adrenal insufficiency. Treatment with exogenous corticosteroids should not be delayed, especially in the setting of possible adrenal crisis.

Type B Lactic Acidosis

Type B lactic acidosis, without associated contribution from hypoperfusion, severe tissue hypoxia, or organ dysfunction, has been reported as a complication of hematologic malignancies, particularly rapidly progressive leukemia and lymphoma. The Warburg effect describes the observation that many cancer cells have higher glycolytic rates than their normal tissues of origin, even in the presence of adequate amounts of oxygen. This may be due to the overexpression of glycolytic enzymes to support malignant cell proliferation. Tumor pyruvate kinase isoenzyme type M2 (M2-PK), a form of pyruvate kinase, has been found in a variety of cancer cells and is associated with rapid glycolysis and accelerated tumor growth. Lactic acidosis secondary to cancer is rare and should prompt further workup for other potentially treatable causes. The prognosis of patients presenting with cancer-related type B lactic acidosis is poor, even among patients who receive chemotherapy with subsequent correction of the acidosis.

Idiopathic Hyperammonemia

Hyperammonemia has been described after high-dose cytoreductive therapy for hematologic malignancy or after HSCT in the absence of marked liver impairment, evidence of deficiencies in urea cycle metabolism, or other causes of elevated serum ammonia, although recent case reports describe idiopathic hyperammonemia among patients treated with corticosteroids for leukemia[37] or chemotherapy for solid tumors.[38] The etiology is unclear; however, the suggested mechanisms include acquired or relative deficiencies in urea cycle metabolism after chemotherapy. Cases of idiopathic hyperammonemia may occur days after chemotherapy or up to 2 months after HSCT. Neurologic sequelae are abrupt and may be irreversible. Recurrence is possible, and mortality is high. Idiopathic hyperammonemia is rare; however, it should be considered in cases of abrupt changes in mental status. Elevation of liver enzymes should trigger evaluation of secondary causes of hepatic dysfunction, such as liver metastases or exposure to hepatotoxic chemotherapy; however, with the exception of asparaginase, severe hepatic failure and hyperammonemia owing to chemotherapy are rare.

Neurologic Complications

Malignant Cord Compression

Malignant cord compression (MCC) owing to bony metastases to the vertebral spine with subsequent collapse and cord compression, local tumor extension into the spinal cord, epidural metastases, or intramedullary spinal cord metastases, occurs in 3% to 5% of all patients with cancer. Although carcinomas of the breast, lung, and prostate and multiple myeloma are common causes of MCC, virtually any tumor can metastasize to the spine. Moreover, MCC is a presenting symptom of cancer in up to 23% of cases. Presenting deficits depend on the level of cord involvement, with the thoracic spinal cord being most common, followed by the lumbosacral cord; however, multilevel involvement is common. Bladder and bowel dysfunction as presenting signs of autonomic dysfunction may be missed among patients with advanced cancer who have multiple reasons for these symptoms. Cervical involvement can be severe and present with quadriplegia or respiratory arrest. Severe back pain on movement may be suggestive of spinal instability. Patients who present with back pain and rapid onset of neurologic signs of spinal cord or cauda equina compression should receive a magnetic resonance imaging scan of the whole spine.

Treatment for MCC starts with maintaining neutral spine alignment until bony and neurologic stability is ensured. Empiric corticosteroids should be started emergently in patients who present with myelopathy and should not be delayed for imaging. Clinical trials demonstrate improved functional outcomes in patients who have received adjunctive corticosteroids. Definitive treatment may include any combination of radiotherapy, surgery, or chemotherapy, and depends on clinical factors, including the presence of spinal instability, the degree of spinal cord compression, and the relative radiosensitivity of the tumor, as well as prognostic indicators, such as age, disease burden, and overall cancer prognosis. The role of surgical decompression is controversial, with conflicting study results on the benefit of surgical decompression followed by radiotherapy over radiotherapy alone. Regardless of modality, minimizing delay to definitive treatment improves functional outcome after treatment.

Vasogenic Edema

Intracranial metastases may be accompanied by significant vasogenic edema. Upregulated production of factors, such as vascular endothelial growth factor (VEGF), acidic fibroblast growth factor, basic fibroblast growth factor, and nitric oxide, by tumor cells stimulates angiogenesis and the production of disorganized and leaky blood vessels, allowing exudative fluid accumulation in the extracellular space. Within the central nervous system (CNS), edema alters neurologic function and can contribute to symptoms, including headache, focal neurologic deficit, seizures, and encephalopathy. Symptomatic plateau waves describe the phenomenon of syncope precipitated by normal activities that transiently further raise intracranial pressure (ICP) above cerebral perfusion pressure. Dysregulated fluid accumulation within the rigid cranium may result in intracranial hypertension and brain herniation.

Glucocorticoids have demonstrated efficacy in reducing peritumoral edema and are indicated in all symptomatic patients. Improvements in ICP and neurologic symptoms are seen within hours, and changes in diffusion-weighted magnetic resonance imaging scans may be seen within 48 hours. The peak effect of glucocorticoids on reducing peritumoral edema may take several days. For patients requiring emergent reductions in ICP, additional therapies including osmotherapy and sedation and paralysis should be considered. Anti–vascular endothelial growth factor monoclonal antibodies such as bevacizumab may be useful as steroid-sparing agents.

Leptomeningeal Metastases

Leptomeningeal spread of cancer should be considered in patients who have multifocal neurologic deficits. Although diffuse involvement throughout the CNS is characteristic, the basal cisterns and cauda equina are the most symptomatic sites, resulting in cranial nerve deficits, ataxia, radiculopathy, and increased ICP. Breast cancer, lung cancer, melanoma, aggressive non-Hodgkin lymphoma, and acute lymphocytic leukemia are the most common cancers to metastasize to the leptomeninges. Brain metastases are not required for leptomeningeal disease, and although the majority of patients have active systemic disease, 20% of patients may present after a cancer-free interval.

Definitive diagnosis of leptomeningeal disease is difficult owing to the limited sensitivity of neuroimaging and cerebrospinal fluid (CSF) studies. CSF yield can be improved by a larger sample size, minimizing processing delays, and repeat sampling. CSF flow cytometry is a more sensitive test in patients with hematologic malignancies. A clinical diagnosis of leptomeningeal disease can

be made based on positive CSF cytology, or supportive clinical findings in the presence of consistent radiologic findings or abnormal CSF. The prognosis of leptomeningeal spread is generally poor, and therapies, including radiation therapy, systemic chemotherapy, and intrathecal chemotherapy, are not curative.

Hematologic Complications

Hyperleukocytosis

Peripheral white blood cell counts exceeding 100,000/μL may be seen in hematologic malignancies, particularly acute myelogenous leukemia and acute lymphoblastic leukemia, and are associated with increased morbidity and mortality. The associated increase in blood viscosity may lead to the development of symptoms or leukostasis owing to reduced tissue perfusion. The number 100,000/μL itself is arbitrary and the degree of leukocytosis needed cause symptoms varies by the type of leukemia. Severe symptoms can occur in acute myelogenous leukemia with a leukocyte count of 50,000/μL, whereas higher cell counts appear to be better tolerated in acute lymphoblastic leukemia or chronic lymphocytic leukemia. Hyperleukocytosis in acute promyelocytic leukemia usually refers to a level above 10,000/μL.

The lungs and CNS are the most common sites of vascular obstruction, and in severe cases, patients may present with hypoxemia, pulmonary infiltrates, altered mental status, focal neurologic deficits, and retinal and intracranial hemorrhage. Evidence of ischemia or vascular congestion involving other organs may be present as well. Disseminated intravascular coagulation (DIC) and spontaneous tumor lysis syndrome may complicate hyperleukocytosis.

Management of hyperleukocytosis involves supportive care with aggressive hydration to promote hemodilution and reduction of viscosity, and management of TLS and DIC until the initiation of cytoreductive therapy, such as corticosteroids or cytarabine. Leukapheresis should be reserved for symptomatic patients who are unable to start induction chemotherapy immediately, after consideration of its benefits and risks for a specific patient. There are conflicting data regarding the efficacy of leukapheresis in reducing early mortality.

Hyperleukocytosis in acute promyelocytic leukemia presents a uniquely complex situation particularly associated with an increased risk of morbidity from DIC-related bleeding. Early treatment with all-*trans* retinoic acid is essential to reducing early mortality. However, this may induce differentiation syndrome characterized by signs and symptoms of a cytokine release syndrome, including life-threatening hypotension, ARDS, and serositis. Prophylactic corticosteroids may offer some benefit in preventing the consequences of differentiation syndrome.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathologic immune activation characterized by marked systemic immune activation and the presence of abnormal immunopathology. It occurs as a familial disorder or a sporadic condition associated with a variety of triggers. Lymphomas and leukemias of T or natural killer cell lineage have been associated with HLH; however, HLH has also been reported with B-cell lymphoblastic leukemia, myeloid leukemias, mediastinal germ cell tumors, and rarely other solid tumors, and in HSCT recipients. Immune dysfunction as a result of malignancy or antineoplastic therapy exposes these patients to bacterial, viral, or fungal infection that may also trigger HLH.

• BOX 76.3 Diagnostic Criteria for Hematophagocytic Lymphohistiocytosis

A. Molecular diagnosis consistent with hematophagocytic lymphohistiocytosis, OR
B. Five of the eight following criteria:
   1. Fever
   2. Splenomegaly
   3. Cytopenias
      a. Hemoglobin < 9 g/dL
      b. Platelets $<100 \times 10^3$/mL
      c. Neutrophils $<1 \times 10^3$/mL
   4. Hypertriglyceridemia (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
   5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
   6. Low or absent natural killer cell activity
   7. Ferritin >500 ng/mL
   8. Elevated sCD25 (α-chain of sIL-2 receptor) ≥ 2400 units/mL

sCD25, *Soluble CD25;* sIL-2, *soluble interleukin 2.*
From Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. *2007;48:124–131.*

The diagnosis of HLH depends on the presence of known associated gene or on a constellation of clinical signs and symptoms (Box 76.3). The presentation is variable, and not all criteria may be met at onset. A ferritin level greater than 10,000 g/dL is a highly sensitive and specific marker for HLH, whereas soluble interleukin-2 receptor (sCD25) may correlate with disease activity. Hemophagocytosis is neither sensitive nor specific for HLH. Additionally, HLH is frequently associated with evidence of liver inflammation and neurologic dysfunction and may present with a variety of skin manifestations and pulmonary infiltrates. There is a notable overlap in these findings with macrophage activation syndrome, as well as in presentations of severe sepsis. Measurement of inflammatory markers may help to distinguish these disorders.

Current treatment of HLH begins with prolonged induction with etoposide and dexamethasone, or intrathecal methotrexate and hydrocortisone in patients with proven CNS involvement, before transitioning to continuation or salvage therapy. The clinical course is unpredictable and may require dose or frequency adjustment. Disease-specific therapies may be initiated once inflammatory markers normalize. Relapse of fever or inflammatory markers after response should trigger a search for opportunistic infection.

Renal Complications

Acute Kidney Injury

Critically ill cancer patients are at risk for AKI caused by underlying comorbidities, fluid and electrolyte disturbances, obstructive uropathy, sepsis, and exposure to nephrotoxic agents including antibiotics, contrast media, and antineoplastic treatments. Although the incidence of AKI in this population varies depending on the diagnostic criteria used and the study population, studies have shown that up 60% of patients with hematologic malignancy and critical illness will develop AKI, and up to 40% of them will need RRT. Cancer patients with AKI have a longer ICU length of stay as well as higher mortality than those without AKI. Furthermore the development of AKI can limit the receipt of additional cancer treatments or increase their toxicity. Given these outcomes,

comprehensive efforts must be made to prevent and mitigate factors that contribute to AKI in critically ill cancer patients.

Notably, decreased creatinine production is often seen in cancer patients owing to loss of cell mass, cachexia, low protein intake, inflammation, volume expansion, or medications, and diagnostic criteria based solely on a fixed serum creatinine will underdiagnose AKI. A novel biomarker, tissue inhibitor of metalloproteinase-2, and insulin-like growth factor-binding protein 7 are reported to be early predictors of AKI in high-risk medical and surgical patients including patients with cancer who are frequently exposed to nephrotoxic medications.

Complications of Novel Biologic Therapies

Chimeric Antigen Receptor T-Cell Therapy

Genetically modified human T cells targeting specific antigens expressed by hematologic and solid malignancies are associated with toxicity through a number of mechanisms. Off-tumor, on-target toxicity occurs when chimeric antigen receptor (CAR) T cells damage normal cells expressing the targeted antigen. Organ damage may result from off-target toxicity when CAR T cells cross-react with normal tissue expressing an antigen similar to the target antigen. Allergic reactions and anaphylaxis to autologous CAR T cells can also occur. TLS has also been reported in association with CAR T-cell therapy.

Cytokine release syndrome is the most common acute toxicity of CAR T cells, resulting in systemic organ dysfunction.[64] It can present with fever, arrhythmia, cardiomyopathy, pulmonary edema, AKI, electrolyte disturbances, gastrointestinal symptoms, transaminitis, and cytopenias. A wide variety of cytokines, including interleukin (IL)-6, IL-2, IL-8, IL-10, IL-2–receptor α, interferon gamma, and tumor necrosis factor, are elevated in patients who develop toxicity after CAR T-cell infusion, and the degree of elevation of these cytokines correlates with the severity of toxicity. Higher disease burden also correlates with degree of cytokine elevation and severity of CRS and may predict toxicity. The presentation can be difficult to differentiate from sepsis, and CRS-associated neutropenia and lymphopenia can predispose patients to opportunistic infection. Neurologic toxicities, including seizures, are also reported and may occur dyssynchronous to, or in the absence of, other CRS toxicity, suggesting a mechanism different from that associated with other CRS presentations.

Supportive management is paramount in CAR T-cell–associated CRS, and medications that may worsen toxicity should be avoided. Fever can be managed with acetaminophen and cooling blankets. Tocilizumab is an IL-6 receptor antagonist that has demonstrated efficacy in mitigating or resolving CRS toxicity after CAR T-cell infusion. Corticosteroids should be reserved for tocilizumab failure as they may inhibit the antineoplastic activity of CAR T cells. It is unclear if tocilizumab is beneficial in relieving neurotoxicity, and in such cases systemic corticosteroids, dexamethasone in particular, are the preferred treatment. The design of CAR T-cell therapies continues to evolve to improve antineoplastic activity and minimize systemic side effects. Some novel next-generation designs include suicide genes to stimulate CAR T-cell apoptosis in the presence of an administered prodrug.

Immune Checkpoint Inhibitors

Blockade of immunomodulation through the use of immune checkpoint inhibitors (ICIs), including antibodies CTLA-4 and programmed cell death protein 1 or its ligand, result in an enhanced immune response to combat cancer cells. ICIs have demonstrated improved survival in metastatic melanoma, lung cancer, and renal cancer. However, the augmented immune response also impairs self-tolerance and has been associated with a spectrum of side effects referred to as immune-related adverse events (irAEs). irAEs can involve any organ; however diarrhea, colitis, hepatitis, skin toxicities and endocrinopathies, hypothyroidism, and hypophysitis in particular, are common. Severe presentations, including intestinal perforation, fulminant hepatic failure, toxic epidermal necrolysis, and primary or secondary adrenal insufficiency, are rare. Pneumonitis is uncommon and neurologic complications are rare. However, severe presentations, including myasthenia gravis, Guillain-Barré syndrome, and posterior reversible leukoencephalopathy, have been reported. As with other complications from antineoplastic therapies, the dosage of ICI, time course to presentation, and histopathology may be helpful in distinguishing irAEs from other etiologies. Anti–programmed cell death protein 1 antibodies appear to have a different toxicity profile compared with anti–CTLA-4 antibodies, with less severe events. However, use of both agents in combination is associated with higher risk for irAEs generally and with more severe irAEs.

Management of irAEs depends on organ involvement and severity. In severe cases, cessation of ICIs and use of high-dose corticosteroids, or other immunosuppressants in refractory cases, should be considered. Hormone replacement alone may be sufficient in cases of isolated endocrinopathy.

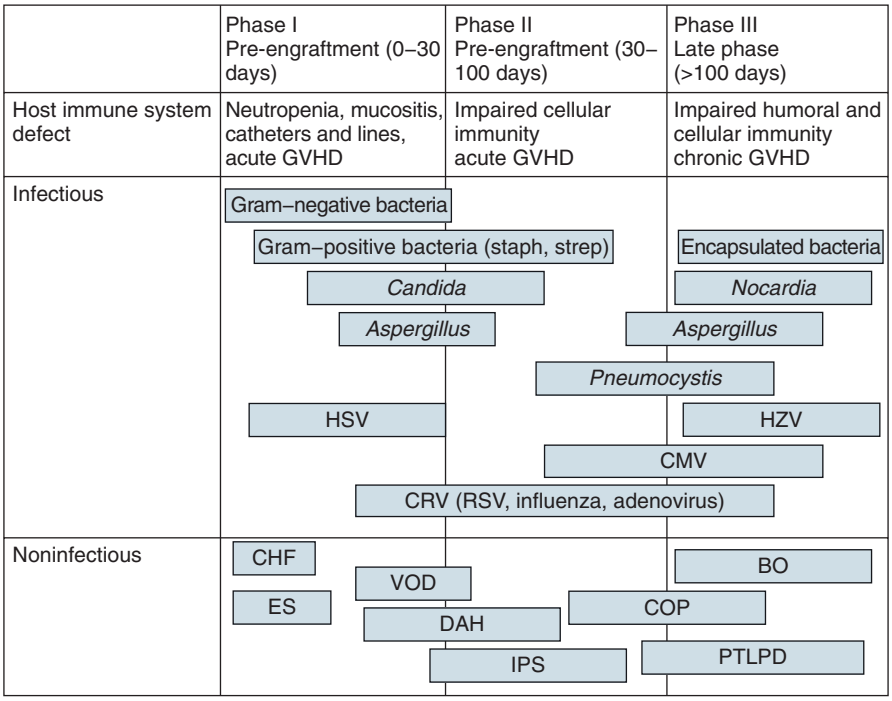
Delivery of Antineoplastic Therapy in the ICU

The delivery of chemotherapy to critically ill patients for life-threatening malignancy-related complications remains controversial. The benefits of antineoplastic therapy must be weighed against their potential to cause further harm in already vulnerable patients. Moreover, many aspects of the administration of antineoplastic therapies in the ICU setting, particularly dose adjustment in the setting of organ failure and the use of extracorporeal life support, and interactions with medications commonly used in the ICU, are not well defined.

Recent studies suggest that antineoplastic therapies can be given safely to select cancer patients with critical illness. In small-cohort studies of patients with predominantly hematologic malignancies admitted to an ICU with critical illness including respiratory failure and severe infection, the administration of chemotherapy was associated with survival rates approximating those seen among critically ill cancer patients in other studies.[39,40] Factors associated with increased mortality included older age, high disease severity scores, septic shock, the use of mechanical ventilation, and DIC. Disease status, severity of neutropenia, and infection at the time of chemotherapy initiation were not associated with ICU mortality.[39] Outcomes were likely biased by the selection of patients deemed to have life-extending therapeutic options before ICU admission, many of whom were treatment naïve and had good performance status, as first presentation of malignancy when receiving chemotherapy in the ICU may be protective.

Complications of Hematopoietic Stem Cell Transplantation

In addition to the life-threatening complications seen among other patients with cancer, HSCT recipients may face a number of complications unique to this form of cancer therapy. The hematopoietic cell donor, the source of progenitor cells, the preparative regimen, and the phase of host immune system dysfunction



• **Fig. 76.1** The timeline of pulmonary complications after hematopoietic stem cell transplantation. *BO,* Bronchiolitis obliterans; *CHF,* congestive heart failure; *CMV,* cytomegalovirus; *COP,* cryptogenic-organizing pneumonia; *CRV,* coronaviruses; *DAH,* diffuse alveolar hemorrhage; *ES,* engraftment syndrome; *GVHD,* graft-versus-host disease; *HSV,* herpes simplex virus; *HZV,* herpes zoster virus; *IPS,* idiopathic pneumonia syndrome; *PTLPD,* posttransplant lymphoproliferative disorder; *RSV,* respiratory syncytial virus; *VOD,* veno-occlusive disease. (From Chi AK, Soubani AO, White AC, et al. An update on pulmonary complications of hematopoietic stem cell transplantation. *Chest.* 2013;144:1913–1922.)

are important factors in determining the risk for complications (Fig. 76.1).[63]

Infectious Complications

The use of myeloablative regimens during preparation and the continued use of immunosuppressive therapies after HSCT results in delayed immune reconstitution and places patients at risk for infectious pneumonias by organisms that can be predicted by phase of immune recovery. During the neutropenic phase, pneumonias caused by gram-negative and gram-positive bacteria are common. In addition, skin and mucosal barriers are disrupted in the period after myeloablative chemotherapy, increasing the risk for aspiration pneumonia and septicemia from intestinal bacteria and *Candida* organisms. Invasive pulmonary aspergillosis is the most common invasive fungal infection among HSCT recipients and may be seen any time after HSCT.

Cellular immunity defects persist for months beyond engraftment while transplanted marrow and gamma globulin infusions provide temporary humoral immunity. Pneumonias from common respiratory viruses and *Pneumocystis jiroveci* pneumonia are seen during the postengraftment phase. During the late phase humoral and cellular immunity defects persist, and pneumonias from encapsulated bacteria, *Nocardia, Aspergillus,* and opportunistic viral infections may be seen until immune recovery.

Pulmonary Complications

Pulmonary complications are common in HSCT recipients and account for a substantial proportion of mortality. Contemporary studies suggest infectious pneumonias account for 68% of pulmonary complications during the first year, whereas noninfectious etiologies were responsible for 29% of complications.[41] Pulmonary complications may be distinguished by radiographic appearance and phase after transplantation; however, noninvasive testing and FB-BAL should routinely be used to identify specific etiologies of ARF. As with ARF in the non-HSCT cancer patient, treatment includes empiric broad-spectrum antimicrobials with de-escalation to organism-specific therapy when possible. Treatment for noninfectious conditions is supportive, with the additional use of immunosuppression in severe cases after excluding infectious etiologies.

Noninfectious Pulmonary Complications

Engraftment syndrome is a noninfectious inflammatory complication seen early after HSCT during neutrophil recovery before engraftment. Findings include fever, nonspecific pulmonary opacities suggestive of noncardiogenic pulmonary edema, and the appearance of an erythematous maculopapular rash. Skin biopsy may distinguish acute graft-versus-host disease (GVHD) from engraftment syndrome.

Diffuse alveolar hemorrhage (DAH) is an uncommon complication of HSCT but is associated with high mortality rates. It may present with patchy or diffuse opacities with air bronchograms on computed tomography imaging late before engraftment or early after engraftment, and hemoptysis is often absent. Progressively hemorrhagic return on sequential bronchoalveolar lavage from the same subsegment during FB-BAL and the presence of hemosiderin-laden macrophages on cytology are diagnostic. In addition to general supportive care, the use of antimicrobials when an infection is present, or immunosuppression, the treatment of DAH includes

blood product support and use of procoagulants such as antifibrinolytics (e.g., ε-aminocaproic acid) or recombinant factor VII.

Idiopathic pneumonia syndrome is a noninfectious complication characterized by clinical and radiographic features of multifocal pneumonia in the absence of lower respiratory tract infection on FB-BAL or lung biopsy. It typically occurs during the postengraftment phase after HSCT. Histology is nonspecific with findings of interstitial pneumonitis and diffuse alveolar damage. Even with appropriate therapy, disease progression in IPS is rapid and is associated with high long-term mortality.[42]

Acute Graft-Versus-Host Disease

Acute GVHD is a common multisystem complication of allogeneic HSCT that occurs when donor cells recognize the transplant recipient as foreign and initiate inflammatory pathways, leading to organ dysfunction within the recipient. Signs and symptoms typically occur around the time of white blood cell engraftment or after a reduction of immunosuppression and most commonly involve the skin, gastrointestinal tract, and liver.

Acute cutaneous GVHD typically begins with a maculopapular rash involving the neck, ears, shoulders, palms, and soles before becoming more generalized and confluent. In severe cases bullous lesions and lesions of the oral mucosa may develop, mimicking Stevens-Johnson syndrome or toxic epidermal necrolysis. Gastrointestinal GVHD usually presents with nonspecific signs of gastrointestinal upset, typically abdominal pain and diarrhea with or without hematochezia. The diarrhea is secretory, and in severe cases may exceed several liters daily. Hepatic GVHD usually presents with a cholestatic pattern on liver function tests, although patients may develop more severe clinical signs of cholestasis. Acute GVHD may be diagnosed clinically in the patient who presents with the triad of a stereotypical rash, diarrhea, and rising serum bilirubin around the time of engraftment; however, other etiologies for the isolated abnormities should be excluded. A definitive diagnosis of acute GVHD may be made by histologic examination of tissue from the gastrointestinal tract or liver. Findings on skin biopsy are nonspecific, and the diagnosis of acute cutaneous GVHD is challenging without the concomitant extracutaneous manifestations.

The severity of acute GHVD is defined by the degree of cutaneous, hepatic, and gastrointestinal involvement (Table 76.2). Treatment relies on the immunosuppression of donor cells through the use of glucocorticoids, methotrexate, and calcineurin inhibitors. High-volume IV fluid infusions may be necessary to account for substantial gastrointestinal and insensible fluid loss. Aggressive wound care may be necessary to prevent skin breakdown, limit insensible loss, and reduce the risk of infection.

TABLE 76.2 International Bone Marrow Transplant Registry Severity Index for Acute Graft-Versus-Host Disease

Index[a]	Extent of Rash	Total Bilirubin (μmol/L)	Volume of Diarrhea (mL/day)
A	<25%	<34	<500
B	25%–50%	34–102	550–1500
C	>50%	103–255	>1500
D	Bullae	>255	Severe pain and ileus

[a]Based on maximum involvement of any individual organ system.

From Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol.* 1997;97:855–864.

Hepatic Sinusoidal Obstruction Syndrome/ Veno-Occlusive Disease

Hepatic sinusoidal obstruction syndrome (SOS) is an uncommon complication of HSCT characterized by progressive injury to sinusoidal endothelial cells, leading to occlusion and then late sclerosis and fibrosis of hepatic venules and centrilobular hemorrhagic necrosis. It has also been described after use of chemotherapies among non-HSCT patients and may be due to hepatic toxicity from the preparative regimen rather than the HSCT. It typically presents early in the posttransplant period with fluid retention, followed by elevated liver function test results, hepatomegaly, and ascites. Severe cases may result in hepatorenal syndrome, hepatic encephalopathy, multiorgan failure, and death. New criteria for the diagnosis and grading of SOS have been proposed (Table 76.3). Additional testing may be required to exclude other causes. Liver biopsy is diagnostic but is often avoided owing to concurrent thrombocytopenia and coagulopathy.

Ursodeoxycholic acid and heparin may be used as prophylaxis for SOS. Supportive measures are recommended in all cases, whereas severe cases are associated with poor outcome and should be treated with defibrotide. Defibrotide stimulates the activity of fibrinolytic enzymes and is contraindicated in patients receiving anticoagulation or fibrinolytic therapies and in patients with significant active bleeding.

Triage of Cancer Patients for ICU Care

Multiple cohort studies demonstrate improved ICU, hospital, and 1-year survival rates among critically ill patients with cancer over the past 2 decades.[43] The general prognosis depends on the type of ICU admission and the type of cancer. Hospital mortality is higher for medical and emergency surgical patients than for patients with cancer scheduled for surgery[44] and higher among those with hematologic malignancies compared with solid tumors.[8,44] Survival among hematologic cancer patients has been improving in recent years.[45] This trend in improved survival is further reflected among mixed cohorts of patients admitted for neutropenic sepsis,[24] septic shock,[46,47] and ARDS.[17]

Although historically patients with cancer may have been denied access to ICU care given their poor prognosis, recent trends of improved survival suggest refusal of care based on cancer alone can no longer be justified. Moreover, risk factors traditionally associated with poorer outcome, including cancer type and neutropenia, are no longer considered significant factors in determining ICU mortality.[48–50] Rather, poor performance status, recurrent or progressive malignancy, and the degree of organ dysfunction have been confirmed as predictors of mortality in several studies across a variety of populations.[24,47–54]

Moreover, delayed admission to the ICU has been associated with worsened outcomes, suggesting that early admission to the ICU is crucial to prevent or ameliorate further organ dysfunction.[55] Although predictive models have been developed and applied to cancer patients with critical illness, none have been sufficiently validated to guide in triage for ICU admission. In addition, whether overall trends in survival are due to real improvements in ICU care or better ICU triage is unclear. More recently organizational

TABLE 76.3 Diagnosis and Grading of Sinusoidal Obstructive Syndrome[62]

Diagnosis

Classical SOS Within first 21 days after-HCT	Late-onset SOS ≥21 days after HCT
Bilirubin ≥2 mg/dL and 2 of the following: • Painful hepatomegaly • Weight gain >5% • Ascites	Classical SOS beyond day 21 OR Histologically proven SOS OR Two or more of the following: • Bilirubin ≥2 mg/dL • Painful hepatomegaly • Weight gain >5% • Ascites AND Hemodynamic or ultrasound evidence of SOS

Severity Grading[a,b]

	Mild	Moderate	Severe	Very Severe[b]
Time since diagnosis (days)	>7	5–7	≤4	Any
Bilirubin (mg/dL)	2–3	3–5	5–8	≥8
Bilirubin kinetics			×2 within 48 h	
Transaminases	≤2× normal	2–5× normal	5–8× normal	>8× normal
Weight increase	<5%	5%–10%	5%–10%	≥10%
Renal function	<1.2× baseline	1.2–1.5× baseline	1.5–2× baseline	≥2× baseline

[a]Grading based on meeting two or more criteria.
[b]Presence of multiorgan dysfunction is classified as very severe.
HCT, hematopoietic stem cell transplantation; *SOS,* sinusoidal obstructive syndrome.
From Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51:906–912.

characteristics, such as the implementation of protocols and presence of clinical pharmacists in the ICU, and close collaboration between oncologists and ICU teams, have been shown to be independently associated with lower mortality and a more efficient resource unit.[56]

Given the overall improved mortality among critically ill cancer patients and the importance of early intervention to prevent further deterioration, as well as the absence of reliable predictors of outcome beyond performance status or disease progression, some authors suggest critically ill cancer patients receive unrestrained access to ICU care. Others have advocated for an "ICU trial" approach, whereby the patient trajectory is considered in the decision to continue full intensive care. Among patients who are not bedridden or for whom palliative care is not the only cancer treatment option, organ failure scores on day 6 of ICU admission may be more accurate in predicting hospital survival than scores on admission.[57] Those who remain critically ill with persistent or increasing organ dysfunction after a trial of ICU care have a significantly higher mortality. Although the results support delayed prognostication of patients with cancer and critical illness, additional multicenter studies are needed to confirm these results.

Palliative, Ethics, and End-of-Life Care Issues

Although the recent outcomes for critically ill cancer patients admitted to the ICU have improved, the overall ICU mortality and hospital mortality rates remain high. Furthermore, the overall long-term survival of cancer patients after ICU discharge remains uncertain, with some contemporary studies demonstrating 13% to 43% survival at 1 year. There is also conflicting evidence regarding the quality of life of ICU cancer survivors.

Ideally triage decisions upon referral to the ICU and reassessments regarding the continuation of intensive care[57] should take into account the expected short-term mortality as well as long-term mortality and quality of life. When a patient's declining medical condition is deemed irreversible or quality of life is expected to be poor, a change from restorative care to end-of-life care should be offered. A recent study showed that early palliative care significantly reduced ICU use at the end of life; however, it did not change patients' experiences within the ICU, such as number of procedures, code status, length of stay, or disposition.[58]

Infrequently, ethical issues or conflicts arise in the care of critically ill cancer patients. Ethics consultations in an oncologic ICU often involve disagreements between the patients' surrogates and the ICU team regarding end-of-life care, including proposed limitations and/or withdrawal of life-sustaining interventions. We find that ethics consultations are helpful in resolving seemingly irreconcilable differences between our ICU team and the patients' surrogates in the majority of cases. Ethics consultation also facilitated the increased provision of palliative care and chaplaincy services for patients and their surrogates at the end of life.[59]

Summary

Intensive care of patients with cancer requires an understanding of the broad and complex disorders unique to these patients as a consequence of their malignancy or its treatment, in addition to the pathologies seen among patients without cancer. A multidisciplinary and collaborative approach to care that incorporates patient values and oncologic prognosis and treatment options in the ICU is crucial. Early identification of patients who are most likely to benefit from ICU care through early intervention, including diagnostic testing, respiratory and hemodynamic support, early administration of effective antibiotics, and other measures to treat cancer and mitigate comorbidities, can improve outcomes such as short- and long-term mortality. Recognition of patients who are unlikely to benefit from initial or continued restorative care is also an important part of high-quality critical care and may improve equally important outcomes, such as patient comfort, relief from unnecessary suffering, and improved quality and length of remaining life through the initiation of end-of-life care.

Key Points

- A cancer diagnosis should not preclude ICU care. Poor performance status, recurrent or progressive malignancy, and severe degrees of organ dysfunction are associated with increased mortality.
- Acute respiratory failure is the most common reason for ICU admission in patients with cancer. Noninvasive testing offers diagnostic yield comparable to that of invasive testing.
- Recent studies suggest no benefit for the use of early noninvasive positive-pressure ventilation compared to standard oxygen among patients with hematologic malignancies and isolated hypoxemic respiratory failure.
- Early identification of infectious etiologies, risk stratification, administration of appropriate antimicrobial therapy, and source control are key components of management in patients with febrile neutropenic sepsis.
- Tumor lysis syndrome is associated with hyperkalemia, hyperphosphatemia, and hyperuricemia in the setting of tumor cell breakdown. Treatment includes hydration, hypouricemic agents, and the mitigation of additional contributions to acute kidney injury.
- Hypercalcemia is the most common metabolic abnormality in patients with cancer. Bisphosphonates are essential in the treatment of hypercalcemia of malignancy, in addition to intravenous hydration and the short-term use of calcitonin.
- Cytokine release syndrome and immune-related adverse events are potentially severe multisystem complications of novel biologic cancer therapies (e.g., CAR T cells).
- Infectious and noninfectious complications of hematopoietic stem cell transplantation can be predicted by the phase of host immune recovery. Infectious pneumonias account for the majority of pulmonary complications.
- Acute graft-versus-host disease is commonly associated with allogeneic stem cell transplantation and typified by nonspecific skin, gastrointestinal tract, and liver involvement around the time of engraftment.
- Recognition of patients with cancer who are unlikely to benefit from initial or continued restorative care in the ICU is an important part of high-quality critical care. Early palliative care significantly reduces ICU use at the end of life.

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Review Questions

1. A 66-year-old male is transferred to the intensive care unit (ICU) with acute respiratory failure associated with persistent fevers to 39.3°C and a dry cough for 2 days. The patient was diagnosed 6 months earlier with osteosarcoma of the thoracic spine for which he underwent T1 to T3 posterolateral resection of epidural tumor with high-grade T2 spinal cord compression and posterior segmental fixation of C7 to T4 followed by adjuvant chemotherapy with cisplatin and doxorubicin, the last dose of which he received through his tunneled central venous catheter 9 days before this ICU admission. Pertinent medical history includes coronary artery disease status post–drug-eluting stents to mid-left anterior descending artery and diagonal branch 10 years ago and hypertension. On ICU admission, his chest radiograph reveals bilateral diffuse patchy opacities. Laboratory data show a white blood cell count of 100/μL (0.1×10^9/L), hemoglobin of 7 g/dL, platelet count of 9×10^3/μL (9×10^9/L), blood urea nitrogen level of 29 mg/dL, creatinine 1.8 mg/dL, and procalcitonin level of 20.1 ng/mL. He required intubation and mechanical ventilation and was treated with intravenous meropenem and blood transfusions. Which of the following organisms is most likely to result in positive blood cultures in this patient?

a. *Corynebacterium jeikeium*
b. *Staphylococcus aureus*
c. *Propionibacterium acnes*
d. *Aspergillus fumigatus*

Answer: b. Fever in neutropenic patients is defined as a single oral temperature of 38.3°C (101°F) or higher or a temperature of 38.0°C (100.4°F) or higher sustained over a 1-hour period. Neutropenia is usually defined as an absolute neutrophil count (ANC) less than 1500 cells/μL, and severe neutropenia is usually defined as an ANC less than 500 cells/μL or an ANC that is expected to decrease to less than 500 cells/μL over the next 48 hours. Low-risk patients are those who are expected to be neutropenic (ANC <500 cells/μL) for 7 days or longer and those with no comorbidities or evidence of significant hepatic or renal dysfunction. High-risk patients are those who are expected to be neutropenic (ANC <500 cells/μL) for >7 days. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk, regardless of the duration of neutropenia. Gram-positive cocci have become the most common pathogens isolated in blood cultures in patients with febrile neutropenic sepsis. These include *Staphylococcus epidermidis* (the most common), *S. aureus*, and streptococci. Less common gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp., *Leuconostoc* spp., *Lactobacillus* spp., *Propionibacterium acnes*, and *Rhodococcus* spp. *Aspergillus* spp. rarely become positive in blood cultures. In addition to intravenous antibiotics, early catheter removal is recommended in neutropenic patients with sepsis and in patients with endocarditis, septic thrombosis, or with persistent culture positivity.

77

Critical Care Medicine in Pregnancy

STEPHEN E. LAPINSKY

CHAPTER OUTLINE

Physiologic Changes in Pregnancy

Critical Care Management
- General Care
- Radiologic Procedures and Fetal Risk
- Drug Therapy in Pregnancy
- Fetal Oxygenation and Monitoring
- Ventilatory Support
- Cardiopulmonary Resuscitation

Pregnancy-Specific Conditions ICU Care
- Preeclampsia
- HELLP Syndrome
- Acute Fatty Liver of Pregnancy
- Amniotic Fluid Embolism
- Obstetric Hemorrhage
- Peripartum Cardiomyopathy
- Tocolytic Pulmonary Edema
- Gestational Trophoblastic Disease

Conditions Not Specific to Pregnancy
- Septic Shock
- Acute Respiratory Distress Syndrome in Pregnancy
- Pulmonary Thromboembolic Disease
- Asthma
- Cardiac Disease
- Trauma

Management of the critically ill pregnant patient is a situation with which few intensive care physicians gain significant expertise. The usual clinical approach may be altered by the physiologic changes induced by pregnancy, by the relatively uncommon pregnancy-specific conditions, and by perceived limitations on therapy produced by the presence of a fetus (Fig. 77.1).

Physiologic Changes in Pregnancy

The pregnant woman undergoes a number of physiologic changes affecting various systems relevant to critical care management. From a respiratory perspective, the upper airways develop edema and hyperemia, which may be relevant during endotracheal intubation. Changes in lung volumes occur, with a 10% to 25% decrease in functional residual capacity (FRC), whereas total lung capacity decreases only minimally as the thoracic cage widens to compensate.[1] Forced expiratory volume in 1 second (FEV_1) is not altered by the pregnant state. Lung compliance remains unchanged, but chest wall and total respiratory compliance are reduced.[2]

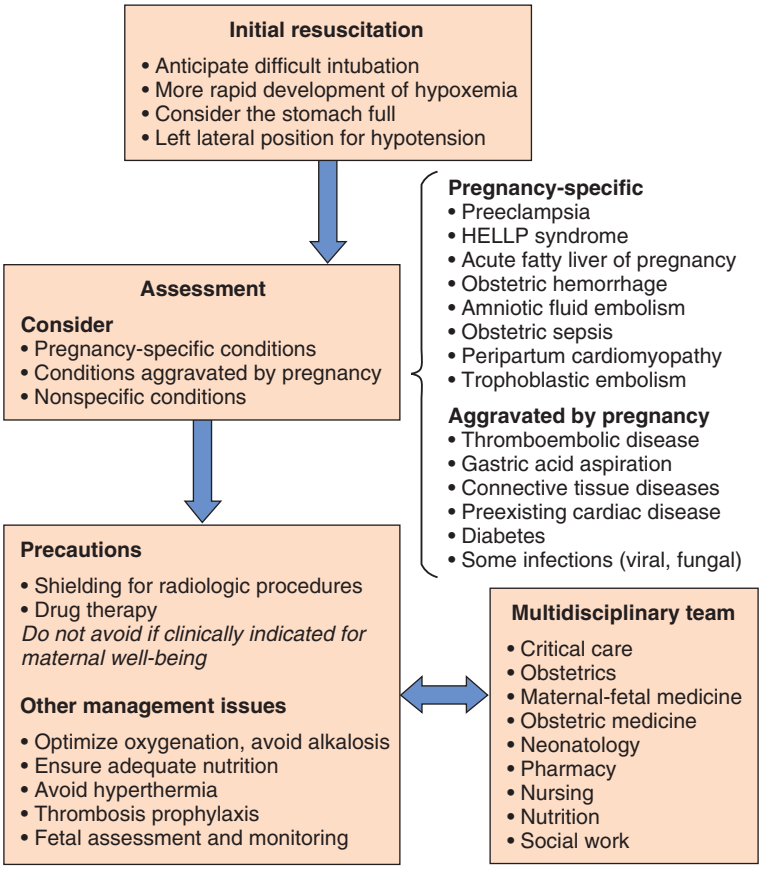
The rising progesterone level stimulates an increase in ventilation. Tidal volume and minute ventilation increase from the first trimester, reaching 20% to 40% above baseline by term (Table 77.1).[3] A mild respiratory alkalosis is produced with compensatory renal excretion of bicarbonate (partial pressure of arterial carbon dioxide [$PaCO_2$] 28–32 mm Hg; bicarbonate [HCO_3^-] 18–21 mEq/L). Oxygen consumption increases because of the demands of the fetus and maternal metabolic processes, reaching levels up to 33% above baseline by term. Arterial partial pressure of oxygen (PO_2) remains normal throughout pregnancy, but mild hypoxemia caused by an increased alveolar-arterial oxygen tension difference may develop in the supine position as FRC diminishes near term.

Maternal blood volume and cardiac output increase through pregnancy, reaching a peak at 30% to 50% above baseline levels by about 28 weeks (Fig. 77.2).[4] Hemodynamic measurements by pulmonary artery catheter in the near-term patient demonstrate increased cardiac output, with a reduced systemic vascular resistance and pulmonary vascular resistance (see Table 77.1).[5] During labor and continuing into the immediate postpartum period, cardiac output is further augmented by the return of 300 to 500 mL of blood to the central circulation.[6]

Oxygen delivery to the fetus is dependent on the maternal arterial oxygen content and the uterine blood flow. Maternal hypotension, alkalosis (e.g., hyperventilation), and endogenous or exogenous catecholamines can vasoconstrict the uterine artery and adversely affect fetal oxygenation.[7] Uterine blood flow is also reduced transiently by uterine contractions. Although umbilical venous blood returning to the fetus has a relatively low oxygen tension, a high oxygen content is maintained by the left shift of the oxygen dissociation curve of fetal hemoglobin.

Glomerular filtration rate increases early in pregnancy, reaching a value 50% above prepregnancy levels in the second trimester, and remains elevated throughout pregnancy (see Fig. 77.2).[8] The normal serum creatinine level is therefore in the range of 0.5 to 0.7 mg/dL (45–60 µmol/L). As pregnancy progresses, mild uteric dilation and mild hydronephrosis may occur as a result of uterine compression and smooth muscle relaxation.

Pregnancy is associated with a reduced lower esophageal sphincter pressure, reaching a nadir at 36 weeks. The position of the stomach is displaced, further decreasing the effectiveness of the gastroesophageal sphincter and reducing gastric emptying. The pregnant woman should therefore always be considered at risk



• **Fig. 77.1** Approach to the assessment and management of the critically ill obstetric patient. *HELLP, H*emolysis, elevated *l*iver enzymes, *l*ow *p*latelets.

TABLE 77.1 Physiologic Changes in Late Pregnancy

Parameter	Change
Respiratory	
Functional residual capacity	Decreased 10%–25%
Minute ventilation	Increased 20%–40%
Arterial partial pressure of oxygen	No change
Arterial partial pressure of carbon dioxide	Reduced to 28–32 mm Hg
Serum bicarbonate	Reduced to 18–21 mEq/L
Cardiac	
Heart rate	Increased 10%–30%
Pulmonary capillary wedge pressure	No change
Cardiac output	Increased 30%–50%
Systemic vascular resistance	Decreased 20%–30%
Pulmonary vascular resistance	Decreased 20%–30%
Renal	
Glomerular filtration rate	Increased 50%
Creatinine	Decreased (24–68 µmol/L; 0.29–0.77 mg/dL)

for aspiration of stomach contents, regardless of the time elapsed since her last meal.

The increase in plasma volume is associated with a lesser increase in red blood cell mass causing a physiologic anemia, with a hematocrit of 32% to 34% by the third trimester. A mild leukocytosis occurs with the white blood cell count rising further during labor. Platelet counts are usually unchanged, although a condition of benign mild thrombocytopenia may occur.[9] Procoagulant factors rise, contributing to the hypercoagulable state of pregnancy. The erythrocyte sedimentation rate rises related to increased levels of plasma globulins.

Critical Care Management

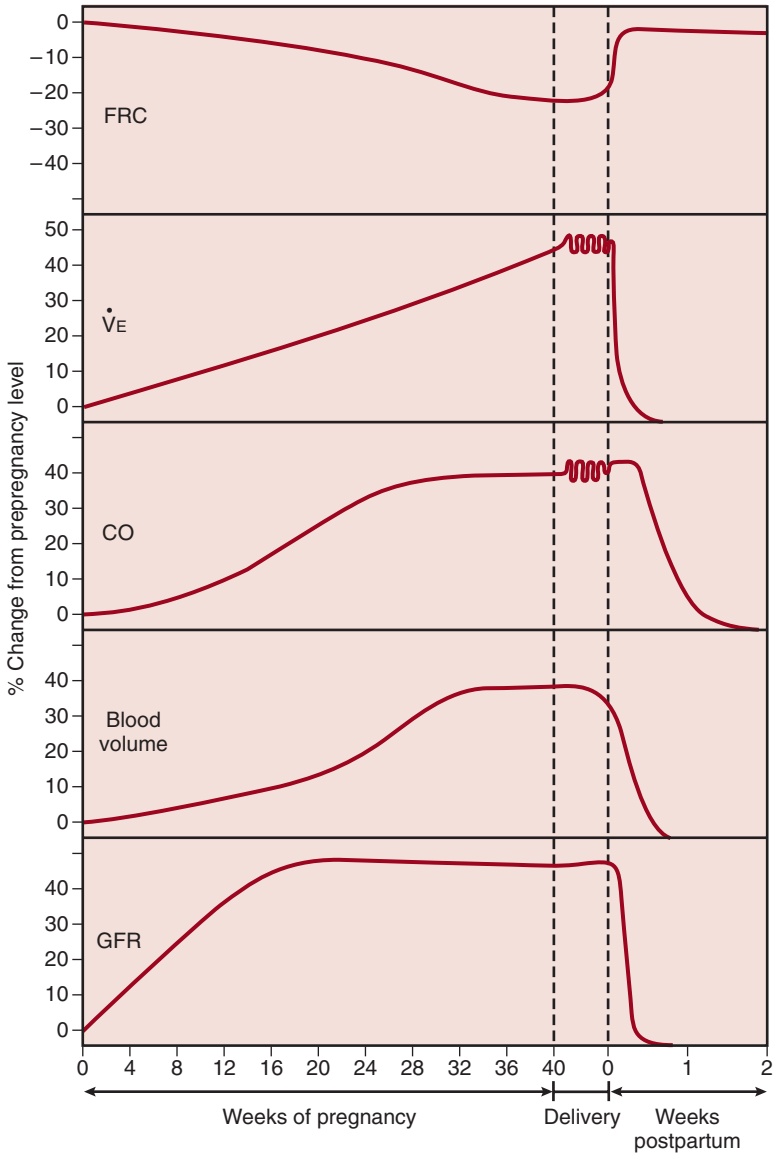
General Care

Positioning

In the supine position the gravid uterus produces mechanical effects on the vena cava and aorta, reducing central venous return. This results in a decrease in cardiac output and hypotension. This "supine hypotensive syndrome" should be considered in hemodynamically unstable patients.[10] Pregnant patients should be positioned on their left side, or at least with the right hip slightly elevated.

Nutrition

During starvation, maternal body stores are protected at the expense of the fetus and inadequate nutrition may result in intrauterine growth retardation and fetal loss. Growth restriction before 26 weeks' gestation may lead to fetal neurologic impairment. Caloric requirements in pregnancy increase by about 300 kcal/day, and protein intake should be augmented by 20% to 50%. Several nutrients have an increased requirement in pregnancy, including iron, folate, and calcium. Total parenteral nutrition has been used successfully to provide nutritional support during pregnancy in



• **Fig. 77.2** Graphic representation of some of the physiologic changes occurring in pregnancy. *CO,* Cardiac output; *FRC*, functional residual capacity; *GFR,* glomerular filtration rate; $\dot{V}_E$, minute ventilation. (From Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. *Am J Respir Crit Care Med.* 1995;152:427–455.)

patients in whom enteral nutrition is not possible. The blood glucose level should be measured frequently in view of the predisposition to hyperglycemia.

Thrombosis Prophylaxis

Pregnancy increases the risks of venous thrombosis caused by hypercoagulability and venous stasis. Antithrombotic measures including physical interventions and heparin prophylaxis should be considered.

Radiologic Procedures and Fetal Risk

Radiologic investigations are often essential for the assessment and management of the critically ill pregnant patient. Although there are potential risks of exposing the fetus to ionizing radiation, fetal well-being depends on maternal recovery and appropriate radiologic procedures should not be avoided. Techniques such as shielding the abdomen with lead and using a well-collimated x-ray beam can effectively reduce exposure. With these precautions, estimated fetal radiation exposure can be limited to safe levels for most procedures, although investigations such as abdominal-pelvic computed tomography (CT) will obviously cause significant fetal radiation exposure (Table 77.2).[11]

The adverse effects of fetal exposure to radiation include oncogenicity and teratogenicity. A twofold increased risk of childhood leukemia may result from fetal exposure in the range of 20 to 50 mGy (2–5 rad). Most intensive care unit (ICU) procedures can be performed well below these levels of exposure to the fetus (see Table 77.2). Teratogenicity does not appear to occur at these radiation doses, requiring radiation exposure greater than 50 to 100 mGy (5–10 rad). Every effort should nonetheless be made to minimize uterine exposure, particularly in the first trimester.

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TABLE 77.2 Risk of Fetal Radiation Exposure Resulting from Radiologic Studies in the Critically Ill Pregnant Patient

Investigation	Fetal Radiation Exposure (mGy) (1 mGy = 0.1 rad)
Chest radiograph (with abdomen shielded)	0.01
Ventilation-perfusion scan	
Perfusion	0.1–5
Ventilation	0.1–0.4
CT pulmonary angiogram	0.5–4
CT pelvis and abdomen	10–50
Radiation effect on the fetus:	
Teratogenicity	50–100
Oncogenicity	20–50

CT, Computed tomography.

Drug Therapy in Pregnancy

Pharmacotherapy during pregnancy requires consideration of the altered drug clearance, metabolism and volume of distribution of drugs in pregnancy, and the potential pharmacologic and teratogenic effects on the embryo. A detailed description of drug therapy in pregnancy is beyond the scope of this chapter. Consultation with an obstetrician and pharmacist is essential, and several excellent resources are available.[12,13] Some common ICU drugs are discussed briefly in the following sections.

Catecholamines

Catecholamines commonly used in the ICU, such as dobutamine, dopamine, norepinephrine, and epinephrine, all have the potential to reduce uterine blood flow. Both ephedrine and phenylephrine boluses are used for transient hypotension induced by neuraxial anesthesia.[14] Nonpharmacologic maneuvers such as volume replacement and left lateral positioning are essential to the management of hypotension, and the rapidity of correction of blood pressure may be more important than the specific inotropic agent used. If vasopressor infusion therapy is required to support maternal hemodynamics, this therapy should not be withheld because of concerns for potential adverse effects on the fetus.

Sedation, Analgesia, and Neuromuscular Blockade

Few data exist on the preferred drugs for prolonged sedation, analgesia, or neuromuscular blockade in pregnancy. Benzodiazepine use in early pregnancy has been associated with a small risk of congenital malformations, mainly cleft lip and palate. Midazolam crosses the placenta to a lesser degree than diazepam, which can accumulate in the fetus at levels greater than in the mother. Propofol has been used as an induction agent for cesarean section, but a single case report describes the development of non–anion gap acidosis in two pregnant women receiving propofol infusion for neurosurgical procedures.[15] Congenital malformations have not been demonstrated with use of narcotic analgesics, such as morphine, meperidine, and fentanyl. The majority of nondepolarizing neuromuscular blocking agents have been shown to cross the placenta, including pancuronium, vecuronium, and atracurium, but transfer is unlikely to have clinical effects on the fetus in the short term. The current approach of minimizing sedation in the ICU patient is clearly advantageous to the fetus. However, if sedative or paralyzing agents are used in the pregnant woman, this information must be communicated to the neonatologist, who should anticipate the need for ventilatory support for the fetus.

Antibiotics

Antibiotic regimens similar to those used in the nonpregnant patient are appropriate, with some precautions. Quinolones are sometimes avoided because of the potential risk of arthropathy. Tetracyclines produce adverse effects on fetal teeth and bone, and aminoglycosides and sulfonamides should be used with caution.

Fetal Oxygenation and Monitoring

Attention to interventions aimed at optimizing fetal oxygenation is important in the management of any critically ill pregnant patient. Depending on gestational age, delivery of the fetus may be the most appropriate intervention. Uteroplacental oxygen delivery can be optimized by increasing oxygen-carrying capacity—by blood transfusion, improving maternal cardiac output, and optimizing maternal oxygenation. The simple maneuver of tilting the patient to the left lateral position to increase cardiac output should always be considered.[10]

Continuous electronic monitoring of fetal heart rate (FHR) can be used to identify changes in fetal physiology. Abnormal patterns of FHR have been described with good sensitivity but varying specificity for fetal distress. Fetal tachycardia may occur in the presence of maternal infection or chorioamnionitis, but fetal bradycardia or sinusoidal variation in FHR is more ominous, suggesting fetal hypoxia. Changes in FHR occur in response to uterine activity. Early decelerations coinciding with contractions are benign, but late decelerations beginning beyond the peak in contraction and persisting after the contraction may indicate fetal compromise, particularly if associated with a reduced beat-to-beat variation. Fetal compromise may occur as a result of uteroplacental or fetal pathology but may also indicate maternal illness with reduced uterine oxygen delivery. The fetus may be further assessed by an ultrasound biophysical profile that evaluates factors such as spontaneous movement, breathing action, and amniotic fluid volume. A normal biophysical profile carries a good prognosis.

Ventilatory Support

Noninvasive Ventilation

Noninvasive ventilation avoids the adverse effects of endotracheal intubation, such as airway trauma, the increased risk of nosocomial pneumonia, and the complications associated with sedation. This modality is ideally suited to short-term ventilatory support, which is the case in many obstetric complications that reverse rapidly. The major concern with mask ventilation in pregnancy is the potential risk of aspiration because of the increased intra-abdominal pressure, delayed gastric emptying, and reduced lower esophageal sphincter tone accompanying pregnancy. Noninvasive ventilation should therefore be reserved for the patient who is alert, protecting her airway, and who has an expectation of a relatively brief requirement for mechanical ventilatory support.

Airway Management

Failed intubation is more common in the obstetric population than in other anesthetic intubations.[16] The reduced oxygen reserve

caused by diminished functional residual capacity and increased oxygen consumption produces rapid desaturation in response to apnea or hypoventilation.[17] Preoxygenation with 100% oxygen is beneficial, but respiratory alkalosis must be avoided. In view of the delayed gastric emptying and elevated intra-abdominal pressure, the pregnant patient should always be considered to have a full stomach and appropriate precautions should be taken. Upper airway hyperemia and edema may reduce visualization and necessitate use of a smaller endotracheal tube. The risk of bleeding is increased and nasal intubation should be avoided.

Mechanical Ventilation

The normal $PaCO_2$ of about 30 mm Hg in late pregnancy should be considered in the interpretation of arterial blood gas values when decisions are made to institute ventilatory support. Data on the prolonged mechanical ventilation of pregnant patients are limited. Hyperventilation should be avoided because this adversely affects uterine blood flow[18] because of the resulting alkalemia and the effect of positive-pressure ventilation in reducing cardiac output. The current ventilatory approach of avoiding excessive lung stretch by pressure limitation and permissive hypercapnia has not been assessed in pregnancy. The usual pressure limits (e.g., plateau pressure of 30 cm H_2O) may not be applicable in the near-term patient, where chest wall compliance is reduced. Transpulmonary pressures may not be elevated at a plateau pressure of 30 cm H_2O, and higher ventilatory pressures may be acceptable in pregnant patients near term. Although late pregnancy is associated with a mild respiratory alkalosis, maternal hypercapnia up to 60 mm Hg in the presence of adequate oxygenation does not appear to be detrimental to the fetus.[19] Maternal hypercapnia and respiratory acidosis may produce fetal acidosis, but this does not have the same ominous implications as fetal acidosis owing to lactic acidosis resulting from fetal hypoxia.[20] However, acidosis produces a right shift of the hemoglobin oxygen dissociation curve that may negate the beneficial oxygen-carrying characteristics of fetal hemoglobin. If marked respiratory acidosis results from permissive hypercapnia, treatment with bicarbonate may improve maternal and fetal acidemia.

It may be considered that, because of the effects of pregnancy on respiratory physiology, delivery of the pregnant patient will result in improvement in the mother's respiratory status.[21] Limited case series addressing this issue have not found a significant benefit to the mother, and delivery carries a risk of harm.[22,23] Improvement in oxygenation may occur in some patients, but without improvement in respiratory system compliance or reduction in positive end-expiratory pressure level.[22] Delivery is therefore not indicated purely in the hope of improving "maternal condition." If the fetus is considered viable but is at risk because of severe maternal hypoxia, consultation with a neonatologist may identify a benefit to delivery of the fetus. Obstetric indications should always determine the mode of delivery.

Cardiopulmonary Resuscitation

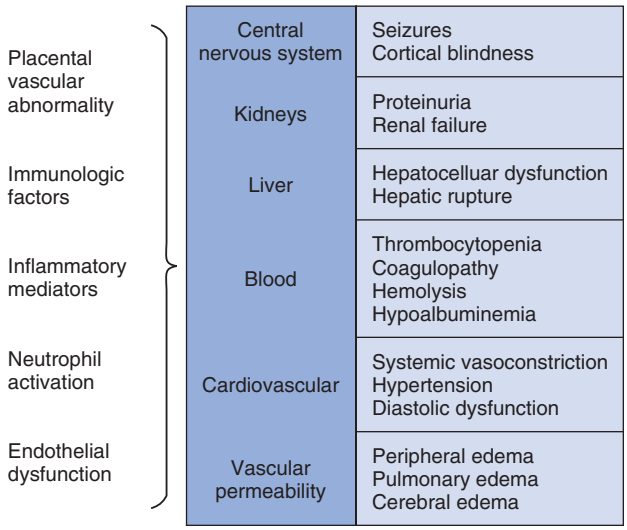
Cardiopulmonary resuscitation requires only minor modifications from standard protocols.[24] Intravenous (IV) access should be established above the diaphragm owing to potentially impeded inferior vena caval blood flow. Electrical cardioversion and defibrillation may be performed in pregnancy, but fetal monitoring leads should be removed to prevent electrical arcing. Management in the supine position may cause aortocaval compression, resulting in impaired venous return and inadequate cardiac output. Manual displacement of the uterus to the left should be used in preference to a left lateral tilt, which may impede cardiac compressions. Appropriate pharmacologic therapy should not be withheld if clinically indicated. Perimortem cesarean section may benefit the mother and save the fetus when initial attempts at resuscitation have failed in a woman with a fetus at a potentially viable gestation (e.g., uterine fundus above the umbilicus). Data suggest that infant survival without neurologic sequelae is highest if the postmortem cesarean section is initiated within 4 minutes of cardiac arrest, aiming for delivery within 5 minutes of arrest.

Pregnancy-Specific Conditions Requiring ICU Care

Preeclampsia

Preeclampsia is a pregnancy-induced condition that usually occurs after 20 weeks' gestation, characterized by hypertension and proteinuria.[25] The cause remains unknown but is likely related to a placental abnormality producing a diffuse maternal endothelial effect, which leads to vasospasm and reduced organ perfusion (Fig. 77.3). Preeclampsia and its complications account for 20% to 50% of obstetric admissions to the ICU.[26–28] Less common multisystem diseases should be considered in the differential diagnosis, including systemic lupus erythematosus (SLE), thrombotic thrombocytopenic purpura (TTP), and hemolytic-uremic syndrome (HUS) (Table 77.3). Complications of preeclampsia may result in critical illness, including pulmonary edema, cerebral edema, renal failure, hypertensive crisis, seizures (eclampsia), and the HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets) with microangiopathic hemolytic anemia, thrombocytopenia, and hepatic involvement.[29]

The only specific treatment is delivery of the fetus and placenta. Delivery is always in the best interest of the mother, but timing may depend on fetal maturity. The role of antihypertensive therapy is to prevent maternal hypertensive complications and it does not alter the natural history of the condition or benefit the fetus.[30] Commonly used agents include IV hydralazine or labetalol, as well as oral calcium antagonists.[25] Rapid reduction in blood pressure should usually be avoided because of the risk of reducing uteroplacental perfusion. Magnesium sulfate is used for seizure prophylaxis and treatment, giving an initial IV bolus (2–4 g) followed by an



• **Fig. 77.3** Pathophysiology and multiorgan effects of preeclampsia.

TABLE 77.3 Differential Diagnosis of Pregnancy-Related Complications

Clinical Finding	TYPE OF COMPLICATION	
	Pregnancy-Specific	Nonspecific
1. Hypertension	Preeclampsia	Essential hypertension Secondary hypertension (renal, pheochromocytoma)
2. Thrombocytopenia	Preeclampsia HELLP syndrome Acute fatty liver of pregnancy	TTP ITP Sepsis SLE
3. Abnormal liver enzymes	Preeclampsia HELLP syndrome Acute fatty liver of pregnancy Cholestasis of pregnancy	Viral hepatitis Drug-induced hepatitis Budd-Chiari syndrome
4. Renal dysfunction	Preeclampsia Acute fatty liver of pregnancy Idiopathic postpartum renal failure	Sepsis Hypovolemia/hemorrhage TTP/HUS SLE
5. Pulmonary edema	Preeclampsia Peripartum cardiomyopathy Tocolytic pulmonary edema Amniotic fluid emboli	Valvular heart disease Ischemic heart disease ARDS Aspiration

ARDS, Acute respiratory distress syndrome; *HELLP, h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets; *HUS,* hemolytic-uremic syndrome; *ITP,* idiopathic thrombocytopenic purpura; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

infusion of 1 to 3 g/h. Toxic magnesium levels may occur (>3.5 mmol/L), particularly in the presence of renal dysfunction, producing respiratory muscle weakness and cardiac conduction defects. Hypocalcemia may be noted during magnesium infusion and should not routinely be corrected because this would negate the therapeutic effects of magnesium. Fluid management in preeclampsia usually requires careful volume expansion, but excessive fluid administration can cause pulmonary or cerebral edema.

HELLP Syndrome

The HELLP syndrome is a condition associated with preeclampsia, characterized by the development of a microangiopathic hemolytic anemia and a consumptive thrombocytopenia.[29] Reduced hepatic perfusion results in periportal and focal parenchymal necrosis, elevated liver enzymes, and rarely, hepatic hemorrhage or rupture. The clinical presentation is often with epigastric or right upper quadrant pain, nausea, vomiting, or evidence of bleeding. Features of preeclampsia do not occur in all patients, and approximately 30% of patients with HELLP develop the disease only in the postpartum period.

The diagnosis is based on the presence of thrombocytopenia ($<100 \times 10^9$/L), with a moderate elevation of liver enzymes, and microangiopathic hemolytic anemia (increased lactate dehydrogenase, bilirubin, abnormal blood smear). Many patients are found to have a more widespread coagulation defect than just thrombocytopenia. The white blood cell count may be elevated, and hypoglycemia is uncommon, in contrast to acute fatty liver of pregnancy.

Management includes early delivery if the fetus is viable, blood product support, and management of associated preeclampsia. Dexamethasone initiated before delivery has been reported to produce more rapid recovery of thrombocytopenia in some studies, but this was not confirmed in a more recent study.[31,32] Delivery may require platelet support, and if cesarean section is necessary, hemorrhage should be anticipated and adequate drains should be inserted. Epidural anesthesia is usually contraindicated in the presence of thrombocytopenia.

The maternal complications of HELLP include hemorrhage, acute respiratory distress syndrome (ARDS), and acute renal failure. An uncommon but catastrophic consequence of the HELLP syndrome is hepatic subcapsular hemorrhage, which occurs in about 2% of patients and can progress to hepatic rupture. Hepatic rupture should be considered in any preeclamptic patient with sudden shock or acute abdominal pain. Management requires aggressive hemodynamic and blood product support, urgent delivery, and invasive control of the hemorrhage with embolization or laparotomy with packing of the liver. Hemorrhage without rupture may be managed conservatively if the patient remains hemodynamically stable.

Significant overlap exists between HELLP and other multisystem conditions and thrombotic microangiopathies (see Table 77.3). A response to plasmapheresis may be noted in some patients, possibly representing those with TTP or HUS rather than HELLP. Plasmapheresis is recommended for patients with delayed postpartum resolution when severe thrombocytopenia, hemolysis, or organ dysfunction persists more than 72 hours after delivery. The maternal mortality for women with HELLP syndrome is reported between 1% and 3% (with isolated reports as high as 25%) and with a significant perinatal mortality at 8% to 60%.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is an uncommon condition affecting about 1 in 15,000 pregnancies. Although early reports described acute fulminant hepatic failure with a high maternal and

fetal mortality rate, the condition is now usually recognized at an earlier stage, allowing early delivery and a significantly improved outcome.[33] Maternal mortality has been reported at 0% to 18% with fetal loss of 23% to 60%. The etiology of this condition is unknown, but an association with a fetal inborn error of metabolism (L-CHAD [long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency]) has been described.[34] Pathologically, diffuse fatty infiltration of the liver occurs with necrosis and inflammation being mild or absent.

Patients usually present toward the end of the third trimester with a range of onset from as early as 30 weeks' gestation up until the puerperium. Prodromal symptoms of malaise, anorexia, and vomiting may precede the onset of jaundice by 1 to 2 weeks. Abdominal pain may occur, which may be diffuse or localized to the right upper quadrant. Laboratory investigations demonstrate a moderate elevation in transaminase levels (e.g., 300–600 units), in contrast with the higher levels occurring in acute hepatitis. The white blood cell count is often elevated and thrombocytopenia and fragmented red blood cells may be demonstrated. Features of hepatic dysfunction, such as hypoalbuminemia, hypoglycemia, and coagulopathy, occur in more severe cases.

The differential diagnosis of liver disease in pregnancy is wide, and the multisystemic effects of AFLP may resemble SLE, TTP, or HUS (see Table 77.3).

The definitive treatment is delivery of the fetus, and early recognition of this condition is responsible for an improved outcome. Because the presentation is usually close to term, the decision is usually easy and carries little additional risk for the fetus. However, AFLP is associated with placental insufficiency because of fibrin deposition, producing increased fetal loss. It has been reported that this process may be exacerbated by therapeutic coagulation factor replacement. Supportive therapy is similar to that for other causes of fulminant hepatic failure, including correction of coagulation abnormalities and hypoglycemia. Hepatic encephalopathy requires attention to airway protection, dietary protein restriction, bowel sterilization, and oral or rectal lactulose administration. Transient worsening of hepatic function may occur after delivery with improvement usually beginning within 2 to 3 days. A small subset of patients continues to experience deterioration after delivery, and liver transplantation may be indicated. Complications, such as hemorrhage, pancreatitis, renal failure, diabetes insipidus, and infection, should be sought and treated.

Amniotic Fluid Embolism

Amniotic fluid embolism is a catastrophic cardiopulmonary complication of pregnancy, carrying a mortality rate of 10% to 86%.[35] It usually occurs in association with labor and delivery but may be precipitated by uterine trauma or manipulations. Amniotic fluid enters the venous circulation and particulate contents or humoral factors produce acute pulmonary hypertension, as well as acute left ventricular dysfunction.[36] The pregnant woman develops sudden onset of dyspnea, hypoxemia, and cardiovascular collapse. The presenting feature may sometimes be seizures related to cerebral hypoxia, or acute fetal hypoxia and distress. Many patients with amniotic fluid embolism die within the first hour. No specific diagnostic test is available, and the diagnosis of amniotic fluid embolism is based on a typical clinical picture and exclusion of other conditions, such as septic shock, pulmonary thromboembolism, abruptio placentae, tension pneumothorax, or a myocardial ischemic event. Recently low levels of C1 esterase inhibitor have been demonstrated in patients with amniotic fluid embolism, suggesting both a new diagnostic and therapeutic option.[37]

Treatment involves routine resuscitative and supportive measures including mechanical ventilation and inotropic therapy. A role for corticosteroids has been suggested on the basis of the hypothesis that the process may involve an anaphylactoid reaction to amniotic fluid contents.[35] Survivors of the initial process may develop disseminated intravascular coagulopathy and ARDS. Neurologic damage caused by the initial hypotension and hypoxemia is common.

Obstetric Hemorrhage

Uterine blood flow reaches 600 mL/min near term, subjecting the pregnant patient to the risk of devastating blood loss. Antepartum hemorrhage occurs from disruption of the placenta, such as with placental abruption or a low-lying placenta (placenta previa) as the cervix dilates. Most hemorrhage occurs postpartum (postpartum hemorrhage) because of uterine atony, cervical or vaginal lacerations, related to antepartum hemorrhage, or associated with coagulopathy. The pregnant woman is physiologically prepared for blood loss and tolerates the loss from a normal vaginal delivery (600 mL) or cesarean section (1000 mL). However, excessive blood loss results in hypovolemic shock with compromise to fetus and maternal vital organs. The pregnant woman is particularly susceptible to hypoperfusion injury to the kidney. A high incidence of myocardial ischemia has been noted in pregnant women with hemorrhagic shock.

Supportive management of obstetric hemorrhage is similar to any cause of hemorrhage and involves rapid volume replacement, supplemental oxygen administration, and red blood cell and blood product support for an associated dilutional coagulopathy. Various pharmacologic agents are used to control uterine bleeding. Intramuscular administration of methylergonovine (0.2 mg) promotes uterine contractions and may be useful in the presence of uterine atony but is contraindicated in the presence of hypertension.[38] Oxytocin also facilitates uterine contraction and is infused intravenously in a dose greater than that used for augmentation of labor, up to 50 to 100 mU/min (e.g., 20 to 40 U in 1000 mL normal saline solution at 150 mL/h). This dose may produce an antidiuretic effect and cause hyponatremia. A prostaglandin $F_{2\alpha}$ analog (carboprost tromethamine [Hemabate]) given intramuscularly (0.25 mg, repeated every 15–90 minutes to maximum 2 mg) or intramyometrially is effective in controlling hemorrhage.[38,39] Side effects include vomiting, hypertension, bronchoconstriction, and increased intrapulmonary shunt.[40] Tranexamic acid, an antifibrinolytic agent, may have a role in the management of postpartum hemorrhage with an IV dose of 1 g within 3 hours of delivery, and repeated once if bleeding continues.[40] Intrauterine balloon devices may be placed to tamponade bleeding, with a high success rate.[41] Antibiotic prophylaxis is often given while the balloon is in place and analgesia is essential.

Isolated reports suggest that recombinant factor VIIa may be useful in the management of severe obstetric hemorrhage.[42] If the previous methods fail to control bleeding, radiologic transcatheter embolization of the internal iliac or uterine artery is usually effective.[43] Surgical exploration with arterial ligation or hysterectomy may become necessary.

Peripartum Cardiomyopathy

Cardiac failure may occur in the absence of preexisting heart disease because of peripartum cardiomyopathy. This idiopathic condition presents in the last month of pregnancy or within 5 months of

TABLE 77.4 Differential Diagnosis of Acute Respiratory Distress in Pregnancy

Disorder	Distinguishing Features
Pregnancy-Specific	
Amniotic fluid embolism	Cardiorespiratory collapse, seizures, DIC
Pulmonary edema secondary to preeclampsia	Hypertension, proteinuria
ARDS secondary to obstetric sepsis	Evidence of obstetric sepsis, shock
Tocolytic pulmonary edema	Tocolytic administration, rapid improvement
Peripartum cardiomyopathy	Gradual onset, cardiac gallop, cardiomegaly
Trophoblastic embolism	Nodular infiltrate, molar pregnancy
Risk Increased by Pregnancy	
Aspiration pneumonitis	Vomiting, aspiration
Venous thromboembolism	Evidence of DVT, positive V̇/Q̇ scan, leg Doppler, CT angiogram
Pneumomediastinum	Occurs during delivery, subcutaneous emphysema
Valvular heart disease	Pulmonary edema, cardiac murmur, cardiomegaly
ARDS secondary to sepsis	Evidence of sepsis (e.g., pyelonephritis)
Unrelated to Pregnancy	
Asthma	Features similar to nonpregnant patient
Pneumonia	Features similar to nonpregnant patient

ARDS, Acute respiratory distress syndrome; *CT,* computed tomography; *DIC,* disseminated intravascular coagulopathy; *DVT,* deep venous thrombosis; *V̇/Q̇*, ventilation-perfusion.

delivery, with an incidence of approximately 1 in 3500 live births.[44] The clinical presentation is usually after 36 weeks' gestation (in contrast to women with preexisting cardiac disease) and involves the gradual onset of symptoms of heart failure. The diagnosis is by the demonstration of left ventricular systolic dysfunction and by the exclusion of other causes of cardiomyopathy. During labor and the early postpartum period, tachycardia and increased cardiac output may precipitate acute pulmonary edema.

Treatment is similar to that of other patients with cardiac failure, although angiotensin-converting enzyme inhibitors should be avoided before delivery. Anticoagulation is essential because of the hypercoagulable state of pregnancy and the high incidence of thrombotic complications. A subset of patients may have an inflammatory myocarditis, and immunosuppressive therapy may be considered in those who do not improve after 2 weeks of standard treatment.[44] Although a high mortality rate has been described (10%–50%), about half of patients recover normal ventricular function.[45]

Tocolytic Pulmonary Edema

β-Adrenergic blockers can be used to inhibit uterine contractions in preterm labor, although this is less frequently used because studies demonstrated a lack of fetal benefit from this practice. A complication of this β-agonist therapy in pregnancy is the development of acute pulmonary edema.[46] Treatment involves discontinuing the β-agonist and supportive treatment including diuresis and oxygen therapy. Failure of the pulmonary edema to resolve within 24 hours should prompt a search for an alternative diagnosis (Table 77.4).

Gestational Trophoblastic Disease

Pulmonary hypertension and pulmonary edema may occur in the setting of benign hydatidiform mole, as a result of trophoblastic pulmonary embolism. This most commonly occurs during evacuation of the uterus, with a higher incidence of pulmonary complications in the woman later in pregnancy.[47] With supportive treatment resolution occurs within 48 to 72 hours. A molar pregnancy (hydatiform mole) occurs as a noncancerous tumor that develops in the uterus. Instead of a normal pregnancy, the uterus is filled with a cystic mass. Molar pregnancy may rarely develop into a choriocarcinoma, which can produce multiple, discrete, pulmonary metastases.

Conditions Not Specific to Pregnancy

Septic Shock

Changes occur in the immune status in pregnant women, facilitating tolerance to paternally derived fetal antigens. An altered T helper 1/T helper 2 (TH1/TH2) balance occurs, with the maternal immune response favoring humoral immunity (TH2 response), and suppressing cell-mediated immunity (TH1 response), which could be harmful to the fetus.[48] This altered immune response may predispose pregnant women to increased incidence or severity of certain infections, including *Listeria monocytogenes* infection, disseminated herpesvirus infections, varicella, and coccidioidomycosis infections. Human immunodeficiency virus infections should always be considered. Obstetric sepsis in the antepartum period produces chorioamnionitis, but most obstetric sepsis occurs in the postpartum period. The most common location of infection is the placental site, causing endometritis, which can spread to a peritonitis. Episiotomy sites or cesarean section wounds may also become infected. Infections often involve a mixed flora, with microorganisms originating from the vagina (e.g., anaerobes, group B streptococci), intestine (gram-negative organisms, enterococci, anaerobes), sexual transmission (e.g., *Neisseria gonorrhoeae*), or hematogenous spread (e.g., *Listeria*, group A streptococci).[49]

Management of septic shock is similar to that in the nonpregnant patient, with prompt resuscitation with volume expansion. If inotropic therapy is necessary in the antepartum patient, the effects of such drugs on uteroplacental perfusion should be considered. Adequate specimens for culture should be obtained including amniocentesis in the antepartum patient. Ultrasonography may be valuable to identify a source of localized infection and exclude retained products of conception.

Initial empiric antibiotic therapy should provide broad gram-negative, gram-positive, and anaerobic cover. Common regimens use drugs such as ampicillin, gentamicin, and clindamycin; ampicillin/sulbactam; ticarcillin/clavulanate; piperacillin and gentamicin; or carbapenems.[50] Urgent delivery may be required for management of chorioamnionitis with sepsis syndrome.

A poor response to antibiotic therapy may indicate a resistant organism (e.g., *Enterococcus*), a localized abscess, myometrial microabscesses, or septic pelvic thrombophlebitis. Gas in the subcutaneous tissues or uterine wall suggests clostridial gas gangrene. Patients with retained products or devitalized tissue are at significant risk. Toxic shock caused by *Staphylococcus aureus* or *Clostridium*

sordellii may occur, often associated with septic abortion. Surgical evacuation of the uterus or laparotomy with debridement or even hysterectomy may be required. Puerperal ovarian vein thrombophlebitis may complicate endometritis, presenting with acute deterioration with fever. The diagnosis can be confirmed with CT or magnetic resonance imaging scanning, and treatment requires anticoagulation and antibiotic therapy. Surgical intervention with venous ligation or excision may be required.

Group A streptococcal necrotizing fasciitis and toxic shock syndrome have been reported to occur unexpectedly after an uncomplicated pregnancy and delivery.[51] Management includes antibiotic therapy with penicillin and clindamycin and early surgical intervention. IV immunoglobulin (2 g/kg over 1 to 3 days) may be beneficial.

Acute Respiratory Distress Syndrome in Pregnancy

The pregnant patient is at risk of developing acute lung injury from pregnancy-associated complications and other conditions (see Table 77.4).[52] The pregnant patient appears to be at increased risk of developing pulmonary edema because of the cardiovascular changes, the reduced albumin level occurring in pregnancy, increased capillary leak, and possibly an upregulation of components of the acute inflammatory response.

Management is similar to that in the nonpregnant patient. Adequate maternal oxygenation is essential for fetal well-being, and in some situations delivery may benefit the mother and the fetus.[53] Survival from ARDS is as good as or better than that in the general population, likely because of these patients' young age, lack of comorbidity, and the reversibility of many of the predisposing conditions.

Pulmonary Thromboembolic Disease

Pulmonary thromboembolism is a leading cause of maternal mortality. Although the risk is significantly increased in pregnant women because of increased coagulation factors, hormonally mediated venous stasis, and local pressure effects, the incidence is relatively low at about 1 per 1000 deliveries. Pulmonary embolism occurs most frequently in the early postpartum period.

Investigation of suspected pulmonary embolism is not different from that in the nonpregnant patient, with duplex ultrasound as the initial investigation. False-positive results may occur with Doppler alone because of venous obstruction by the gravid uterus. Ventilation-perfusion scanning and CT pulmonary angiography can be performed with low risk of fetal radiation exposure (see Table 77.2).[11]

Warfarin is generally avoided in pregnancy because of the risk of a first-trimester embryopathy and central nervous system abnormalities with second- and third-trimester exposure. Heparin does not cross the placenta and can be readily reversed, and low–molecular-weight heparins are safe and effective in pregnancy although less easy to reverse acutely.[54] Thrombolysis has been used successfully in pregnancy but should be limited to life-threatening situations. Transvenous inferior vena caval filters have been used in the pregnant patient, although there is a risk of dislodgment because of venous dilation and pressure effects.

Asthma

The hormonal changes of pregnancy can affect asthma variably, with worsening, improvement, or no substantial change occurring. Asthma is a common condition, and acute asthmatic attacks are therefore an important cause of respiratory compromise in pregnancy. In assessment of the patient with a severe acute attack, the reduced $PaCO_2$ occurring in late pregnancy should be considered; a normal $PaCO_2$ level associated with acidosis may imply respiratory failure. Treatment is similar to that in the nonpregnant patient, including β-agonists and corticosteroids. Although there is a natural reluctance to prescribe drug therapy in these patients, pregnancy is not an absolute contraindication to systemic corticosteroid therapy.[55] Uncontrolled asthma is more dangerous to the fetus than appropriate drug therapy, and management should highlight the importance of adequate oxygenation.

Cardiac Disease

Overt or occult preexisting heart disease may produce acute cardiac decompensation as the blood volume and cardiac output increase during pregnancy. Women with prior cardiac events, cyanotic disease, or pulmonary hypertension are at particular risk. Patients with mitral and aortic stenosis are at risk of developing hemodynamic deterioration as the physiologic changes peak at about 28 weeks, but mild to moderate regurgitant valvular disease is generally well tolerated.[56] The onset of atrial fibrillation or severe hypertension can precipitate sudden hemodynamic deterioration even in those women with less severe cardiac disease.

Patients with moderate to severe mitral stenosis are likely to experience hemodynamic deterioration during the third trimester or during labor. Treatment is similar to the nonpregnant patient using digoxin and β-blockers to control heart rate and diuretics to reduce left atrial pressure.[57] Angiotensin-converting enzyme inhibitors should be avoided. Most patients with mitral stenosis can undergo vaginal delivery with consideration to invasive hemodynamic monitoring during labor and the early postpartum period. Epidural anesthesia is usually better tolerated hemodynamically than general anesthesia during labor and delivery. Electrical cardioversion can be performed safely if indicated.

Severe aortic stenosis is associated with significant risk during pregnancy,[57] with symptoms such as dyspnea, angina, or syncope appearing from late in the second trimester. Percutaneous aortic balloon valvuloplasty can be performed during pregnancy. Spinal and epidural anesthesia during labor may adversely affect hemodynamics because of the vasodilatory effects.

Ischemic heart disease is uncommon in pregnancy but may be missed because of masking of the symptoms, signs, and cardiac enzyme levels by pregnancy. Coronary artery dissection may occur, particularly in the immediate postpartum period. Aortic dissection may occur related to hypertension, aortic coarctation, or Marfan syndrome and is associated with significant maternal and fetal mortality.[58]

Woman with cyanotic congenital heart disease, particularly those with associated pulmonary hypertension, are at significant risk during pregnancy. Because of the inability of the right ventricle to tolerate the increases in cardiac output, primary or secondary pulmonary hypertension is associated with a high mortality rate in pregnancy.[59] New specific treatments are now available, and although clinical trials in pregnancy are lacking, mortality appears to be decreasing to some degree.[60] Vasodilators such as prostacyclin (inhaled or IV) or inhaled nitric oxide, as well as phosphodiesterase-5 inhibitors such as sildenafil, have been used successfully in pregnancy.[61,62] Endothelin receptor antagonists (e.g., bosentan) are avoided because of potential teratogenicity, and anticoagulation is recommended for most patients. Patients with pulmonary

hypertension should be managed in a center with expertise and experience in this area.

Trauma

The anatomic and physiologic changes of pregnancy may alter the manifestations and severity of traumatic injury. Uterine injury can produce severe hemorrhage because of the high uterine blood flow and may precipitate placental abruption or rarely, uterine rupture. Uterine rupture manifests with maternal shock, abdominal pain, and palpable fetal parts. Penetrating injury to the abdomen predominantly affects the uterus in later pregnancy, but because intra-abdominal viscera are compressed in the upper abdomen, minor injury may result in significant damage.[63] Fractures of the pelvis can produce severe retroperitoneal hemorrhage because of dilation of pelvic veins.

Maternal trauma is associated with a significant increase in fetal loss owing to maternal shock or hypoxia, placental injury, or direct fetal injury.[64] Direct fetal injury resulting from blunt trauma usually involves head injury related to maternal pelvic fracture. Other fetal injuries may occur after blunt or penetrating trauma, sometimes with minimal maternal injury. A high fetal mortality occurs in the presence of maternal burns to greater than 30% of the body surface area. Placental abruption is an important cause of fetal demise,[63] and may present with vaginal bleeding, abdominal cramps, uterine tenderness, amniotic fluid leakage, and unexplained fetal distress or maternal hypovolemia. Placental abruption is often complicated by disseminated intravascular coagulopathy owing to release of thromboplastin into the maternal circulation.

Evaluation of the pregnant trauma patient should include a detailed abdominal examination, but physical signs may be affected by changing organ position and the reduced peritoneal sensitivity that occurs in pregnancy.[65] Initial investigations should include blood type, including Rh status. Ultrasound is useful for evaluation of the fetus for injury and biophysical profile, and to assess intra-abdominal organ damage. Ultrasound-guided paracentesis or diagnostic peritoneal lavage (by open technique, above the uterus) may aid in detecting bowel perforation or intraperitoneal hemorrhage. Transplacental hemorrhage of fetal blood into the maternal circulation may occur and can result in fetal exsanguination and maternal Rh sensitization. Fetomaternal hemorrhage is detected by the Kleihauer-Betke test, which identifies fetal cells in the maternal blood smear, and can estimate the volume of fetal hemorrhage by the percentage of red blood cells of fetal origin. Fetal evaluation includes heart rate assessment by auscultation (possible from 20 weeks) or Doppler probe. Obstetric consultation and continuous fetal cardiotocography are important when the fetus is at a viable gestation.

Care of the severely injured pregnant patient requires a multidisciplinary approach involving the emergency physician, trauma surgeon, obstetrician, intensivist, and neonatologist. Initial resuscitation follows usual principles with efforts directed primarily at stabilizing the mother's condition. Fluid replacement may need to be given more rapidly than in nonpregnant women because of the physiologic increase in plasma volume, and maternal blood pressure and heart rate may not be reliable predictors of the degree of hemorrhage.[65] Left lateral positioning to prevent supine hypotensive syndrome is an important consideration in the hypotensive patient. Rh-negative mothers with abdominal trauma should receive Rh immune globulin even in the presence of a negative Kleihauer-Betke test. Higher doses of Rh immune globulin are necessary in the presence of significant fetomaternal hemorrhage.

In the unstable mother, management of maternal injuries takes precedence over fetal distress because correction of maternal hemodynamics is beneficial to the fetus. The fetus is extremely vulnerable to hypotension and hypoxemia, and uterine blood flow will be markedly reduced when maternal circulation is compromised. If the mother's condition is stable, cesarean section may be appropriate if the fetus is considered viable, the limits of viability being largely dependent on the level of neonatal care available.

Key Points

- The reduced FRC and increased oxygen consumption in pregnancy result in rapid oxygen desaturation during apnea or intubation.
- Although there is a risk to the fetus from radiologic procedures and drug therapy, necessary investigations and treatment should not be withheld, with appropriate precautions.
- The various pregnancy-specific conditions should be considered in the differential diagnosis of a critically ill pregnant woman, including preeclampsia, HELLP syndrome, acute fatty liver of pregnancy, and amniotic fluid embolism.
- Hypotension may occur in the supine position in late pregnancy because of aortocaval compression—the clinician should position the hypotensive pregnant patient in the left lateral position.
- Management of preeclampsia, the commonest cause of ICU admission, involves delivery of the fetus, seizure prophylaxis with magnesium sulfate, correction of fluid balance, and treatment of hypertension if clinically significant.

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Review Questions

1. Which one of the following is an expected change in maternal respiratory physiology?
   - **a.** A 40% increase in respiratory rate
   - **b.** A compensated respiratory alkalosis
   - **c.** Reduced airflow (forced expiratory volume in 1 second [FEV_1]) as pregnancy progresses
   - **d.** Increased alveolar to arterial oxygen tension difference (P_{AO_2}-Pa_{O_2})
   - **e.** A decrease in diaphragmatic function

   Answer: b. Increased ventilation occurs as a result of central stimulation by progesterone and is mediated by an increased tidal volume rather than increased respiratory rate. This results in a compensated respiratory alkalosis. FEV_1 and P_{AO_2}-Pa_{O_2} are not affected by pregnancy and diaphragmatic function remains unchanged.
2. Which of the following is true regarding the investigation and treatment of pulmonary thromboembolic disease in pregnancy?
   - **a.** Radioisotope ventilation-perfusion scan in contraindicated.
   - **b.** Ultrasound of the legs has no role owing to a high false-positive rate.
   - **c.** Empiric treatment is usually preferable to diagnostic tests to minimize fetal harm.
   - **d.** Low–molecular-weight heparin (LMWH) is the default treatment of choice.
   - **e.** Computed tomography (CT) contrast angiography exposes the fetus to unacceptably high radiation levels.

   Answer: d. Investigation of pulmonary thromboembolic disease in pregnancy involves either ventilation-perfusion scan or CT contrast angiography, both of which have an acceptably low radiation exposure to the fetus. Although Doppler ultrasound may have an increased false-positive rate, compression ultrasound remains a useful and safe diagnostic test. Empiric anticoagulation likely carries more risk than diagnostic procedures, and the treatment of choice is LMWH.
3. Which of the following statements is incorrect regarding respiratory infections in pregnancy?
   - **a.** Bacterial pneumonia in pregnancy is caused by the same organisms as in the nonpregnant patient.
   - **b.** Alterations in cell-mediated immunity predispose the pregnant women to increased severity of certain respiratory infections.
   - **c.** Pregnant women should receive influenza vaccination.
   - **d.** Treatment of tuberculosis in pregnancy may include isoniazid, rifampin, and ethambutol.
   - **e.** Acyclovir therapy is contraindicated for the treatment of varicella pneumonia in pregnancy.

   Answer: e. Bacterial pneumonia is caused by the same organisms as in nonpregnant patients. Altered cell-mediated immunity predisposes to more severe influenza and varicella infection, mandating the use of influenza vaccination during pregnancy. Triple-drug therapy of tuberculosis with isoniazid, rifampin, and ethambutol is accepted in pregnancy. Acyclovir should be used in the treatment of severe varicella infection and may reduce mortality—it is not contraindicated.
4. Which of the following statements is true regarding cardiac arrest in pregnancy?
   - **a.** Cardiopulmonary resuscitation (CPR) should be performed with the woman in a 30-degree left lateral tilt position.
   - **b.** Perimortem cesarean section should be initiated at 4 minutes if the fetus is full term.
   - **c.** Defibrillation should be performed only with anteroposterior pads to avoid fetal harm.
   - **d.** Survival is worse than in nonpregnant patients owing to the cardiorespiratory physiologic changes of pregnancy.
   - **e.** Hypoxemia is an important cause, and early intubation when hypoxemia is present is advised.

   Answer: e. CPR is less effective at a 30-degree tilt and the uterus is preferably manually displaced to the left, while the woman remains supine during CPR. Perimortem cesarean section should be performed at any gestation over about 20 to 24 weeks (uterine height above the umbilicus) and not just at term. No changes to usual defibrillation are required due to pregnancy, and the survival is better than in nonpregnant patients (at about 58%). Pregnant women develop hypoxemia more rapidly than nonpregnant women, and early attention to oxygenation is warranted.
5. Which of the following statements is true regarding the management of respiratory failure in pregnancy?
   - **a.** Delivery does not always improve the maternal respiratory function.
   - **b.** Tidal volume needs to be adjusted for the increased maternal weight.
   - **c.** Ventilation to low partial pressure of arterial carbon dioxide (Pa_{CO_2}) levels is optimal for fetal well-being.
   - **d.** Oxygen saturation measurement is not reliable in pregnancy.
   - **e.** Noninvasive ventilation is contraindicated in pregnancy.

   Answer: a. Delivery does not necessarily improve respiratory function in women with respiratory failure. The precise tidal volume and blood gas targets during pregnancy remain unclear. Tidal volume is usually based on ideal body weight, a function of height, so unaffected by maternal weight gain in pregnancy. Low Pa_{CO_2} levels are potentially harmful to the fetus by causing uterine vasoconstriction. Oxygen saturation should not be unreliable in pregnancy and noninvasive ventilation is not contraindicated in the awake and alert pregnant patient.
6. Which of the following statements is *false* regarding obstetric hemorrhage?
   - **a.** The average blood loss from a cesarean delivery is 1 L.
   - **b.** Tranexamic acid is contraindicated because of the high risk of thromboembolism in pregnancy.
   - **c.** Inflatable balloon devices may be used to tamponade the uterus.
   - **d.** Oxytocin infusion may be complicated by hyponatremia.
   - **e.** Radiologic transcatheter embolism may avoid the need for surgical intervention.

   Answer: b. The average blood loss from a cesarean delivery is usually given as approximately 1 L. Inflatable balloon devices (e.g., Bakri balloon) are effective in tamponading the uterus and reducing blood loss. Oxytocin, related to its similarity with vasopressin, may cause hyponatremia in high doses. Embolism by interventional radiology is commonly used to stop bleeding and avoid surgical intervention. The World Maternal Antifibrinolytic Trial (WOMAN) demonstrated a reduction in death owing to bleeding by the early (<3 hour) administration of tranexamic acid.

78

Nutrition Support

RICHARD G. BARTON

CHAPTER OUTLINE

Malnutrition

Starvation Versus Stress Metabolism
- Carbohydrate Metabolism in Critical Illness
- Fat Metabolism in Critical Illness
- Protein Metabolism in Critical Illness

Indications for Nutrition Support

Goals of Nutrition Support

Nutrition Support in Critical Illness
- Calories
- Carbohydrate
- Fat
- Protein
- Electrolytes, Vitamins, and Trace Elements

Route and Timing of Administration
- Trophic Feeding

Types of Nutritional Formulas
- Organ-Specific Enteral Formulas
- Immunomodulating Enteral Formulas

Nutritional Assessment and Monitoring
- Complications of Nutrition Support

Malnutrition

Malnutrition is a disorder in body composition in which inadequate macronutrient (protein, carbohydrate, and fat) or micronutrient (vitamins, minerals, and trace elements) intake results in decreased body mass, reduced organ mass, and most important, decreased organ function. Although malnutrition is most frequently associated with a risk for immune dysfunction-related infection, wound healing/fascial dehiscence, and breakdown of surgical anastomoses, it can affect virtually all organ systems when severe. Skeletal muscle wasting, decreased myocardial mass, diastolic cardiac dysfunction and decreased sensitivity to inotropic agents, respiratory insufficiency/need for prolonged mechanical ventilation, renal cortical atrophy, and loss of gastrointestinal absorptive/barrier functions have all been associated with malnutrition.

Malnutrition can occur as a result of combined protein-calorie deficiency (marasmus), predominantly protein deficiency (kwashiorkor), and deficiencies in specific micronutrients, as well as altered metabolism arising from a disease state such as sepsis, burns, or trauma. Critically ill patients may be affected by a combination of these causes. Malnutrition is thought to be present in as many as 25% to 50% of patients on hospital admission and may affect an additional 25% to 30% of patients during their hospital stay. The National Surgical Quality Improvement Program has shown preoperative serum albumin, a measure of chronic nutritional status, to be an independent predictor of mortality risk in a study of more than 400,000 surgical patients and specifically in patients undergoing colectomy, proctectomy, transurethral resection of bladder tumors, and major lung resection.[1–4] Malnutrition becomes particularly important in critically ill patients, in whom the combination of bed rest and catabolic illnesses, such as sepsis, multiple trauma, burns, pancreatitis, and acute respiratory distress syndrome (ARDS), hasten the malnutrition, loss of lean body mass, and organ system dysfunction.

The purpose of this chapter is to contrast starvation and stress metabolism with emphasis on protein, carbohydrate, and fat metabolism; review the basic concepts of nutrition support with regard to energy and substrate requirements; discuss routes of nutrition support; provide an overview of organ-specific nutrition and immunonutrition; briefly summarize nutritional assessment and monitoring; and discuss the complications of nutrition support and their prevention.

Starvation Versus Stress Metabolism

Starvation is a clinical situation that develops whenever nutrient supply is inadequate to meet nutrient demand. It is characterized by a specific metabolic adaptive response aimed at preserving lean body mass, as well as by decreased energy expenditure, utilization of alternative fuel sources, and reduced protein wasting. During the initial 12 to 24 hours of starvation, glycogen is the primary oxidative fuel source. Thereafter gluconeogenesis increases temporarily and glucose synthesized from amino acids becomes the primary fuel source for the production of "obligate" glucose for use by tissues such as the brain and, to some degree, the liver and skeletal muscle. Over time, gluconeogenesis decreases as these organs adapt to ketone bodies as the primary oxidative fuel source, and in the fully adapted starved state, fatty acids, ketones, and glycerol become the primary fuel source in all tissues except the brain and red blood cells. The respiratory quotient (i.e., the ratio of carbon dioxide produced to oxygen consumed) is 0.6 to 0.7 as a result of the use of fat as the primary fuel source. Ultimately, rates of net protein catabolism and ureagenesis are decreased, relative to the fed state, during starvation. From a clinical perspective, it is important to understand that the metabolic response to starvation is reversible with feeding.

Stress metabolism is a generalized response whereby energy and substrate are mobilized to support inflammation, immune function,

TABLE 78.1 Starvation Versus Stress Hypermetabolism

Characteristic	Starvation	Hypermetabolism
Energy expenditure	Decreased	Increased
Respiratory quotient	Low (0.7)	High (0.85)
Response to feeding	+++	+
Mediator activation	+	+++
Primary fuels	Fat	Mixed
Gluconeogenesis	+	+++
Proteolysis	+	+++
Protein synthesis	+	++
Ureagenesis/urinary urea nitrogen	+	+++
Ketone formation	++++	+

and tissue repair. It occurs in response to a variety of stimuli, such as sepsis, multiple trauma, burns, pancreatitis, bone marrow transplantation, and major surgery. This mobilization of energy and substrate occurs at the expense of lean body mass. It is driven by endocrine hormones, such as cortisol, glucagon, and catecholamines, as well as by a multitude of inflammatory mediators. The stress response is often related to some degree of perfusion deficit (shock) and resultant microcirculatory injury. Clinically, the response is characterized by increased energy expenditure and increased oxygen consumption. The stress response is further characterized by hyperglycemia, elevated lactate levels, and increased urinary nitrogen excretion. The respiratory quotient is often elevated in the range of 0.80 to 0.95 as a result of the use of a mixed oxidative fuel source. Loss of lean body mass occurs more rapidly than with simple starvation because skeletal muscle protein stores become the "fuel" for the stress response. Most important, the malnutrition associated with stress metabolism is less responsive to nutrition support than is starvation metabolism. Reversal of stress-associated malnutrition is dependent not only on the provision of adequate nutrients but also on elimination of the underlying stress response (i.e., control of infection, stabilization of fractures, grafting of burns, or resolution of the inflammatory state). Starvation and stress metabolism are summarized in Table 78.1.

Carbohydrate Metabolism in Critical Illness

Carbohydrate metabolism in critical illness is characterized clinically by hyperglycemia, often described as being due to "insulin resistance" based on increased blood glucose levels in the presence of high circulating levels of insulin. In fact, cellular glucose uptake and oxidation in the critically ill are increased,[5–7] and hyperglycemia is associated with increased glucose production, decreased insulin-mediated glucose uptake, and increased non–insulin-mediated glucose uptake.[5,8]

Glucose production is increased primarily by increased hepatic gluconeogenesis, to a lesser extent by renal gluconeogenesis,[9] and by increased glycogenolysis. Increased glucose production occurs under the influence of glucagon, catecholamines, and cortisol, with glucagon being the most important stimulant of hepatic gluconeogenesis and epinephrine being the primary stimulant of glycogenolysis.[10,11] The hormonal changes observed in critical illness appear to be mediated by cytokines in both the central nervous system and peripheral tissues. Interleukin 1 (IL-1) stimulates the release of adrenocorticotropic hormone, which in turn favors the release of cortisol and glucagon, and tumor necrosis factor (TNF) stimulates increased secretion of glucagon.[12] Gluconeogenic substrates include lactate and alanine, as well as glutamine, glycine, serine, and glycerol. The amino acids used for gluconeogenesis are derived largely from proteolysis in skeletal muscle.

Glucose uptake into cells is regulated by a process of facilitated transport in which a carrier protein promotes the movement of glucose across the cell membrane down its concentration gradient. Three isoforms of this glucose carrier protein (glucose transporter 1 [GLUT-1], GLUT-2, and GLUT-4) are thought to be important in glucose transport.[13] Non–insulin-mediated glucose uptake is dependent on the GLUT-1 isoform, whereas insulin-mediated glucose transport is dependent on the GLUT-4 isoform. During stress, total body glucose uptake is increased, but largely via non–insulin-mediated pathways.[8] Non–insulin-mediated glucose uptake is particularly important in the central nervous system and in tissues rich in macrophages and neutrophils (e.g., lung, liver, intestine, spleen, wound), which use glucose for energy and in the process generate the respiratory burst.[5,14] Inflammatory cytokines may promote the uptake of glucose by increasing the synthesis, plasma membrane concentration, or activity of the glucose transporter.[15,16] Insulin-mediated glucose transport is suppressed in the liver, heart, and skeletal muscle.[17,18] Hepatic insulin resistance is characterized by elevated circulating levels of insulin-like growth factor–binding protein-1.[17,18] The mechanisms of insulin resistance are incompletely understood, although proinflammatory cytokines may alter insulin receptor signaling.[14,19,20]

The net result of these alterations in carbohydrate metabolism in critical illness is hyperglycemia inasmuch as the liver seems to be unresponsive to high levels of circulating insulin and glucose and continues to synthesize glucose via gluconeogenesis. In other tissues, non–insulin-mediated glucose uptake is enhanced and results in increased glycolytic oxidation to pyruvate and a stoichiometric rise in lactate.[5,6] Although hyperlactatemia is usually thought of as being reflective of anaerobic metabolism, it can be indicative of glycolytic flux and the level of metabolic stress when observed in conjunction with elevated pyruvate.[5]

Fat Metabolism in Critical Illness

In both starvation and stress metabolism, fat metabolism is characterized by increased lipolysis and decreased lipogenesis as fat stores are mobilized for energy. In the stressed state there is a marked increase in lipolytic activity in adipose tissue as a result of catecholamine-mediated stimulation of β_2-receptors; cytokines may also participate in this process.[21,22] Fatty acids are released from adipose tissue in quantities that exceed the amount oxidized, and approximately half of these fatty acids are re-esterified in the liver.[23] In this triglyceride–fatty acid cycle, triglycerides and fatty acids are shunted back and forth between the liver and adipose tissue in an apparently futile pathway.[24]

Stress fat metabolism is further characterized by increased oxidation of fatty acids of all chain lengths and decreased plasma levels of medium- and long-chain essential fatty acids relative to the quantities of oleic acid. The latter may reflect preferential oxidation of essential fatty acids, suppressed mobilization because of hyperinsulinemia, or conversion of ω-6 fatty acids to inflammatory mediators.

Hypertriglyceridemia is common in critically ill patients, particularly in the presence of multiple-organ dysfunction, and results from the combination of increased hepatic triglyceride production and decreased clearance.[25,26] Hepatic steatosis has classically been attributed to overfeeding because triglycerides are constructed from fatty acids synthesized from excess carbohydrate. This theory has been called into question inasmuch as a substantial proportion of hepatic triglyceride may be synthesized from recycled fatty acids rather than from fatty acids synthesized de novo from carbohydrate.[27] It is possible that fatty infiltration of the liver reflects a cytokine-mediated defect in triglyceride secretion that represents an organ-specific response to critical illness rather than an adverse effect of carbohydrate overfeeding.[28,29] Regardless of the immediate source of the fatty acids used in triglyceride synthesis, experience suggests that clinically apparent fatty infiltration of the liver can be prevented by avoiding overfeeding.

Ketonemia is common in starvation, whereas ketogenesis is decreased in stress metabolism.[30] Acetoacetate continues to be used as an oxidative fuel source, although the reduction of β-hydroxybutyrate to acetoacetate is impaired.[31] With the development of multiple-organ dysfunction, there is a progressive decrease in the acetoacetate/β-hydroxybutyrate ratio.[32] This alteration in hepatic redox potential reflects a disturbance in the cellular energy charge that may be associated with hepatic mitochondrial damage by toxic oxygen radicals and other inflammatory mediators.[33]

Protein Metabolism in Critical Illness

Protein synthesis is increased in the stressed state relative to that seen in starvation. Protein breakdown is markedly increased compared with the synthetic rate, thereby resulting in net protein catabolism and a rapid decrease in lean body mass.[30] There is a net efflux of amino acids from skeletal muscle as protein breakdown via the ubiquitin-proteosome pathway of protein degradation is accelerated by catecholamines, cortisol, and cytokines.[34–37] Amino acid uptake by skeletal muscle is impaired despite excess amino acids circulating in the bloodstream early in the course of stress metabolism; the situation deteriorates further as plasma concentrations of specific amino acids such as leucine begin to fall.[38] Decreased plasma glutamine is known to have deleterious effects on immune function and gastrointestinal barrier function.[39,40] Although it has long been thought that the accelerated protein catabolism associated with critical illness is unresponsive to the provision of amino acids or other fuel sources, the fact that muscle amino acid uptake is in part compromised by decreased plasma levels of specific amino acids suggests the possibility that protein catabolism during stress may be attenuated with the provision of appropriate nutrition support.[41]

Amino acids mobilized from skeletal muscle are redistributed to other areas of the body to support immune function, wound healing, and tissue repair, as well as for the hepatic synthesis of acute-phase proteins, presumably in an attempt to enhance survival. It has recently been demonstrated that endotoxemia induces significant increases in protein synthesis in the liver, spleen, kidney, jejunum, diaphragm, lung, and skin at the expense of skeletal muscle catabolism.[42] Amino acids such as alanine, glutamine, glycine, and serine are used as gluconeogenic substrate, and branched-chain amino acids (leucine, isoleucine, and valine) can be used as an oxidative fuel source, particularly in skeletal muscle. The net result of stress protein metabolism is a rapid decrease in lean body mass that exceeds that associated with bed rest or simple starvation, along with increased ureagenesis, azotemia, and increased urinary nitrogen excretion.

Indications for Nutrition Support

Nutrition support should be considered once hemorrhage has been controlled, devitalized tissue debrided, fractures stabilized, and the patient resuscitated from shock. Limited data are available regarding the appropriate timing for the institution of nutrition support, although there are suggestions in the literature that early enteral feeding, within 24 to 72 hours of admission, may help decrease postburn and postinjury hypermetabolism and reduce infectious complications. In general, nutrition support should be initiated in any patient who is malnourished on admission to the intensive care unit (ICU), for any patient who is likely to become malnourished during a long and complicated ICU stay, and for any patient who has not eaten for 5 to 7 days.

Goals of Nutrition Support

The goals of nutrition support in a critically ill patient are to minimize the effects of starvation to provide appropriate doses of macronutrients and micronutrients, to modulate the metabolic processes of the disease, to minimize complications of nutrition support, and to improve outcomes. More specifically, the goals of nutrition support in the critically ill or injured are to provide sufficient calories to meet the energy requirements of the hypermetabolic state while avoiding the complications associated with overfeeding, provide sufficient protein to attain nitrogen balance or minimize the nitrogen deficit, provide electrolytes to maintain normal levels while taking into account excessive losses or impaired excretion, and provide appropriate vitamins and trace elements with consideration of disease-specific requirements.

Nutrition Support in Critical Illness

Calories

In any metabolic state, energy requirements must be met to minimize the use of stored energy reserves and to decrease the loss of lean body mass. In the setting of adapted starvation, the protein-sparing effect of an adequate caloric intake is well recognized; however, in the stressed state, protein catabolism is only partially responsive to caloric intake and continues to a significant degree regardless of caloric intake.[30,41] Overfeeding is of particular concern in a critically ill patient because it can result in excess carbon dioxide production and ventilator dependence,[43] lipogenesis and fatty infiltration of the liver,[44–46] and hyperglycemia with its attendant hyperosmolar and infectious complications.[14,47–49]

The daily caloric requirement depends on total energy expenditure (TEE), which is the sum of basal energy expenditure (BEE), diet-induced thermogenesis (DIT), and activity energy expenditure (AEE). BEE is the caloric expenditure of a person in the recumbent position who has fasted for at least 10 hours. DIT is the energy expended to perform all aspects of food consumption, including eating and hydrolysis and absorption of nutrients, and may account for 15% to 40% of TEE. Resting energy expenditure (REE) is the energy expenditure of a recumbent person who is not fasting and is the sum of BEE and DIT. These relationships can be expressed by the following equations:

$$REE = BEE + DIT$$

$$TEE = REE + AEE$$

Caloric requirement can be estimated by using a number of formulas or can be measured with indirect calorimetry. Most commonly, BEE is estimated with the Harris-Benedict equations, which are based on sex, age, height, and weight and then multiplied by stress and activity factors to estimate caloric requirement. The Harris-Benedict equations are as follows:

For males:

$$\text{BEE} = 66.42 + (13.75 \times \text{Wt[kg]}) + (5.0 \times \text{Ht[cm]}) - (6.77 \times \text{Age[yr]})$$

For females:

$$\text{BEE} = 655.10 + (9.65 \times \text{Wt[kg]}) + 1.85 \times \text{Ht[cm]}) - (4.68 \times \text{Age[yr]})$$

Classically, REE is then estimated by multiplying the calculated BEE by a stress factor ranging from 1.0 in a stable, mechanically ventilated patient to 2.0 in a patient with a 50% total body surface area burn. Stress factors for patients with multiple trauma or sepsis fall somewhere between the two extremes. TEE is estimated by multiplying REE by an activity factor of 1.2 to 1.3 for ambulatory patients. The caloric requirement is decreased to varying degrees (6%–30%) in mechanically ventilated patients receiving narcotics or sedatives and is reduced by as much as 33% in chemically paralyzed patients.[50] In nonventilated postoperative patients or in patients with decreased lung compliance, energy expenditure related to the work of breathing may increase. Although estimation of energy expenditure is relatively accurate in healthy people, it is much less reliable in critically ill patients because of the heterogeneity of the metabolic response and variations in sedation, work of breathing, and physical activity. Most critically ill patients should receive calories to supply 100% to 120% of calculated BEE. Estimation of energy expenditure in obese patients is particularly difficult. If indirect calorimetry is unavailable, the provision of calories should be based on body mass index (BMI) and ideal body weight rather than on obesity-adjusted body weight.[51]

Indirect calorimetry can be used to measure REE and does not require the addition of estimated stress factors. REE is based on measured oxygen consumption and carbon dioxide production and is calculated according to the Weir equation:

$$\text{REE} = (3.94 \times \text{V}_{\text{O}_2}) + (1.1 \times (\text{V}_{\text{CO}_2}),$$

where V_{O_2} is oxygen consumption and V_{CO_2} is carbon dioxide production.

Even when not used routinely, indirect calorimetry can still be helpful in assessing the energy needs of obese patients, to rule out overfeeding in patients with seemingly excessive ventilatory demands, in severely malnourished patients, and in patients with apparently high levels of metabolic stress.

In general, critically ill patients should receive 25 to 30 kcal/kg per day, with sedated mechanically ventilated patients receiving closer to 25 kcal/kg per day. Chemically paralyzed patients generally require 20 kcal/kg per day.[50] In obese patients, hypocaloric feeding may induce some degree of weight loss and improve insulin sensitivity and may decrease ventilator days and length of ICU stay.[52] In patients with a BMI greater than 30, calories should not exceed 60% to 70% of target energy requirements or 11 to 14 kcal/kg actual body weight per day or 22 to 25 kcal/kg ideal body weight per day.[51]

Carbohydrate

Carbohydrate is usually the primary source of calories in human beings. The maximal rate of glucose oxidation is approximately 5 mg/kg per minute, or 7.2 g/kg per day.[53] In stressed patients, part of this maximally tolerated glucose load will be provided by glucose synthesized endogenously from amino acids via gluconeogenesis. In a severely hypermetabolic patient, gluconeogenesis may provide as much as 4 mg/kg per minute of glucose[54] and result in significant hyperglycemia when large exogenous glucose loads are administered. Insulin tends to be ineffective in controlling this hyperglycemia, in part because glucose oxidation may already be maximal, endogenous insulin levels are already high, and insulin-mediated glucose uptake in the liver and other tissues is suppressed in a septic and hypermetabolic patient.[17,18] Complications of excess glucose administration include hyperglycemia and its attendant hyperosmolar/infectious complications, excess carbon dioxide production and ventilator dependence, and hepatic steatosis. In general, glucose should initially be provided at a rate of 5 g/kg per day or approximately 20 kcal/kg per day. Carbohydrate should generally constitute 60% to 70% of nonprotein calories in a hypermetabolic patient (Table 78.2).

Fat

In a hypermetabolic patient, fat should constitute 15% to 40% of daily caloric intake, both to prevent essential fatty acid deficiency and to meet caloric needs in the face of a fixed capacity to oxidize glucose. In the starved state, as little as 2% to 5% of calories can be provided as fat, primarily to prevent essential fatty acid deficiency. Substituting lipid calories for carbohydrate calories

TABLE 78.2 Nutrition Support in a Hypermetabolic Patient

Nutrient	General Recommendation
Total calories	25–30 kcal/kg/day OR BEE × 1.2–2.0 OR REE by IDC
Glucose	5 g/kg/day OR 20 kcal/kg/day OR 60%–70% of calories
Fat	15%–40% of calories OR <1 g/kg/day
Amino acids or protein	1.2–2.0 g/kg/day
Trace elements and vitamins	RDA
Electrolytes	Maintain normal levels

BEE, Basal energy expenditure; *IDC*, indirect calorimetry; *RDA*, recommended dietary allowance; *REE*, resting energy expenditure.

can reduce carbon dioxide production, although avoiding excess calories in general is probably most important in minimizing carbon dioxide production and ventilator dependence. Complications of excess lipid administration, particularly when given parenterally, include hyperlipemia, immunosuppression, and hypoxemia as a result of both impaired oxygen diffusion and ventilation-perfusion mismatching. In general, a hypermetabolic patient should receive 15% to 40% of calories as fat, not to exceed 1.0 to 1.5 g/kg per day (see Table 78.2).[55]

Protein

Protein needs in a hypermetabolic patient are increased compared with those in a patient with simple starvation. Protein catabolism in a stressed patient has long been thought to be unresponsive to protein or amino acid administration or glucose infusion,[56] and attainment of nitrogen balance is thought to depend largely on the support of stress protein synthesis.[41] However, recent evidence suggests that protein catabolism may be attenuated by the provision of appropriate nutrition support.[42] Regardless of the specific mechanisms involved, lean body mass decreases during catabolic illness because of bed rest and inactivity. Amino acids are redistributed from skeletal muscle to support hepatic protein synthesis, the cellular inflammatory response, and gluconeogenesis and are used as oxidative fuel sources. The critically ill or injured patient may require 1.2 to 2.0 g/kg per day to promote nitrogen balance or at least minimize the nitrogen deficit. With the exceptions noted later, the provision of more than 2.0 g/kg per day of protein rarely promotes nitrogen balance and usually results simply in increased urinary nitrogen excretion (see Table 78.2).

To meet the protein requirements of the stressed state and at the same time avoid excess calories and the attendant complications, an injured or septic patient may require nutrition support with a nonprotein calorie-to-nitrogen ratio of 80:1 or 100:1, as compared with a patient with starvation metabolism, who may tolerate a nonprotein calorie-to-nitrogen ratio of 150:1 or higher. The higher protein needs of a patient with catabolic illness can be met with custom-compounded total parenteral nutrition (TPN) or with numerous commercially available enteral formulas specifically designed for such patients (Table 78.3).

In summary, most critically ill patients should receive 1.2 to 2.0 g/kg per day of protein. Obese patients with BMI 30 to 40 should receive at least 2.0 g/kg per day of protein, and patients with BMI greater than 40 should receive at least 2.5 g/kg per day in conjunction with hypocaloric feeding.[51] Critically ill patients with renal failure should generally receive 1.25 to 1.75 g/kg per day, and those requiring continuous renal replacement therapy (CRRT) may require up to 2.5 g/kg per day.[51]

Electrolytes, Vitamins, and Trace Elements

Fluid and electrolytes should be provided to maintain adequate urine output and normal serum electrolyte levels. Typical daily electrolyte requirements include sodium 60 to 100 mEq/day, potassium 60 to 100 mEq/day, magnesium 10 to 20 mEq/day, calcium 10 to 15 mEq/day, chloride 80 to 120 mEq/day, and phosphorus 20 to 30 mmol/day.[57] Intravenous amino acid formulations contain acetate, but more acetate can be added in the setting of metabolic acidosis. Particular attention should be paid to the intracellular electrolytes (potassium, phosphorus, and magnesium), which are required for attainment of nitrogen balance[58] and serum levels of which can fall precipitously when nutrition support is initiated.

The requirements for vitamins and trace elements in critical illness are largely unknown, and in general the recommended dietary allowance for both should be provided. Antioxidant vitamins (including vitamins E and ascorbic acid) and trace minerals (including zinc, copper, and particularly selenium) may improve outcome in burns, in trauma, and in critically ill patients requiring mechanical ventilation[59] and should be provided to all critically ill patients receiving specialized nutrition support.[51] Patients with prolonged diarrhea or large burns or those undergoing dialysis have increased trace element loss and vitamin requirements, and deficiencies can develop if intake is inadequate. Initial limitation of trace elements should be considered in patients with renal failure. Routine supplementation of vitamins is necessary in patients receiving TPN. Typically, one ampule of a standard multivitamin preparation is added to TPN daily. Vitamin K, which is light sensitive, must be added separately in a light-impermeable bag or given by another route once or twice weekly. Excessive doses of vitamin C should be avoided in renal failure because of the accumulation of oxalate. Vitamin A accumulates and should not be supplemented beyond the recommended dietary allowance.[60]

Route and Timing of Administration

Nutrition support can be delivered enterally (via the gastrointestinal tract) or parenterally (via the intravenous route). The preferred route has been the subject of considerable controversy during the past 40 years.

Both routes have advantages and disadvantages, and nitrogen balance can be achieved by either route. TPN does not require an intact or functioning gastrointestinal tract, it is convenient to use, and its use virtually guarantees that the nutrients prescribed will be administered and that these nutrients will appear in the bloodstream. Disadvantages of parenteral nutrition include cost, procedure (central venous catheter)-related complications, an increased likelihood of metabolic complications, including hyperglycemia, and an increased risk of infectious complications. Enteral nutrition is much less expensive, is more physiologic, is associated with fewer metabolic complications such as electrolyte abnormalities and hyperglycemia, and stimulates gut function and preserves mucosal integrity and barrier function better than parenteral nutrition does. Disadvantages of enteral nutrition include the requirement for an intact and functioning gastrointestinal tract, procedure (feeding tube placement)-related complications, pulmonary aspiration, malabsorption, feeding intolerance (pain, vomiting, bloating, diarrhea), and as a result, an inability to deliver the entire nutrient prescription.

The gastrointestinal tract is a major interface between the host and the environment and not only regulates the ingestion and absorption of nutrients but is also responsible for defending the host against noxious microorganisms and toxins.[61] Malnutrition impairs gastrointestinal barrier function,[62] as does the lack of luminal nutrients independent of general nutritional status.[63,64] Enteral nutrition has been shown to promote mucosal growth, improve absorptive capacity, alter digestive enzyme production, improve gut mucosal weight, generate DNA and protein synthesis, and improve the efficiency of nutrient utilization.[65] Enteral nutrition stimulates intestinal contractility; the release of trophic substances such as bile salts, gastrin, and motilin; and the release of secretory IgA.[66–69] Enteral nutrition supports commensal bacteria, which in turn degrade bacterial toxins and prevent gut colonization by pathogenic organisms.[66,70] Further, enteral nutrition stimulates gut blood flow and supports gut-associated lymphoid tissue.[66–69] Enteral

TABLE 78.3 Enteral Nutrition Formulas

Type	General Information	Sample Formulas	Concentration (kcal/mL)	Osmolality	Nonprotein Calorie/ Nitrogen Ratio	Protein (g/1000 kcal)	Carbohydrate (% kcal)	Fat (% kcal)
Intact Protein								
Standard	Some may be taken by mouth; generally lactose-free, low-residue, and isotonic	Jevity	1.06	300	139:1	44	54.3	29
		Isosource HN	1.2	510	113:1	44.9	53	29
		Nutren 1.5	1.5	530	114:1	45	47	35
High protein	Similar to above formulas except contain >45 g protein/L	Replete	1.0	300	73:1	64	45	30
		Isosource VHN	1.0	335–355	77:1	62	50	25
		Promote	1.0	340	75:1	62.5	52	23
Fluid concentrated	Calorically dense (1.5–2.0 cal/mL), lactose-free, moderate to high osmolality	Nutren 2.0	2.0	780	123:1	42	43	41
		TwoCal HN	2.0	725	125.1	41.8	43.2	40.1
Immunity-enhancing	May contain fiber, MCT, fish oil, added vitamins/minerals; 22%–25% protein	Impact	1.0	375	71:1	56	53	25
		Perative	1.3	385	97:1	51.2	54.1	25.4
Diabetic	33%–40% carbohydrate, contains fiber, standard to high protein	Diabetisource AC	1.2	450	95:1	50	36	44
		Resource Diabetic	1.06	450	79:1	59.4	36	40
		Glucerna	1.0	355	125:1	42	38.4	49
		Glucerna 1.5	1.5	875	91:1	55	35.4	45
		Glytrol	1.0	280	114:1	45	40	42
Hepatic	High BCAA, 1.2–1.5 cal/mL	NutriHep	1.5	790	209:1	27.5	77	12
Pulmonary	40%–55% fat, lactose-free	Nutren	1.5	330–450	113:1	45.3	26	56
		Oxepa	1.5	535	125:1	41.6	28.1	55.2
		Pulmocare	1.5	475	125:1	41.7	28.2	55.1
Renal	2 cal/mL, low to standard protein, low to no electrolytes	Renalcal	2.0	600	300:1	17.2	57	36
		Suplena	1.8	780	239:1	24.9	42	48
		Novasource Renal	2.0	800	113:1	45.3	37	45
		Nepro	1.8	745	121:1	44.5	34	48
Hydrolyzed Protein								
Immunity-enhancing	Standard to high protein, may have added vitamins/minerals or amino acids	Vital AF 1.2 Cal	1.2	425	75:1	41.6	36	39
		Pivot 1.5	1.5	595	75:1	62.5	45	30
GI-compromised	Mix of peptides and amino acids, >40% fat as MCT	Peptamen	1.0	270–380	131:1	40	51	33
		Peptamen 1.5	1.5	550	116:1	45.3	49	18
		Osmolite	1.06	300	153:1	35	57	29
Crystalline amino acids	Powdered form, 8%–18% protein, <6% fat	Vivonex T.E.N.	1.0	630	149:1	38.3	83	3
		Vivonex Plus	1.0	650	115:1	45	77	6

BCAA, Branched-chain amino acid; *GI*, gastrointestinal; *MCT*, medium-chain triglyceride.

nutrition supports the processing of naive CD4 helper lymphocytes by exposure to bacterial antigens in the gut. These IgA-producing lymphocytes then migrate to distant organs such as lungs, liver, and kidneys, where they form mucosal-associated lymphoid tissue and produce secretory IgA.[66–69] T_H2 CD4 helper lymphocytes, the proliferation of which are stimulated by feeding, enter the circulation and have an antiinflammatory effect.[66,71,72] Enteral nutrients stimulate the proliferation of T_H1 and T_H3 lymphocytes,[71] which in turn release transforming growth factor β (TGF-β), resulting in a further downregulatory or antiinflammatory effect.[66,71]

Several randomized prospective trials in a variety of critically ill patient populations, including trauma, burns, head injury, major surgery, and acute pancreatitis, have documented the benefits of enteral compared to parenteral nutrition.[73–78] Few studies showed a beneficial effect on mortality rate, but most demonstrated reduced infectious morbidity, primarily pneumonia and central line infections. Several meta-analyses comparing enteral and parenteral nutrition have shown significant reductions in infectious complications with the use of enteral nutrition.[79–82]

Traditionally, it has been assumed that parenteral nutrition does not offer the benefits related to gut mucosal integrity and immune function mentioned earlier. Whether this is the primary reason for the increased infection risk associated with parenteral nutrition is less clear. In several of the studies mentioned in previous paragraphs, many of the patients managed with parenteral nutrition received significantly more calories and had a higher incidence of hyperglycemia[80] than did their enterally fed counterparts. In a study in which parenterally fed patients had a higher incidence of sepsis, twice as many patients receiving parenteral nutrition had hyperglycemia as enterally fed patients.[77] In a large prospective trial comparing tight glucose control with standard glucose control, patients with tight glucose control had significantly lower rates of morbidity, infectious complications, and mortality.[49] Further analysis of these data revealed that when glucose was tightly controlled, there was no difference in infection when patients were nourished parenterally rather than enterally.[83] Recently in a large multicenter, randomized, controlled trial involving 2400 critically ill patients who could be fed via either route, the patients were randomly assigned to receive either early enteral or early parenteral nutrition. Caloric intake was similar between groups. There was no difference in 30-day mortality, and secondary endpoints were largely similar with the exception of more vomiting in the enterally fed patients.[84] In a more recent meta-analysis of randomized controlled trials comparing early enteral and early parenteral nutrition, there was no difference in mortality. The incidence of infection was lower in the enterally fed group, but this difference was explained by the subset of trials in which the parenterally fed group received more calories and presumably had poor glucose control.[85] These data suggest that dose may be more important than the route by which nutrition is supplied. A potential explanation for this phenomenon is the suppression of autophagy. Autophagy is an important housekeeping process that is normally activated by cellular stress to remove cellular damage.[86] Overfeeding, as can result from the use of parenteral nutrition, particularly early in the ICU course, can suppress autophagy.[87–90]

In summary, because it is less costly and is associated with fewer metabolic complications and possibly a lower incidence of infection, the enteral route continues to be the recommended route for nutrition support.[91] That said, in as many as 15% of critically ill patients, enteral nutrition is either contraindicated or not tolerated, and parenteral nutrition remains a viable option, particularly when overfeeding is avoided and hyperglycemia is controlled.[91]

The timing for the initiation of nutrition support in critically ill patients has also been controversial. It has been suggested that enteral nutrition started early (within 24–72 hours of admission or the onset of the hypermetabolic insult) is associated with less gut permeability, release of inflammatory cytokines, and reduced systemic endotoxemia.[76] Further, the accumulation of an energy deficit early in the course of an ICU admission has been significantly associated with the occurrence of ARDS, renal failure, pressure ulcers, and the need for surgery[92] and with longer ICU length of stay and more days of mechanical ventilation.[83,93] In a meta-analysis by Heyland and associates, early enteral nutrition was associated with a trend toward reduced infectious morbidity and mortality rates.[76] A second meta-analysis by Marik and Zaloga demonstrated significant reductions in infectious morbidity and hospital length of stay with early enteral nutrition as compared to delayed feedings.[94] In patients who are hemodynamically stable, it is recommended that enteral nutrition be started within 48 hours of admission.[91]

The early use of TPN to supplement enteral nutrition and thus prevent a caloric deficit has been controversial.[76,78,88,93] In a recent prospective, randomized, multiinstitutional trial 2312 patients were randomly assigned to initiation of parenteral nutrition to supplement insufficient enteral nutrition within 48 hours of ICU admission (early initiation group) and compared to 2328 patients randomly assigned to receive supplementary parenteral nutrition no earlier than 8 days after ICU admission (late initiation group). All patients received early enteral nutrition by protocol and had insulin infused to maintain normoglycemia. The late initiation group was slightly more likely to be discharged alive from the ICU and from the hospital without evidence of decreased functional status. Further, patients in the late initiation group had significantly fewer infections, a significant reduction in the proportion of patients requiring more than 2 days of mechanical ventilation, a significant median reduction of 3 days in the duration of renal replacement therapy, and a mean reduction in health care costs of approximately $1600. These patients were considered to be at nutritional risk but not malnourished on admission based on BMI.[95,96] In the past 5 years, three additional large randomized controlled trials have examined the use of parenteral nutrition to supplement inadequate enteral nutrition during the first week of critical illness.[97–99] These results suggest that early parenteral nutrition, even when used to supplement enteral nutrition, is not beneficial and may be harmful and should be avoided unless the patient is chronically malnourished.[100]

Trophic Feeding

The subject of trophic or permissive hypocaloric feeding has received considerable attention recently. In a single-center study, Rice et al. randomly assigned 200 patients with acute respiratory failure to receive trophic or full enteral feedings for the first 6 days in the ICU. The patients receiving trophic feeds received low protein and calories. There was no difference in ventilator-free days between the groups and the fully fed group had more gastrointestinal intolerance.[101] The Trophic vs Full-Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Lung Injury (EDEN) trial, a subsequent multicenter randomized controlled trial, confirmed these findings in a larger population of 1200 patients.[102] Long-term follow-up at 1 year did not reveal any effect on mortality or physical or neurocognitive function.[103,104] A recent meta-analysis of randomized controlled trials comparing intentional hypocaloric to normocaloric feeding found no difference in outcome.[105] Together

these studies suggest that restricting calories during the acute phase of critical illness is safe and may even be superior to normocaloric feeding. The most recent Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient (Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition) suggest that patients at low nutritional risk with normal baseline nutritional status and low disease severity (Nutrition Risk Screening [NRS-2002] of ≤3, Nutrition Risk in the Critically Ill [NUTRIC] score ≤5[106]) who cannot maintain volitional intake do not require specialized nutrition support over the first week of hospitalization in the ICU.[91] On the other hand, these guidelines also suggest that for patients at high nutritional risk (NRS-2002 ≥5 or NUTRIC score ≥5) or severely malnourished should be advanced toward goal as quickly as possible over 24 to 48 hours, and that every effort should be made to achieve 80% of estimated or calculated goal energy and protein needs within 48 to 72 hours.[91]

Types of Nutritional Formulas

Parenteral nutrition is most commonly administered as a three-in-one solution of dextrose, lipid, and amino acids. TPN order forms typically allow the physician to order "standard" or custom solutions, fluid-restricted solutions, and in some cases, disease-specific solutions such as renal failure or hepatic failure solutions. Electrolytes can usually be added in standard stock concentrations or individually. Vitamins and trace elements are generally added in standard quantities but can be supplemented. Histamine 2 (H_2) blockers for stress ulcer prophylaxis and regular insulin can also be added.

Enteral formulas are usually premixed with a fixed nonprotein calorie-to-nitrogen ratio, and the needs of a specific patient are generally met by changing the formula. Protein and carbohydrate supplements can be added at the bedside to alter premixed formulas. Enteral formulas can be classified in numerous ways, including the form in which protein is provided (e.g., intact protein, hydrolyzed protein [chemically defined or peptide], or crystalline amino acids [elemental]), the quantity of protein contained, the caloric density of the formula, and the disease state for which they were designed. Examples of different formulas are shown in Table 78.3. More detailed information is available elsewhere.[107,108]

Intact protein solutions contain protein as caseinate or soy isolate–based products that are lactose-free, gluten-free, and low in residue. Such solutions contain 45% to 60% of calories as carbohydrate (oligosaccharides), 20% to 35% of calories as long-chain fats (e.g., linoleic acid), and 15% to 20% of calories as protein. Intact formulas are usually isosmotic and may contain 1 to 2 kcal/mL of solution. Some formulas contain fiber as a means to improve diarrhea or glycemic control. Hydrolyzed formulas provide protein as peptides or amino acids, are generally low in fat, and are designed for patients with gut dysfunction or malabsorption.[109] Elemental solutions contain protein exclusively as amino acids and are intended for similar indications. Controlled studies comparing hydrolyzed or elemental formulas with intact formulas have not demonstrated improved tolerance or outcomes.

High-protein formulas contain more than 45 g protein per 1000 kcal and are designed for patients with increased protein needs, such as patients with catabolic illness.

Calorie-dense formulas are designed for patients in whom fluid restriction is required. They are generally relatively low in protein and not ideal for a stressed patient.

Organ-Specific Enteral Formulas

Organ-specific formulas are products designed to meet the nutritional requirements of patients with specific organ failures. None has been consistently shown to improve outcomes when compared with conventional formulas.

Pulmonary failure formulas are designed for patients with acute respiratory failure associated with chronic lung disease. They contain at least 50% of calories as fat and thus reduce carbon dioxide production and decrease the work of breathing relative to high-carbohydrate formulas. Few data suggest a benefit with specific pulmonary formulas, and avoidance of overfeeding is more important in reducing ventilatory demand.[82,110] In the 2016 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient, published jointly by the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition, it is recommended that these high-fat/low-carbohydrate formulas, designed to manipulate the respiratory quotient and reduce carbon dioxide production, not be used in critically ill patients.[91]

Hepatic failure formulas were developed for patients with encephalopathy. They contain high concentrations of branched-chain amino acids and reduced concentrations of aromatic amino acids. Although these solutions have been shown to correct the abnormal amino acid profile characteristic of patients with liver failure,[111,112] it is less clear that they actually treat hepatic encephalopathy.[112] Hepatic failure formulas should be reserved for the rare encephalopathic patient who is refractory to lactulose and luminal antibiotics.[51]

Renal failure formulas have reduced concentrations of electrolytes and decreased protein content to minimize nitrogenous waste in patients with renal failure. Patients with acute renal failure frequently have associated catabolic illness and as a result need more protein rather than less. Although these formulas may be useful in patients with electrolyte abnormalities not yet being dialyzed, they are inappropriate for patients with catabolic illness who are undergoing dialysis and particularly CRRT. Current recommendations for critically ill patients with acute renal failure are that standard recommendations for protein and calories should be followed, and that specialty formulas only be used for management of significant electrolyte abnormalities.[91] Patients receiving CRRT may require up to 2.5 g/kg per day of protein.[91]

Immunomodulating Enteral Formulas

Immunomodulating enteral formulas are supplemented with various combinations of specific nutrients, arginine, ω-3 polyunsaturated fatty acids, nucleotides, glutamine, and antioxidants aimed at improving immune function and reducing inflammation in critically ill patients.

Arginine is a nonessential amino acid that has both beneficial and deleterious effects. It is a secretagogue for anabolic hormones, supports T-cell function, detoxifies ammonia, and supports wound healing via metabolism to polyamine and proline.[113,114] An arginine deficiency may develop after trauma or major surgery that is mediated by pathologic release of arginase from granulocytes.[114–116] Arginine deficiency impairs the immune response, which may result in increased infections and in impaired wound healing.[114,115,117] Arginine is a precursor for the synthesis of nitric oxide, which in turn is a modulator of hepatic protein synthesis and vascular tone. This nitric oxide–induced vasodilation may be beneficial in some circumstances but in the setting of severe sepsis and hypotension may aggravate hemodynamic collapse. Further, nitric oxide is

metabolized to peroxynitrite,[114,118] which is a potent oxidizing and nitrating agent that may damage mitochondria, increase gut barrier permeability, and promote organ dysfunction.[114,118–123]

Omega-3 *fatty acids* are incorporated into the phospholipid fraction of cell membranes and converted to trienoic prostaglandins and pentaenoic leukotrienes, which are less "inflammatory" than their ω-6 counterparts. Omega-3 fatty acids have been shown to decrease prostaglandin E_2, TNF, and IL-1 production in rat Kupffer cells[124] and alter TNF and IL-1 production in human monocytes.[125] Furthermore, ω-3 fats have been shown to be beneficial in animal models of chronic inflammation and in humans with psoriasis[126] and rheumatoid arthritis.[127]

Glutamine is an important fuel for enterocytes and cells of the immune system. Considered a nonessential amino acid, glutamine may become conditionally essential when skeletal muscle stores and plasma levels become depleted during catabolic illness, thereby resulting in adverse effects on gut barrier and immune function.[128–130] Glutamine has been shown to improve nitrogen balance and decrease bacterial translocation in animals.[131–133] It also promotes the synthesis of glutathione, an important antioxidant. A meta-analysis of 14 randomized trials in which glutamine-supplemented nutrition was compared with standard nutrition demonstrated reduced infectious morbidity and mortality rates with glutamine supplementation, particularly in parenterally nourished surgical patients.[134] The addition of glutamine to an enteral formula not containing glutamine has been shown to reduce mortality in a small group of burn patients,[135] but analysis of aggregate data[136] from 5 randomized controlled trials involving 588 patients from burn, trauma, and mixed ICU populations has shown no benefit in terms of mortality, infections, or hospital length of stay.[135–141] Glutamine supplementation in enterally fed patients is not currently recommended.[91]

Antioxidant vitamins, including vitamins E and C, and trace minerals selenium, zinc, and copper offer the potential to reduce oxidant injury and may improve patient outcomes in burns, trauma, and critical illness requiring mechanical ventilation.[142–144] Aggregated results of 15 trials demonstrated that antioxidant and trace element supplementation was associated with a significant reduction in mortality, but no differences in infectious complications, length of stay, or duration of mechanical ventilation.[91,145–159] Current guidelines suggest that antioxidant vitamins and trace elements in doses known to be safe should be administered to patients receiving specialized nutrition support.[91] Numerous studies comparing immunity-enhancing enteral nutrition with conventional nutrition have produced contradictory results. In a 2001 meta-analysis of 22 studies (2419 patients) in which enteral nutrition supplemented with various combinations of arginine, ω-3 fatty acids, glutamine, and nucleotides was compared with conventional enteral nutrition, the supplemented patients had decreased infectious morbidity but no difference in mortality rates when compared with patients receiving the control diet.[160] The majority of studies demonstrating benefit involved elective surgery patients and not critically ill patients. In the subsequently published and largest (597 patients) randomized trial to date, immunonutrition had no benefit in terms of infectious morbidity, length of hospital stay, number of ventilator days, or mortality rate.[161] In retrospect, it appears that a number of factors may have been responsible for the conflicting results mentioned earlier. First, there was considerable heterogeneity in the patient populations studied (major elective surgery, burns, trauma, sepsis, and ARDS). Second, the immunomodulating enteral formulas studied contained varying combinations of arginine, ω-3 polyunsaturated fatty acids (fish oil), glutamine, and antioxidants. These differences were addressed in a 2008 meta-analysis of 24 studies by Marik and Zaloga in which studies were analyzed by patient type (ICU, burns, and trauma) and by the combination of immunomodulating nutrients in the subject study formula (fish oil, arginine, glutamine, fish oil plus arginine, fish oil plus arginine plus glutamine).[162] All enteral formulas contained antioxidants, primarily selenium, though in varying doses, and could not be studied separately. Overall, the immunomodulating diets had no effect on mortality rate but did demonstrate significant reductions in secondary infections. Mortality rates, infections, and length of stay were significantly reduced only in ICU patients with sepsis, systemic inflammatory response syndrome, and ARDS receiving a formula supplemented with fish oil alone.[163–165] Infection and length of stay were reduced in the 13 ICU studies, but this effect disappeared when the three fish oil studies were excluded.[162] The 2009 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient recommended the use of an immunomodulating enteral formula supplemented with fish oil and antioxidants for patients with acute lung injury/ARDS.[82] In 2011 Rice et al., working with the NIH NHLBI ARDS Network, reported a randomized, double-blind, placebo-controlled trial of 272 patients with lung injury, comparing twice-daily supplementation of ω-3 fatty acids, γ-linolenic acid, and antioxidants with an isocaloric diet. The supplemented group had an eightfold increase in plasma eicosapentaenoic acid levels but fewer ventilator-free days, fewer ICU-free days, and fewer organ failure–free days. The adjusted 60-day mortality was 25.1% in the supplemented group compared to 17.6% in the control group ($P = 0.11$).[166] The 2016 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient recommend that immune-modulating enteral formulas not be used in the medical ICU, but that such formulas may be appropriate in patients with head injuries and gastrointestinal surgical patients in the surgical ICU. Because of conflicting data, formulas containing ω-3 fatty acids and antioxidants are not currently recommended for patients with acute lung injury or ARDS.[91]

Nutritional Assessment and Monitoring

The history and physical examination remain the mainstay of nutritional assessment, although they are perhaps more useful in the ambulatory setting or in patients with chronic malnutrition.[167] Pertinent historical information includes height and weight, a history of recent weight change, genetic background, recent nutritional intake, and a history of disease that might affect nutrient intake, absorption, or tolerance. The physical examination might, on occasion, demonstrate abnormal end-organ function that reflects malnutrition, but more commonly it is useful for the assessment of body mass and detection of specific nutrient deficiencies. Signs and symptoms of selected vitamin and mineral deficiencies are presented in Tables 78.4 and 78.5.

Anthropometric measurements such as triceps skinfold thickness (SFT), midarm circumference, and arm muscle area, which is derived from SFT and midarm circumference, can be used to estimate fat mass and lean body mass.[168] Although serial measurements may be useful in certain patients over long periods, SFT measurements are less reliable in the elderly because of changes in fat distribution and skin compressibility associated with aging[168,169] and are inaccurate in patients with peripheral edema.[170] In general, these measurements are not practical for nutritional monitoring in a recumbent, critically ill patient.[171]

Visceral protein levels have long been used in nutritional assessment and monitoring and can be useful in the appropriate

TABLE 78.4 Selected Vitamin Deficiencies

Vitamin	Function	Signs of Deficiency
Niacin (vitamin B_5)	Component of the coenzymes NAD and NADP, which catalyze oxidation-reduction reactions and play a role in the oxidative catabolism of carbohydrates, proteins, and lipids and the biosynthesis of fatty acids	Pellagra, dermatitis, headaches, loss of memory, dementia, glossitis, diarrhea
Folate (vitamin B_9)	Transfer of single-carbon units; DNA synthesis	Megaloblastic anemia, diarrhea, glossitis
Cyanocobalamin (vitamin B_{12})	Maintains normal folate metabolism; coenzyme in reactions involving isomerizations and reductions; participates in the metabolism of fat, carbohydrate, and protein and in myelin synthesis	Pernicious anemia, glossitis, peripheral neuropathy, spinal cord degeneration
Thiamine	Carbohydrate metabolism coenzyme in oxidative decarboxylation	Paresthesias, impaired memory, nystagmus, congestive heart failure, Wernicke-Korsakoff syndrome
Riboflavin (vitamin B_2)	Electronic transport as flavin nucleotides	Mucositides, dermatitis, cheilosis, vascularization of the cornea, photophobia, decreased vision, lacrimation, impaired wound healing
Pyridoxine (vitamin B_6)	Coenzyme in transformations of amino acids	Neuritis, dermatitis, convulsions
Pantothenic acid	Precursor of coenzyme A (Krebs cycle)	Headache, fatigue, malaise, insomnia, vomiting, abdominal cramps
Biotin	Coenzyme for carboxylation reactions	As with other B vitamins (normally synthesized and absorbed from gut)
Ascorbic acid (vitamin C)	Reducing agent, wound healing, integrity of blood vessels, folate metabolism	Enlargement and keratosis of hair follicles, impaired wound healing, anemia, ecchymosis, lethargy, depression, bleeding
Vitamin A	Normal vision, mucopolysaccharide synthesis, protease release, entry of macrophages and leukocytes into an acute wound, immune stimulation, mucosal integrity	Dermatitis, keratomalacia, xerophthalmia, night blindness
Vitamin D	Calcium and phosphorus homeostasis	Rickets, osteomalacia
Vitamin E	Antioxidant	Hemolysis
Vitamin K	Clotting factors II, VII, IX, X	Bleeding

NAD, Nicotinamide-adenine dinucleotide; *NADP,* nicotinamide-adenine dinucleotide phosphate.

TABLE 78.5 Selected Mineral Deficiencies

Trace Element	Function	Signs of Deficiency
Chromium	Glucose tolerance; possible role in maintenance of normal serum lipid levels	Elevated serum lipids, insulin-resistant glucose intolerance
Copper	Metalloenzyme biochemical processes, component of ceruloplasmin, connective tissue metabolism, melanin formation	Anemia, neutropenia, leukopenia, depigmentation of skin
Iron	Constituent of hemoglobin, myoglobin, and the cytochrome enzymes	Microcytic hypochromic anemia, fatigue, faulty digestion, decreased serum iron
Zinc	Essential for the function of many enzymes and a component of lipid, protein, carbohydrate, and nucleic acid metabolism; cell replication and connective tissue synthesis	Dermatitis; impaired wound healing; alopecia; depressed cell-mediated immunity, taste acuity, and dark adaptation; sexual retardation; depressed visceral protein status
Cobalt	Biologic methylation	Pernicious anemia, methylmalonic aciduria
Manganese	Oxidative phosphorylation, fatty acid metabolism, protein and mucopolysaccharide synthesis	Growth retardation, bony abnormalities, central nervous system dysfunction

clinical setting. They are affected by a number of variables other than nutritional status, such as hydration state and gastrointestinal and urinary losses, and must therefore be used cautiously in a critically ill patient.

Albumin is contained in a large body pool (4–5 g/kg) and has a half-life of 20 days, so it is insensitive to acute changes and responds slowly to nutritional therapy. Serum albumin levels are decreased in nephrotic syndrome, enteropathies, hepatic failure, and dialysis (particularly peritoneal dialysis), as well as in the setting of acute volume expansion. Levels may be increased in the presence of dehydration, hypercortisolemia, and anabolic hormones, such as insulin, growth hormone, and estrogen. Although serum albumin levels are useful in predicting surgical mortality rate and monitoring nutritional status over the long term, they are much less useful in monitoring a critically ill patient.[172]

Transferrin is contained in a smaller body pool and has a shorter half-life than albumin does (8–10 days), so it is a more sensitive indicator of nutritional status. It is subject to the same influences as mentioned for albumin and, in addition, is affected inversely by serum iron levels.[173]

Retinol-binding protein is a specific carrier involved in vitamin A transport and is linked with thyroxine-binding prealbumin in a constant molar ratio.[174] It has a 12-hour half-life and is sensitive to synthesis and utilization rates. Levels rise in patients with renal disease[175] and with excess vitamin A administration and are reduced in patients with liver disease, cystic fibrosis, hyperthyroidism, and vitamin A deficiency.

Transthyretin (thyroxine-binding prealbumin) is involved in the transport of thyroid hormone and is a carrier for retinol-binding protein. It has a small body pool and a short half-life (2–3 days) and as such may be a sensitive indicator of nutritional status.[176,177] Levels are affected by the same variables that affect albumin and transferrin. Levels are low in patients with hyperthyroidism, cystic fibrosis, chronic illness, and acute stress. Because of its short half-life and ease of measurement, transthyretin is the visceral protein of choice for nutritional assessment and monitoring, although its use in a critically ill patient is controversial. During catabolic illness, hepatic protein synthesis is reprioritized, under the influence of cytokines, with increased synthesis of acute-phase reactant proteins and decreased synthesis of visceral proteins.[178–180] Transthyretin levels fall early in the course of catabolic illness and rise with the subsequent decrease in acute-phase reactant proteins as a result of reversal of the reprioritized hepatic protein synthesis. The association of this response with specific nutrients,[181–184] nitrogen balance,[52,185–188] and outcomes[78,187,189] has been variable. Whether transthyretin levels are reflective of appropriate nutrition support or simply a reflection of the course and severity of the inflammatory response is unclear. An initial transthyretin level lower than 50 mg/L or failure to increase by 40 mg/L per week has been associated with a poor prognosis.[177]

In general, because visceral protein levels are affected by a variety of nonnutritional factors, they are not recommended for the monitoring of nutritional status in critically ill patients.[51]

Nitrogen balance is the nutritional parameter most consistently associated with improved outcomes, and nitrogen balance studies are used routinely in many ICUs to monitor nutrition support. Ideally, positive nitrogen balance is the goal, but minimizing the nitrogen deficit in a critically ill patient is probably more realistic when one considers the fact that proteolysis in the skeletal muscle compartment, which constitutes 70% of body protein stores, is likely to exceed protein synthesis related to the inflammatory response and wound healing, simply because of the size of the compartments involved. Nitrogen balance is calculated as follows:

$$\text{Nitrogen balance (g)} = \text{Nitrogen intake (g)} - \text{Nitrogen output (g)}$$

$$\text{Nitrogen intake (g)} = \text{Protein or amino acid intake (g)}/6.25$$

$$\text{Nitrogen output (g)} = \text{Urinary nitrogen losses (g)} + 2\text{ g (stool and skin losses)}$$

Urinary nitrogen consists of several components, including urea, creatinine, uric acid, ammonia, and amino acids. In health, urea constitutes 90% of urinary nitrogen, whereas in catabolic states, urea may represent as little as 70% of urinary nitrogen. Measurement of total urinary nitrogen (TUN) is complex and not done in most hospitals, whereas urinary urea nitrogen (UUN) is measured routinely. When UUN is used in the calculation of urinary nitrogen excretion, an additional 20% of the UUN is added to account for nonurea nitrogen losses. In the absence of abnormal stool or skin losses, nitrogen output is calculated as

$$\text{Nitrogen output (g)} = \text{TUN (g/24 h)} + 2\text{ g (stool and skin losses)}$$

or

$$\text{Nitrogen output (g)} = \text{UUN (g/24 h)} + 20\%\text{ UUN} + 2\text{ g (stool and skin losses)}$$

Classically, measurement of urinary nitrogen excretion involves a 24-hour urine collection, but recent evidence suggests that a carefully collected 12- or even 6-hour urine collection can be obtained and extrapolated to a 24-hour period.[190] Nitrogen balance is usually calculated weekly.

Numerous techniques for assessment and monitoring of energy balance have been studied, including continuous whole-body calorimetry,[191] the doubly labeled water technique,[191] and nuclear magnetic resonance spectroscopy using phosphorus 31,[192] but no method is ideal. Although they are potentially useful, these methods are either cumbersome, expensive, or impractical for use in critically ill patients.

Indirect calorimetry is used to determine the heat produced by oxidative processes by measuring oxygen consumption and carbon dioxide production, which are then used to calculate REE via the abbreviated Weir equation.[193,194] Indirect calorimetry is widely used at the bedside, is convenient and relatively inexpensive, and accurately estimates REE when compared with standard predictive formulas.[195–201] Indirect calorimetry is performed on patients at rest and therefore does not account for energy expenditure during periods of activity. Many clinicians will increase caloric input by 20% to 25% above measured REE to account for physical activity, particularly in patients who are agitated, ambulatory, or involved in intense physical therapy.[202–204]

In addition to the nutrition-specific monitoring techniques mentioned, the usual laboratory values should be monitored for fluid and electrolyte composition, hepatic function, infection, and any coagulopathy that might reflect vitamin K deficiency. In a critically ill patient, serum electrolytes (sodium ions [Na^+], potassium ions [K^+], chloride ions [Cl^-], and bicarbonate [HCO_3^-]) should be determined daily and as needed. Special attention should be paid to the intracellular electrolytes (K^+, magnesium ions [Mg^{2+}],

and phosphate ions [PO_4^{2-}]), which are required for the attainment of nitrogen balance[80] and can fall precipitously when nutrition support, particularly glucose, is initiated. Rapid uptake into cells can result in dangerously low serum levels acutely. Intracellular electrolyte levels should be measured before starting nutrition support, 1 or 2 days after starting support, and at least weekly thereafter. Liver function and coagulation parameters should be evaluated weekly and as needed. Glucose should be measured every 6 hours initially and then as needed; it can be measured as often as every 2 hours when continuous insulin infusions are being used.

Complications of Nutrition Support

Complications of nutrition support include those related to the route of nutrition support and those related to nutrition support in general and are discussed in the following paragraphs. Perhaps the most important problem with nutrition support is failure to achieve therapeutic goals. Recommendations for appropriate doses of protein and calories, electrolytes, vitamins, and trace elements are discussed in previous text.

Complications of Enteral Nutrition Support

Complications specific to enteral nutrition support include mechanical or technical complications, gastrointestinal complications, and aspiration pneumonia.

Mechanical and technical complications of enteral nutrition include feeding tube misplacement, gastrointestinal perforation, sinusitis, otitis media, ulceration of the nasal septum, and obstruction of the feeding tube. Proper placement of feeding tubes in the gastrointestinal tract should be confirmed radiographically or with pH testing before feeding is initiated. Auscultatory techniques for confirmation of proper tube placement are unreliable.[205] Nasally placed feeding tubes are a potential cause of sinusitis or otitis media (or both), particularly when stiff, large-bore nasogastric tubes are used as feeding tubes. Soft, small-caliber tubes such as Miller-Frederick or Dobhoff tubes seem to cause sinusitis less frequently. In mechanically ventilated patients, feeding tubes may be placed orally to minimize the incidence of sinusitis.[206] Perforation of the esophagus or other parts of the gastrointestinal tract is a disastrous complication and seems to occur most frequently in the setting of stricture, obstructing tumor, or abnormal anatomy as a result of surgery. In these situations, tube placement under fluoroscopic guidance or endoscopic tube placement should be considered. Dislodgment of the feeding tube is a frequent and frustrating problem and can be disastrous when the tube dislodged is a recent, surgically placed tube such as a gastrostomy or jejunostomy tube. When a surgically placed tube has been present for longer than 1 to 2 weeks, the stomach or intestine should be adherent to the abdominal wall and the tube can usually be replaced through the existing tract, as long as the tube is replaced within a few hours before the tract begins to close. A radiograph with contrast enhancement should be used to verify replacement of the tube in the appropriate location. Dislodgment of a surgically placed tube within a week of placement can result in peritonitis from spillage of enteral formula or gastrointestinal contents into the abdominal cavity. Care should be taken to properly secure all feeding tubes either with sutures and tape or with commercially available fixation systems, and tubes should be protected with appropriate patient restraints and caregiver attention when the patient is being moved. Feeding tube obstruction occurs most frequently when tubes are not routinely flushed or when crushed medications are delivered through the tubes. Tubes should be flushed every 6 hours and after every medication dose. Numerous techniques have been used to clear obstructed tubes, including flushing with cola, pancreatic enzymes, cranberry juice, and streptokinase, although none is universally successful. Clearing a nasoenteric tube with a stylet or wire carries the risk of perforating the gastrointestinal tract and should be avoided unless done under fluoroscopic guidance to ensure that the stylet remains within the tube lumen.

Gastrointestinal complications such as abdominal distention, nausea, vomiting, diarrhea, and constipation occur in approximately 60% of critically ill patients receiving nutrition support.[207] Gastrointestinal motility is often decreased in these patients,[207,208] although gastric stasis and high gastric residual volumes occur more frequently than decreased small intestinal motility does.[208] Potential causes of gastroparesis include increased sympathetic tone, elevated intracranial pressure, opiates, benzodiazepines, dopamine, hyperglycemia, recent abdominal surgery, and pancreatitis. Prokinetic agents such as metoclopramide may restore gastric motility and allow gastric feeding.[209] Postpyloric feeding tube placement will often allow the continuation of enteral nutrition. Advancement of the feeding tube into the proximal jejunum facilitates enteral nutrition in patients with pancreatitis.

Diarrhea occurs in as many as 70% of critically ill patients.[207] Potential causes include antibiotics and other drugs, hyperosmolar formulas, infected solutions, hypoalbuminemia, chronic malnutrition and disuse mucosal atrophy, intolerance to lactose or other nutrients, pancreatic insufficiency, biliary fistula, and short-gut syndrome.

Clostridium difficile overgrowth is perhaps the most serious cause of antibiotic-associated diarrhea, and stool should be assayed for *C. difficile* toxin in every case of persistent diarrhea in the critically ill. *C. difficile* enterocolitis should be treated with appropriate antibiotics. Antibiotics may also cause diarrhea by eliminating the bacteria that ferment dietary fiber into short-chain fatty acids. Short-chain fatty acids are important for maintaining colonic mucosal integrity and enhance water and electrolyte absorption.[210] Enteral formulas should be replaced daily to avoid bacterial contamination of the solution.

A change in formula or more gradual institution of nutrition support can be used to overcome problems caused by nutrient intolerance, disuse atrophy, and short-gut syndrome. Semi-elemental or peptide formulas may reduce diarrhea in patients with mucosal atrophy. H_2 blockers can be used to decrease the contribution of gastric secretions to diarrhea in patients with short-gut syndrome. Drugs with the potential to cause diarrhea should be identified and eliminated if possible. Pancreatic insufficiency should be treated with commercially available pancreatic enzymes. Diarrhea secondary to a biliary fistula may be improved with reinfusion of bile into the intestine distal to the fistula. Once correctable causes of diarrhea have been identified and eliminated, bismuth subsalicylate (Kaopectate) can be given for symptomatic relief. Antiperistaltic agents such as loperamide (Imodium) or opiates should be avoided until infectious causes of diarrhea have been ruled out. Fiber may be used to thicken stool and lessen perineal irritation, but it may be associated with constipation and fecal impaction in critically ill patients. Intractable diarrhea may warrant the discontinuation of enteral nutrition and the initiation of parenteral nutrition.

Aspiration pneumonia is the major infectious complication of enteral nutrition. Bolus feeding carries a higher risk of aspiration than continuous feeding does. Gastric residual volume, which has traditionally been used to assess gastric feeding tolerance, does not appear to correlate with risk for aspiration.[211] Gastric feeding is

routinely used in many ICUs, but because a nasogastric tube is one of the leading causes of aspiration, gastric feeding should probably be done with a soft, small-caliber tube designed for feeding. The risk of aspiration associated with gastric feeding may be lower when done via a percutaneous gastrostomy tube,[211] which avoids compromising the function of the gastroesophageal junction and swallowing mechanics. Multiple studies have compared the risk of aspirating gastric versus postpyloric feedings, but the results have been contradictory.[78,212,213] In a recent meta-analysis of seven randomized trials, small bowel feeding was associated with a lower risk of aspiration pneumonia than was gastric feeding.[214] Nursing protocols for the bedside placement of postpyloric feeding tubes have been developed,[215,216] although placement under fluoroscopic guidance is more likely to be successful and is cost-effective.[217] The semirecumbent body position has been shown to significantly reduce aspiration pneumonia compared with the supine body position.[218]

Complications of Parenteral Nutrition Support

The primary complications of parenteral nutrition include mechanical or technical complications and infectious complications. Mechanical and technical complications are related to central venous catheter placement and include pneumothorax, arterial injury, hemothorax, hydrothorax, cardiac arrhythmia, and cardiac perforation with tamponade. The incidence of severe complications with subclavian vein catheterization is 1% to 3%, with an overall complication rate of 5%.[219] The incidence of complications with jugular venous catheterization ranges from 0.1% to 4.2%.[220] Jugular venous catheterization under ultrasound guidance is increasingly being recommended.[221–224] Jugular or subclavian vein thrombosis is a postprocedural complication that is manifested as neck or arm swelling and should be managed by catheter removal and anticoagulation; thrombolytics have also been recommended.[225]

Catheter infection and catheter-associated bloodstream infection are the major infectious complications of parenteral nutrition and occur in 2% to 8% of patients with central venous catheters. The most common infecting organisms are coagulase-negative staphylococci, *Staphylococcus aureus*, and *Candida* species. Infection is more likely when parenteral nutrition is administered through a multilumen catheter than through a single-lumen catheter,[226] although the incidence of infection may be reduced when parenteral nutrition is infused through a dedicated port.[227] Jugular and femoral catheters have higher rates of infection than do subclavian catheters.[228] Dedicated central line care teams and regular dressing change protocols may reduce the incidence of catheter infection.[227] Antibiotic-coated or antibiotic-impregnated catheters are expensive but appear to be effective in reducing catheter-related bloodstream infections.[229] Guidewire exchange is associated with a decreased incidence of technical complications but an increased incidence of catheter infections.[230] Although the possibility of catheter infection increases with time, routine catheter exchange is probably not indicated.[229] Catheters should be replaced, ideally at a fresh site, for obvious site infection, for the evaluation and treatment of fever of unknown origin, and after any positive blood culture. If guidewire exchange is used and the removed catheter proves to be infected, the new catheter often becomes infected during the exchange and should in turn be removed and replaced at a fresh site.

Metabolic Complications of Nutrition Support

Common metabolic complications of nutrition support include hyperglycemia, hepatobiliary complications, disturbances in water and electrolyte balance, and acid-base abnormalities. Although more common in patients receiving parenteral nutrition, metabolic complications can occur with either form of nutrition support.

Hyperglycemia occurs frequently in critically ill patients receiving nutrition support and is most common in diabetic patients and those with catabolic illness. Complications related to hyperglycemia include infection, hyperosmolarity, and osmotic diuresis. The first step in the control of blood sugar is avoidance of overfeeding, as discussed previously. Insulin, whether by intermittent dosing or continuous infusion, is the mainstay for maintenance of acceptable blood glucose levels. The appropriate glucose level has been the subject of controversy. In a large, prospective, randomized trial in critically ill surgical patients, tight glucose control (80–120 mg/dL) was associated with significantly decreased mortality rate, infection, neuropathy, and renal failure.[49] In medical ICU patients the same tight glucose control protocol was associated with decreased renal failure, ventilator days, and reduced ICU and hospital length of stay, but not improvements in mortality rate or infection.[231] Subsequently, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial compared tight glucose control to glucose levels less than 180 mg/dL and demonstrated similar infection and mortality rates and fewer episodes of dangerous hypoglycemia with more liberal glucose control.[232] Currently, most practitioners aim for blood glucose levels below 150 to 180 mg/dL. Symptomatic hypoglycemia has been reported in children after sudden withdrawal of TPN but is rare in adults, and weaning of TPN in adults is not usually necessary.[233]

Hepatobiliary complications of nutrition support include hepatic steatosis (fatty infiltration of the liver) and intrahepatic and extrahepatic cholestasis. Progression to chronic liver disease occurs in premature infants[234] but is rare in adults. Hepatic steatosis may develop after 7 to 21 days of parenteral nutrition and is characterized initially by elevated transaminases. Usually asymptomatic, fatty infiltration can, in severe cases, be accompanied by hepatomegaly and right upper quadrant abdominal pain. Histologically, mild cases are characterized by periportal fat infiltration and severe cases by centrilobular infiltration. Overfeeding, hyperinsulinemia, essential fatty acid deficiency, and carnitine deficiency may predispose to fatty infiltration. Cholestasis occurs later in the course of parenteral nutrition and is characterized by elevations in bilirubin and alkaline phosphatase. Histologically, periportal or pericentral canalicular bile plugging, bile staining of surrounding hepatocytes, and lymphocytic triaditis characterize cholestasis. Cholelithiasis has been linked to long-term TPN use. Gallstone formation is almost certainly related to the lack of enteral feeding and the resultant lack of neural and hormonal stimulation of gallbladder contraction. Other potential but unproven causes of cholestasis include overfeeding, the production of toxic bile acids by intestinal bacteria, hormones, endotoxin, and taurine deficiency.[31,235–238] Management of hepatobiliary complications is aimed at prevention. Overfeeding should be avoided. Cyclical TPN and enteral feeding, even if only partial, may help prevent cholestasis. A trial of oral neomycin and metronidazole may be helpful.[238]

Serum electrolyte levels should be monitored and electrolytes added to or eliminated from TPN as indicated, with consideration of excess losses or abnormal accumulation. Hypernatremia or hyponatremia can be managed by increasing or decreasing free water. Particular attention should be paid to the intracellular electrolytes potassium, magnesium, and phosphorus. In malnourished individuals, these electrolytes rapidly move intracellularly when nutrition support is initiated. In what is termed the refeeding syndrome, serum levels of these intracellular electrolytes fall precipitously, with

hypophosphatemia resulting in hemolysis, rhabdomyolysis, and heart failure with hypokalemia and hypomagnesemia leading to cardiac arrhythmias.[239,240] Serum levels of intracellular electrolytes should be corrected before and, in particular, 24 hours after the institution of nutrition support. Abnormally high levels of the intracellular electrolytes are of concern in renal failure and often need to be reduced or eliminated from TPN solutions. Hyperkalemia and hypomagnesemia may lead to weakness and cardiac arrhythmia, and hyperphosphatemia may result in hypotension, hypocalcemia, and metastatic calcification. Hyperphosphatemia is often treated with oral phosphate binders such as calcium carbonate.

Metabolic acidosis related to nutrition support is most commonly caused by excess chloride administration and resultant renal bicarbonate losses, but it can also occur as a result of thiamine deficiency with resultant lactic acidosis.[241,242]

Key Points

- Malnutrition is a significant contributor to morbidity and mortality rates in critically ill patients.
- Distinguishing stress metabolism from starvation metabolism is critical to the provision of appropriate nutrition support.
- Critically ill patients may require more energy but are less able to tolerate glucose than starved patients and require a significant portion of calories as fat.
- Critically ill patients require increased protein to achieve nitrogen balance.
- Enteral nutrition is less costly and more physiologic, is associated with fewer metabolic disturbances, and may be associated with fewer infections than parenteral nutrition and thus remains the preferred route for nutrition support.
- Parenteral nutrition is acceptable when enteral nutrition cannot be used, particularly if blood glucose is tightly controlled.
- Nutrition support should be closely monitored to avoid complications.

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Review Questions

1. A patient weighing 75 kg on admission is recovering from sepsis and acute lung injury and is difficult to wean from the ventilator despite an improving chest radiograph. Minute ventilation is 15 L/min. Respiratory quotient (RQ) by indirect calorimetry is 1.15. He is receiving 3000 kcal/day (80% from carbohydrate and 20% from lipids) as total parenteral nutrition (TPN). Which of the following is the most appropriate nutritional modification?

a. Change to an enteral pulmonary failure formula.
b. Substitute protein calories for part of the carbohydrate calories.
c. Decrease total calories to 2250 kcal/day.
d. Increase the proportion of fat calories to 50% of total calories (1500 fat kcal/day).
e. Increase total calories to 4000 kcal/day.

Answer: c. It is recommended that critically ill patients receive 25 to 30 kcal/day. Overfeeding, which results in lipogenesis, would be expected to produce an increase in the RQ, whereas underfeeding, which promotes use of endogenous fat stores, would be expected to produce a decrease in the RQ. Marked increases in carbon dioxide production (VCO_2, with subsequent increases in RQ) in response to overfeeding may cause respiratory compromise in patients with limited pulmonary reserve. An RQ above 1.0 supports overfeeding. The RQ of 1.15 in this case suggests fat synthesis and thus overfeeding. Specialized pulmonary failure formulas contain 50% of calories as fat, which will decrease the RQ, but avoidance of overfeeding is more important.

2. A patient with multiple organ dysfunction syndrome including renal failure is receiving continuous renal replacement therapy (CRRT). Which one of the following represents the most appropriate nutritional prescription?

a. A specialized renal failure formula with low protein
b. A standard nutritional formula with a nonprotein calorie-to-nitrogen ratio of 150 : 1
c. A high-protein enteral formula and possibly the addition of a powdered or liquid protein supplement
d. A specialized immunomodulating enteral formula containing fish oil and supplemental arginine
e. "Standard TPN" with a nonprotein calorie-to-nitrogen ratio of 150 : 1

Answer: c. Although low-protein feeding may be appropriate for patients with chronic renal failure who are not acutely ill, any critically ill patient with acute renal failure needs a high-protein diet primarily because of the catabolic illness that caused the renal failure. Patients receiving CRRT actually need increased protein, usually 2.0 to 2.5 g/kg per day, to account for losses via the dialysis filter. Specialized renal failure formulas are generally not recommended for any critically ill patient with renal failure. Immunomodulating formulas are not currently recommended for critically ill patients with renal failure. Use of TPN is not recommended for patients tolerating enteral feeding.

3. A previously well-nourished patient develops undifferentiated shock and acute respiratory distress syndrome after a difficult coronary artery bypass procedure. The patient becomes hemodynamically stable within 48 hours but still needs ventilator support. Enteral nutrition via a nasojejunal tube is started. After another day, the patient is not tolerating full enteral feeds and continues feeding at 20% of goal rate. Which of the following is the most appropriate nutritional intervention at this point?

a. Discontinue enteral feedings and start TPN.
b. Use TPN to supplement the enteral nutrition to meet calorie and protein requirements.
c. Force enteral feedings, disregarding gastric residual volume, to achieve full enteral feedings.
d. Continue "trophic feedings" for up to a week before considering the addition of TPN.

Answer: d. Early TPN is not indicated in low-risk patients. In higher-risk patients such as this one, Casaer et al.[95] demonstrated in a large randomized controlled trial of ICU patients that late TPN supplementation (at 8 days), compared with earlier TPN supplementation of inadequate enteral feedings, reduced infections, renal replacement therapy and cost, and led to improved functional status. Although full enteral feedings are generally considered a "good thing," in a randomized controlled trial, Rice et al.[102] demonstrated that in patients with acute respiratory distress syndrome, full enteral feedings were no better than trophic feedings during the first 6 days of enteral nutrition support and were associated with fewer gastrointestinal complications. All critically ill patients should receive full feedings, by whatever route, after 6 to 8 days of critical illness.

4. A morbidly obese patient is admitted for multiple trauma 2 months after gastric bypass via Roux-en-Y gastrojejunostomy. The patient is intubated after multiple rib fractures, pelvic fractures, and lower extremity fractures. His family notes that he has been complaining of numbness in his hands and feet and on examination has what appears to be lateral nystagmus. He has multiple surgical procedures planned and will be intubated for an extended period. Which one of the following represents the most appropriate nutrition support prescription?

a. A standard enteral formula with supplemental vitamin D
b. Thiamine supplementation with 2.0 to 2.5 g/kg per day of protein and 11 to 14 kcal/kg per day
c. Thiamine supplementation with 1.5 g/kg per day of protein and 25 to 30 kcal/kg per day
d. Niacin supplementation with 2.0 to 2.5 g/kg per day of protein and 25 to 30 kcal/kg per day
e. Thiamine supplementation with 2.0 to 2.5 g/kg per day of protein and 25 to 30 kcal/kg per day

Answer: b. Patients undergoing gastric bypass for morbid obesity are at risk for Wernicke encephalopathy, which presents with stocking and glove neuropathy and lateral nystagmus, and thus thiamine supplementation is appropriate. The American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine recommend 2.0 to 2.5 g/kg per day of protein and 11 to 14 kcal/kg per day for the provision of nutrition support for the morbidly obese patient.